Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

Sildenafil citrate monohydrate

Hemmige S. Yathirajan,[a] Basavegowda Nagaraj,[a] Padmarajaiah Nagaraja[a] and Michael Bolte[b]*

[a]Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore 570 006, India, and [b]Institut für Anorganische Chemie, J. W. Goethe-Universität Frankfurt, Marie-Curie-Straße 11, 60439 Frankfurt/Main, Germany

Correspondence e-mail: bolte@chemie.uni-frankfurt.de

Key indicators

Single-crystal X-ray study
T = 173 K
Mean σ(C–C) = 0.008 Å
R factor = 0.079
wR factor = 0.154
Data-to-parameter ratio = 13.7

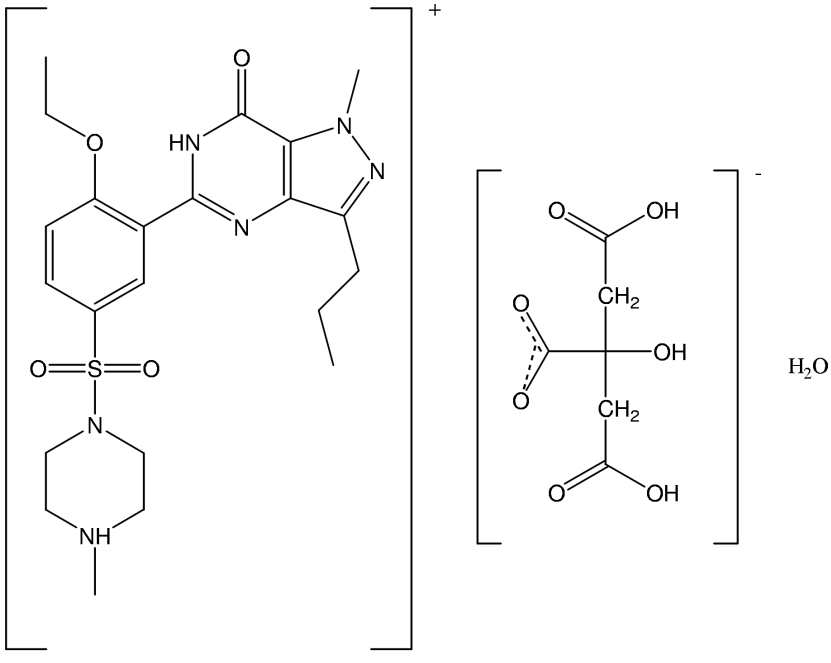
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Sildenafil citrate is well known as Viagra for the treatment of erectile dysfuncion. In the title compound (systematic name: 1-{[3-(6,7-Dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl}-4-methylpiperazinium citrate monohydrate), $C_{22}H_{31}N_6O_4S^+\cdot C_6H_7O_7^-\cdot H_2O$, the pyrazolopyrimidone ring system and the benzene ring are almost coplanar, enabling an intramolecular hydrogen bond between the pyrazolopyrimidone NH group and the O atom of the ethoxy group. One of the N atoms of the piperazine ring is protonated and the citrate molecule exists as an anion. The crystal packing is stabilized by several hydrogen bonds.

Received 7 January 2005
Accepted 24 January 2005
Online 29 January 2005

Comment

Sildenafil citrate is used to treat male erectile dysfunction under the trade name Viagra. The parent base, sildenafil, is a potent selective inhibitor of the enzyme phosphodiesterase (PDE-5), which destroys cyclic guanosine monophosphate (cGMP), itself a dilator of blood vessels in the body (Terrett *et al.*, 1996). The discovery and development of sildenafil has been a revolutionary event in medicine and society. A detailed review of sildenafil citrate has been published by McCullough (2002).



(I)

A perspective view of the title compound, (I), the monohydrate of sildenafil citrate, is shown in Fig. 1. Bond lengths

