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Tedisamil sesquifumarate

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Key indicators

Single-crystal X-ray study
T = 153 K
Mean σ(C–C) = 0.003 Å
R factor = 0.059
wR factor = 0.166
Data-to-parameter ratio = 16.1

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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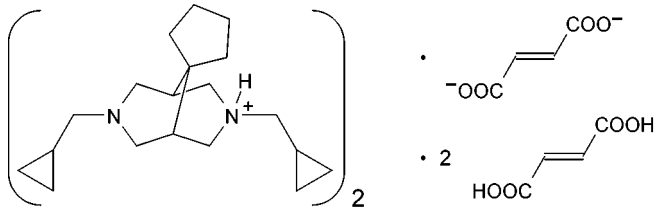
In the title compound, bis[3,7-bis(cyclopropylmethyl)-7-aza-3-azoniaspiro[bicyclo[3.3.1]nonane-9,1′-cyclopentane]] (2*E*)-but-2-enedionate bis[(2*E*)-but-2-enedioic acid], $2C_{19}H_{33}N_2^+\cdot C_4H_2O_4^{2-}\cdot 2C_4H_4O_4$, the cations are protonated at only one N atom and there is no evidence of any disorder involving the alternative nitrogen. The system $N^+—H\cdots N$ represents an intramolecular hydrogen bond. The fumarate and fumaric acid residues form a network of 50-membered rings by classical hydrogen bonding; the cations are linked to these by C—H···O contacts.

Comment

Tedisamil (CAS 90961-53-8) is a potassium channel blocker (class III anti-arrhythmic agent) being developed for the treatment of atrial fibrillation and flutter (Flores, 2001; Fischbach *et al.*, 1999, 2001), and additionally displaying anti-ischaemic properties (Grohs *et al.*, 1989). Tedisamil was synthesized as part of a series of 3,7,9,9-tetraalkyl-3,7-diazabicyclo[3.3.1]nonanes (Schön *et al.*, 1998). In view of the facile chair–boat interconversion and because of the effects on the cardiovascular system (Zefirow & Palyulin, 1991; Jeyamaran & Avila, 1981), the conformation of the bicyclo[3.3.1]nonanes has attracted considerable interest. The determination of the crystal structure of the salt tedisamil sesquifumarate (CAS 150501-62-5), (I), was therefore undertaken.



(I)

The structure of (I) is shown in Fig. 1. The asymmetric unit consists of one singly charged cation, one uncharged fumaric acid molecule and half a doubly charged fumarate anion; the latter is completed by inversion symmetry. The protonation site of the cation is established as N3; the hydrogen H03 was located in a difference synthesis and refined freely. In solution, Fernández *et al.* (1995) have demonstrated rapid exchange of the proton between the two nitrogen sites in another protonated 3,7-diazabicyclo[3.3.1]nonane (for which they also determined the structure; see below). Despite this, and the formal equivalence of the two halves of the uncharged base, there is no evidence for disorder of this H atom in the current structure; its *U* value is acceptably low at 0.035 (6) Å^2, and

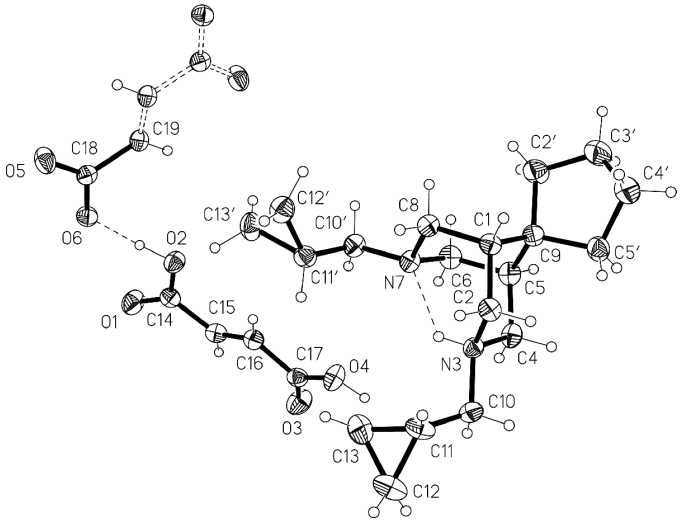


Figure 1
A view of the title compound in the crystal structure, extended by the symmetry-generated second half of the fumarate anion. Displacement ellipsoids are drawn at the 50% probability level. H-atom radii are arbitrary.

