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Rasagiline ethanedisulfonate: an inhibitor for monoamine oxygenase B (MAO_B)

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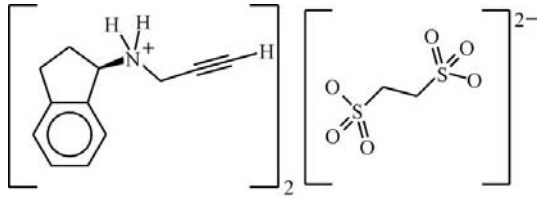
Rasagiline is a selective and potent drug used for the treatment of Parkinson's disease. The first crystal structure of a salt of rasagiline, the title compound, bis[(1*R*)-*N*-prop-2-ynyl-2,3-dihydro-1*H*-inden-1-aminium] ethanedisulfonate, $2C_{12}H_{14}N^+\cdot C_2H_4O_6S_2^-$, was determined from crystals grown by gas diffusion. The compound has monoclinic (*C*2) symmetry. The ethane group of the ethanedisulfonate anion is disordered over three positions. The C_2-symmetric ethanedisulfonate anions are connected by four N—H···O hydrogen bonds to four rasagiline cations. This leads to large 18-membered rings which are arranged in ladders in the [010] direction. The extended hydrogen-bonding architecture may explain the stability of the structure. Rasagiline ethanedisulfonate is nonhygroscopic. During a polymorph screen, no hydrates, solvates or polymorphs were found.

Comment

Rasagiline [systematic name: (1*R*)-*N*-prop-2-ynyl-2,3-dihydro-1*H*-inden-1-amine] is one of the most potent selective and irreversible monoamine oxygenase B (MAO_B) and apoptosis inhibitors known to date (Nayak & Henchcliffe, 2008; Kupsch, 2002). However, despite its pharmaceutical importance, no crystal structure of any rasagiline salt has to our knowledge been published. The compound is traded by Teva Pharmaceutical Industries Ltd under the brand name Azilect as a drug against Parkinson's disease (Frenkel *et al.*, 2007). The compound shows few side effects and is generally well tolerated. One major problem in the production of rasagiline is that most salts of the compound are hygroscopic. This property leads to agglutinates during the synthesis which cause problems in the tabletting of rasagiline. Therefore, most rasagiline salts cannot be directly compressed into tablets (Stahl, 2008). In contrast, the new title compound, rasagiline ethanedisulfonate, (I), is not hygroscopic; in the synthesis it is obtained as a fine crystalline powder which is easy to handle and can be compressed into tablets. Furthermore, the storage stability is increased.



(I)

To understand why rasagiline ethanedisulfonate shows these good stabilities, the crystal structure was determined. Additionally, in order to search for hitherto unknown crystallographic phases, hydrates or solvates, a polymorph screen was carried out on this ethanedisulfonate salt. Different crystallization methods were applied including: (i) recrystallization from various solvents and solvent mixtures by heating and subsequent slow cooling; (ii) diffusion by overlaying a solution of the compound with an antisolvent (Fock, 1888); (iii) diffusion of an antisolvent into a solution of the compound *via* the gas phase. Numerous crystallization experiments were performed using the most common organic solvents, *e.g.* dimethyl sulfoxide, *N*-methylpyrrolidone, dimethylformamide, ethers, esters, alcohols and water. Even acids like acetic acid and bases like sodium hydroxide were used. The powder patterns of all samples were recorded and examined for polymorphs. The samples were measured on a Stoe Stadi-P powder diffractometer [curved Ge(111) primary monochromator, $\lambda = 1.5406$ Å] in transmission geometry from 2 to 74° in 2θ. Samples were prepared between two polyacetate films. For detection, an image-plate position-sensitive detector was used with a resolution ~0.1° in 2θ. For data acquisition, the program *WINXPOW* (Stoe & Cie, 2004) was used.

All powder patterns obtained from recrystallizations, gas diffusions and overlays showed the same phase (a representative powder pattern can be found in the supplementary material). Single crystals suitable for X-ray structure analysis could be grown from dimethyl sulfoxide. To check if the measured single crystal corresponded to the same phase as all other experiments, a powder diagram of the single-crystal data was simulated and compared with the experimental powder diagram. It proved to be the same phase.

The molecular structure of (I) is shown in Fig. 1. In the crystal structure, the five-membered ring has a conformation close to an envelope. Atom C2 deviates by 0.40 Å from the plane through C1/C3/C4/C9. The ring-puckering parameters defined by Cremer & Pople (1975) are $q = 0.256$ (3) Å and $\varphi = 210.4$ (8)°. The C1—N1 bond is in a pseudo-axial position with respect to the five-membered ring. The benzene ring shows a very small deviation from planarity, which may result from crystal packing forces. The mean deviation from the best plane is 0.012 (2) Å.

The ethanedisulfonate anion has crystallographic C_2 symmetry and displays threefold disorder on the $CH_2—CH_2$ group. Both H atoms of the $–NH_2^+–$ group of the rasagiline

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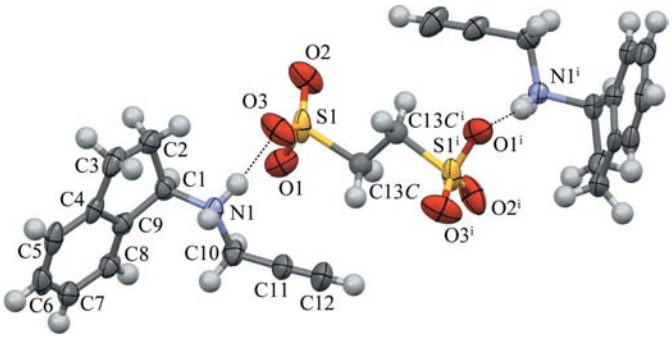

Figure 1
A view of the molecular structure of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. Only the atoms in the major disorder component of the ethanedisulfonate anion are shown. Hydrogen bonds are drawn as dashed lines. [Symmetry code: (i) $-x, y, -z+2$.]