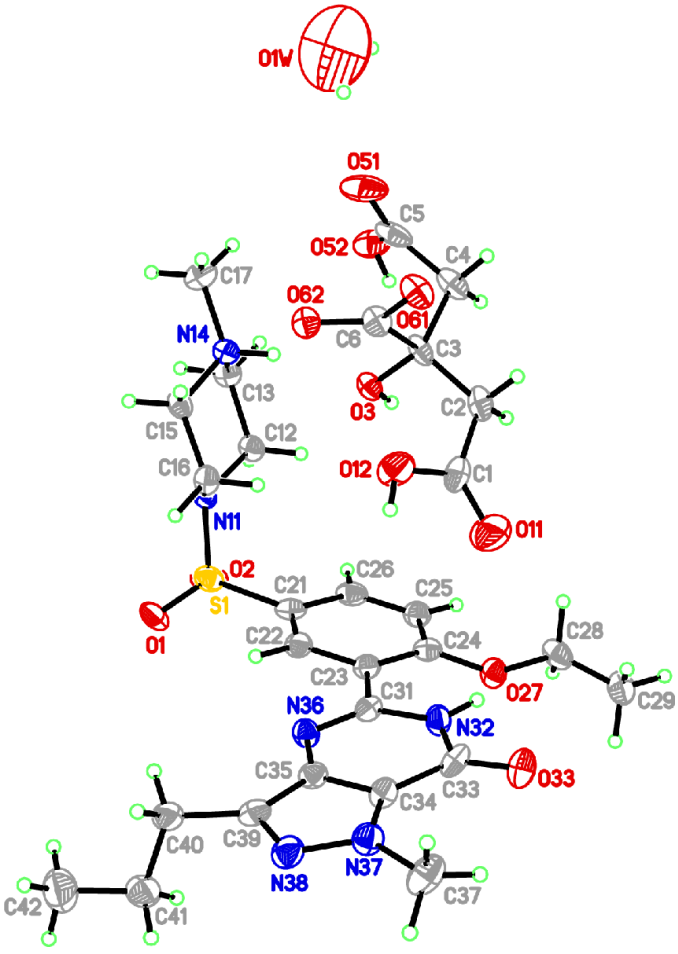


Figure 1
Perspective view of the title compound, with the atom numbering; displacement ellipsoids are drawn at the 30% probability level.

and angles can be regarded as normal (Cambridge Structural Database, Version 1.6 plus three updates; *MOGUL* Version 1.0; Allen, 2002). The piperazine ring shows the expected chair conformation, with the methyl and sulfonyl groups attached equatorially. The propyl and ethoxy side chains are in a *trans* conformation.

The crystal structure of isosildenafil, an isomeric compound of sildenafil, methylated at N2 of the pyrazolopyrimidone ring system, has been reported by El-Abadelah *et al.* (1999). The main difference between (I) and isosildenafil is that in the sildenafil cation of (I), the pyrazolopyrimidone ring system and the benzene ring are almost coplanar. The dihedral angle between the two cyclic groups is 11.6 (3)°, whereas this angle is 43.3 (1)° in isosildenafil. As a result, in (I), there is a hydrogen bond between the pyrazolopyrimidone NH group and the O atom of the ethoxy group (Table 2). In isosildenafil, however, this interaction is significantly weaker (N—H = 0.95 Å, H···O = 2.35 Å, N···O = 2.767 Å and N—H···O 106.1°). Furthermore, the conformation of the propyl chains differ. The conformation is *trans* [−173.4 (6)°] in (I) and *gauche* in isosildenafil [−60.6 (7)°]. A least-squares fit of (I) with isosildenafil is shown in Fig. 2. Apart from the intramolecular

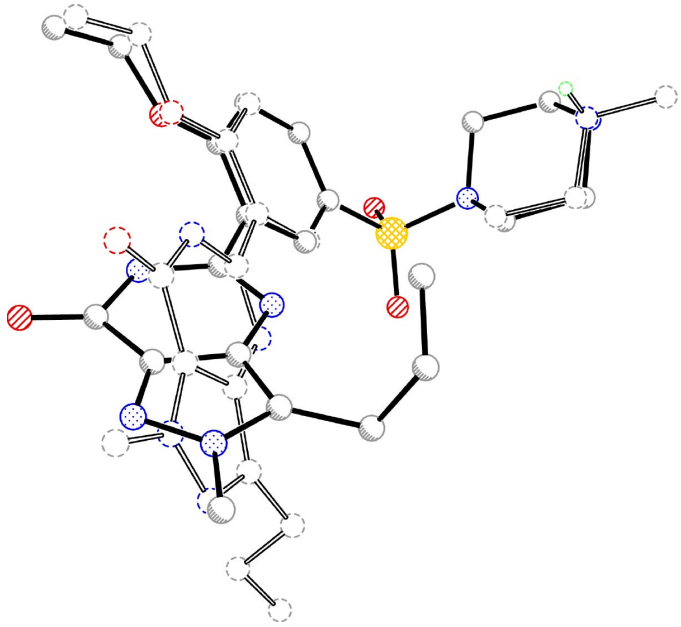


Figure 2
Least-squares fit of sildenafil (open bonds) and isosildenafil (closed bonds). The benzene ring, the SO_2 group and the piperazine ring were fitted (r.m.s. deviation = 0.122 Å).

hydrogen bond, there are several intermolecular hydrogen bonds. It is interesting to note that there is no direct hydrogen bond between the sildenafil molecules, but the citrate anions function as a link between them. The water molecule does not act as an acceptor but just as a donor to a citrate anion and to sulfonyl atom O1 of a sildenafil cation (Table 2). The deprotonated carboxy group of the citrate molecule shows a significantly different geometry than the two other carboxyl groups: the two C—O bonds have the same length and the O—C—O angle is enlarged (Table 1).

The cell parameters of sildenafil citrate without any solvent, determined by powder diffraction (Melnikov *et al.*, 2003), are totally different from those of the title compound: a = 26.98 Å, b = 11.95 Å, c = 16.68 Å, and β = 106.96° V = 5143.9 Å^3.