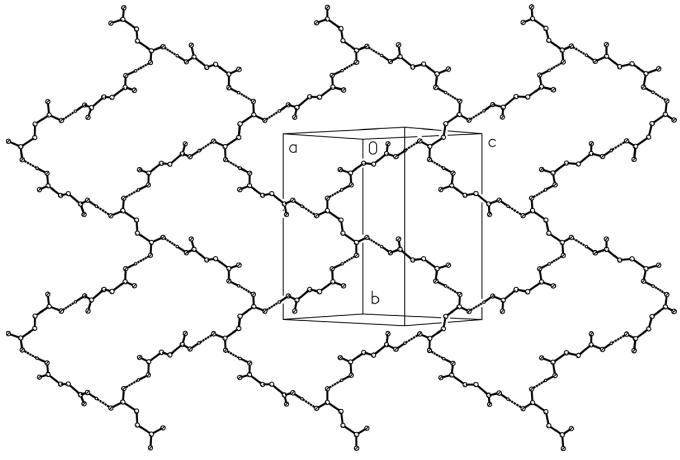


Figure 2
Hydrogen-bonded array of fumarate and fumaric acid residues. Radii are arbitrary.

there is no significant residual electron density near the alternative site N7. Furthermore, the N—C bonds at N3 are lengthened (mean value 1.505 Å compared with 1.479 Å for N7), as would be expected for a protonated system. The intramolecular hydrogen bond has an N···N distance of 2.645 (2) Å. The protonation sites were also unambiguous in the structure by Fernández *et al.* (1995) and in two protonated sparteine derivatives (Farina *et al.*, 1999; Lee *et al.*, 2002), with respective N···N distances of 2.68 (2), 2.714 (4) and 2.755 (5) Å. There is no obvious explanation for the preferred protonation at N3 in the current structure; the two side-chain conformations are also similar.

The cyclopentane ring displays an envelope conformation, with atom C4′ lying 0.628 (4) Å out of the plane of the other four atoms (r.m.s. deviation 0.017 Å). Both six-membered rings show typical chair conformations, with absolute torsion angles in the range 54.0–62.6°.

The cation is not involved in classical hydrogen bonding to the other residues. These form hydrogen bonds amongst themselves, resulting in the formation of large rings of graph set $R_8^8(50)$, linked to form two-dimensional arrays parallel to (101) (Fig. 2). The cations are linked to these *via* a series of C—H···O interactions (Table 2), which are not symmetrically distributed with respect to the two halves of the cation.

Solid-state ^{13}C NMR spectroscopy discriminates the carboxylate anion from both distinct neutral carboxyl groups. The double-bond C atoms C15 and C16, and also the bridgehead C atoms C1 and C5 are equivalent; all other C atoms give rise to single resonances. In contrast to the solid state, in solution, atoms C2, C4, C6 and C8 are symmetry-equivalent. The same holds true for the pairs C2′/C5′ and C3′/C4′. Both cyclopropylmethyl groups are also equivalent (statistical weight of two). Thus, on the NMR time scale, tedisamil sesquifumarate in solution possesses C_{2v} symmetry. To facilitate interpretation, we compared the scalar one-bond C—H coupling constants (in perdeuteromethanol) of the free base, the sesquifumarate and the dihydrochloride (CAS 132523-84-3) of tedisamil, since it is well known that the magnitude of ^1J(C—H) in CH_n groups adjacent to nitrogen reflects the protonation state. In the sesquifumarate, the magnitude of ^1J(C—H) of the N—CH_2 C atoms lies between the corresponding values of the free base and of the diprotonated cation in the dihydrochloride [C10/C10′: 133, 138, 144; C2/C4/C6/C8: 135, 140, 146 Hz; other atoms: no significant differences between free base, sesquifumarate and dihydrochloride]. Thus, we conclude that in solution, the positive charge is spread equally over the two N atoms, resulting in an adamantane-like structure, as proposed for monocationic 3,7-diazabicyclo[3.3.1]nonanes by Douglass & Ratliff (1968). However, the C_{2v} symmetry observed on the NMR timescale in solution could also be explained by rapid proton hopping between the two N atoms (Katrusiak *et al.*, 1988) or, alternatively, by a rapid intra- or intermolecular cation exchange (Fernández *et al.*, 1995).