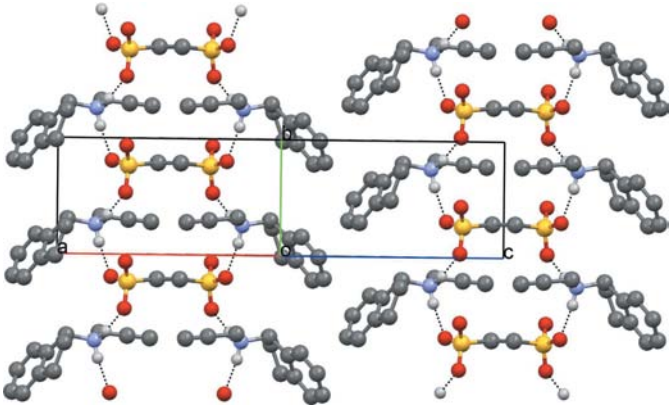

Figure 2
The hydrogen-bonded architecture of (I). Hydrogen bonds are drawn as dashed lines. H atoms that are not involved in the hydrogen bonding have been omitted for clarity.

cation are involved in N—H···O hydrogen bonding (Table 1). Each rasagiline cation is hydrogen bonded to two ethanedisulfonate anions and each anion accepts hydrogen bonds from four cations (Fig. 2). The rasagiline and ethanedisulfonate ions form 18-membered rings. These rings are annellated and form a ladder structure in the [010] direction. Using the graph-set analysis of Etter *et al.* (1990) and Bernstein *et al.* (1995), the hydrogen-bonding pattern is reported as $C_2^2(6)[R_4^4(18)]$. The ethanedisulfonate anion is the central element in the formation of the ladder; a monoanion such as methane sulfate would probably lead to the formation of two individual chains. The extended ladder-type hydrogen-bond system stabilizes the crystal structure and may explain why the ethanedisulfonate salt is not hygroscopic and does not form hydrates. The ladders are connected in the *a*-axis direction by a weak intermolecular C—H···O interaction to form layers parallel to the (001) plane. Along the *c*-axis direction, the rasagiline cations are connected by a weak intermolecular benzene–benzene (*Cg*) C—H···π interaction (Table 1).

Experimental

All solvents and reagents were of reagent grade and were used without further purification. Single cystals of rasagiline ethanedisulfonate, (I), were obtained by gas diffusion. Rasagiline ethanedisulfonate (50 mg) was dissolved in dimethyl sulfoxide (1 ml) in a small flask at room temperature. The small flask was placed inside a larger flask and acetone (5 ml) was placed next to the smaller flask. The larger flask was sealed and left for crystallization. After 1 d, colourless crystals were formed.

Crystal data

$2C_{12}H_{14}N^+\cdot C_2H_4O_6S_2^{2-}$
M_r = 532.66
Monoclinic, *C*2
a = 17.483 (3) Å
b = 5.8363 (9) Å
c = 13.086 (2) Å
β = 99.033 (6)°
V = 1318.7 (4) Å^3
Z = 2
Mo *K*α radiation
μ = 0.25 mm^{-1}
T = 166 (2) K
0.7 × 0.14 × 0.04 mm

Data collection

Siemens SMART 1K CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2000)
T_{min} = 0.862, T_{max} = 0.990
10594 measured reflections
3400 independent reflections
2109 reflections with $I > 2\sigma(I)$
R_{int} = 0.051

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.056
$wR(F^2)$ = 0.117
S = 1.01
3400 reflections
169 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.36 e Å^{-3}
$\Delta\rho_{min}$ = −0.33 e Å^{-3}
Absolute structure: Flack (1983), with 1487 Friedel pairs
Flack parameter: 0.05 (11)

Table 1
Hydrogen-bond geometry (Å, °).

Cg represents the centroid of the benzene ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*B*···O3^{i}	0.92	1.84	2.747 (4)	169
N1—H1*C*···O1	0.92	1.85	2.755 (4)	169
C7—H7*A*···O3^{ii}	0.95	2.36	3.218 (5)	151
C5—H5*A*···*Cg*^{iii}	0.95	2.79	3.512	133

Symmetry codes: (i) $x, y+1, z$; (ii) $x+\frac{1}{2}, y+\frac{1}{2}, z$; (iii) $-x+\frac{1}{2}, y-\frac{1}{2}, -z+1$.

The ethanedisulfonate anion was found to be disordered. Three positions were found for the central ethane fragment. Thus, the C atom of the ethane group was refined as a split atom using three positions. The occupancy factors refined to 0.276 (6) for atoms C13*A* and C13*B*, and to 0.448 (12) for atom C13*C*. The rather large displacement parameters of the sulfonate atoms also showed this group to be disordered, but it was not possible to resolve this disorder. H atoms were positioned geometrically with planar C—H = 0.95 Å, alkyne C—H = 0.95 Å, primary C—H = 1.00 Å, secondary C—H = 0.99 Å and N—H = 0.92 Å, and were treated as riding, with U_{iso}(H) = 1.2U_{eq}(C,N). Friedel opposites were not averaged. The absolute configuration was determined from 1487 Friedel pairs.

Data collection: *SMART* (Siemens, 1995); cell refinement: *SMART*; data reduction: *SAINT* (Siemens, 1995); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics:

Mercury (Macrae *et al.*, 2008); software used to prepare material for publication: *publCIF* (Westrip, 2008).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: DN3098). Services for accessing these data are described at the back of the journal.

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