Experimental

The compound was recrystallized by slow evaporation from 2-propanol. The bulk drug substance used for the NMR studies (ARS0119AA) was provided by Solvay Pharmaceuticals BV, Weesp, The Netherlands. The single-crystal data were used to calculate the idealized XRPD pattern for Cu $K\alpha$ radiation with the program *PowderCell for Windows* (Kraus & Nolze, 1997) to ensure, by good correspondence with the experimental XRPD pattern of ARS0119AA, that the single crystal indeed represented the bulk drug substance. The solid-state ^{13}C NMR spectrum was acquired under cross-polarization (CP) and magic angle spinning (MAS) conditions on a Bruker Avance 300 NMR spectrometer using standard pulse sequences. Processing was performed with Gaussian resolution enhancement. The proton-coupled and the proton-decoupled one-dimensional ^{13}C NMR spectra were acquired on a Bruker ARX 400 NMR spectrometer in methanol-d_4 as solvent.

Crystal data

$2C_{19}H_{33}N_2^+\cdot C_4H_2O_4^{2-}\cdot 2C_4H_4O_4$	$D_x = 1.263$ Mg m^{-3}
$M_r = 925.15$	Mo $K\alpha$ radiation
Monoclinic, $P2_1/n$	Cell parameters from 4119 reflections
$a = 10.6692$ (15) Å	$\theta = 2.2$–$30.0°$
$b = 17.257$ (2) Å	$\mu = 0.09$ mm^{-1}
$c = 13.3990$ (18) Å	$T = 153$ (2) K
$\beta = 99.70$ (2)°	Prism, colourless
$V = 2431.8$ (6) Å^3	0.40 × 0.28 × 0.27 mm
$Z = 2$	

Data collection

Bruker SMART 1000 CCD diffractometer	3349 reflections with $I > 2\sigma(I)$
ω scans	$R_{int} = 0.136$
Absorption correction: none	$\theta_{max} = 26.4°$
15 020 measured reflections	$h = -10 \rightarrow 13$
4981 independent reflections	$k = -20 \rightarrow 21$
	$l = -15 \rightarrow 16$

Refinement

Refinement on F^2	H atoms treated by a mixture of independent and constrained refinement
$R[F^2 > 2\sigma(F^2)] = 0.059$	$w = 1/[\sigma^2(F_o^2) + (0.089P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.166$	$(\Delta/\sigma)_{max} < 0.001$
$S = 0.98$	$\Delta\rho_{max} = 0.43$ e Å^{-3}
4981 reflections	$\Delta\rho_{min} = -0.36$ e Å^{-3}
310 parameters	

Table 1
Selected bond distances (Å).

N3—C4	1.502 (2)	N7—C8	1.487 (2)
N3—C10	1.505 (3)	N7—C10′	1.474 (2)
N3—C2	1.508 (2)	N7—C6	1.476 (2)

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N3—H03···N7	0.89 (2)	1.98 (2)	2.645 (2)	131 (2)
O2—H02···O6	0.99 (3)	1.52 (3)	2.5067 (19)	175 (3)
O4—H04···O5^{i}	0.98 (3)	1.58 (3)	2.544 (2)	168 (3)
C12′—H12D···O3^{ii}	0.99	2.54	3.495 (3)	161
C6—H6B···O6^{i}	0.99	2.57	3.484 (3)	154
C2—H2A···O6^{iii}	0.99	2.42	3.271 (2)	144
C4—H4B···O1^{iii}	0.99	2.64	3.500 (2)	146
C10—H10B···O1^{iii}	0.99	2.63	3.468 (3)	143
C5—H5···O2^{i}	1.00	2.69	3.452 (3)	133
C12—H12B···O5^{iv}	0.99	2.63	3.452 (3)	140

Symmetry codes: (i) $x-\frac{1}{2}, \frac{1}{2}-y, \frac{1}{2}+z$; (ii) $\frac{1}{2}-x, y-\frac{1}{2}, \frac{1}{2}-z$; (iii) $x, y, 1+z$; (iv) $\frac{3}{2}-x, \frac{1}{2}+y, \frac{1}{2}-z$.

At the initially attempted measurement temperature of 133 K, the crystals invariably shattered, but only after some time. This is presumably attributable to a phase transition, but more detailed investigations of this were not undertaken. The measurement reported here was therefore conducted at 153 K and as rapidly as possible, consistent with adequate results. The NH and OH H atoms were refined freely. Other H atoms were included using a riding model, with fixed C—H bond lengths of 1.00, 0.99 and 0.95 Å for Csp^3—H, CH$_2$ and Csp^2—H, respectively; U_{iso}(H) values were fixed at 1.2 times U_{eq} of the parent atom.

Data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT* (Bruker, 1998); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *XP* (Siemens, 1994); software used to prepare material for publication: *SHELXL*97.

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