Experimental

Sildenafil citrate was obtained as a gift sample from CIPLA, Mumbai, India, and used without further purification. Recrystallization from dimethylformamide yielded needles of (I) after slow evaporation of the solvent. The title compound melts at 460 K. IR (KBr, ν cm^{-1}): 3616 (*m*), 3478 (*m*), 3300 (*s*), 3029 (*m*), 2962 (*m*), 2870 (*m*), 2563 (*w*), 2362 (*m*), 1702 (*vs*), 1581 (*s*), 1491 (*m*), 1462 (*m*), 1394 (*m*), 1359 (*m*), 1280 (*m*), 1250 (*m*), 1172 (*s*), 1096 (*w*), 1027 (*m*), 995 (*s*), 940 (*m*), 808 (*m*), 736 (*s*), 690 (*m*), 657 (*m*), 617 (*m*), 588 (*s*), 557 (*m*); ^{1}H NMR (DMSO-d_6, p.p.m.): 0.86–0.90 (*t*, 3H, CH_3–), 1.27–1.31 (*t*, 3H, CH_3—), 1.64–1.73 (*m*, 2H, CH_2—), 2.29 (*s*, 4H, CH_2—), 2.55–2.75 (*t*, 2H, CH_2—), 2.96 (*bs*, 1H, NH—), 3.94 (*bm*, 13H, N—CH—), 4.11–4.2 (*s*, 3H, N^+—CH_3—), 7.34–7.36 (*d*, 1H, ArH—), 7.79–7.83 (*d*, 2H, ArH—), 12.19 (*bs*, 1H, N^+H—); ^{13}C NMR (DMSO-d_6, p.p.m.): 14.24 (*q*, C42, CH_3—), 14.67 (*q*, C29, CH_3—), 22.13 (*t*, C41, CH_2—), 27.53 (*t*, C2, CH_2—), 38.3 (*t*, C40, CH_2—), 39.1–40.35 (*t*, C12,C13,C15,C16, CH_2—), 43.64 (*q*, C37, CH_3—), 44.71 (*d*, C35, C═C—), 53.34 (*d*, C34, C═C—), 65.39 (*t*, C28, CH_2—), 72.59 (*q*, C17, CH_3—), 124.03

(*d*, C26, ArCH—), 124.82 (*d*, C22, ArCH—), 126.52 (*s*, C23), 130.43 (*d*, C25, ArCH—), 132.02 (*s*, C24, ArC—), 138.18 (*s*, C21, ArC), 145.45 (*s*, C39, C═N—), 148.55 (*s*, C6, COO^-—), 154.24 (*s*, C5, HOOC—), 160.45 (*s*, C33, C═O–), 171.87 (*s*, C31), 175.81 (*s*, C3, citrate C—). Analysis calculated for $C_{28}H_{40}N_6O_{12}S$: C 49.11, H 5.89, N 12.27%; found: C 49.31, H 5.81, N 12.4%.

Crystal data

$C_{22}H_{31}N_6O_4S^+\cdot C_6H_7O_7^-\cdot H_2O$
M_r = 684.72
Orthorhombic, *Pbca*
a = 24.002 (4) Å
b = 10.9833 (17) Å
c = 24.364 (3) Å
V = 6422.9 (17) Å^3
Z = 8
D_x = 1.416 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 8732 reflections
θ = 2.0–23.1°
μ = 0.17 mm^{-1}
T = 173 (2) K
Rod, colourless
0.26 × 0.12 × 0.11 mm

Data collection

Stoe IPDS-II two-circle diffractometer
ω scans
Absorption correction: multi-scan (*MULABS*; Spek, 2003; Blessing, 1995)
T_{min} = 0.937, T_{max} = 0.951
44385 measured reflections
5856 independent reflections
1970 reflections with $I > 2\sigma(I)$
R_{int} = 0.098
θ_{max} = 25.4°
$h = -28 \rightarrow 28$
$k = -13 \rightarrow 13$
$l = -29 \rightarrow 27$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.079
$wR(F^2)$ = 0.154
S = 0.78
5856 reflections
428 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0407P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.38 e Å^{-3}
$\Delta\rho_{min}$ = −0.42 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

S1—O1	1.428 (4)	C34—C35	1.385 (8)
S1—O2	1.443 (4)	C35—N36	1.361 (7)
S1—N11	1.630 (5)	C35—C39	1.417 (8)
N11—C16	1.470 (7)	N37—N38	1.352 (6)
N11—C12	1.485 (6)	N37—C37	1.450 (7)
C13—N14	1.507 (7)	C1—O11	1.204 (7)
N14—C17	1.486 (7)	C1—O12	1.293 (7)
N14—C15	1.504 (7)	C3—O3	1.423 (6)
C31—N36	1.295 (7)	C5—O51	1.224 (8)
C31—N32	1.383 (7)	C5—O52	1.318 (8)
N32—C33	1.367 (7)	C6—O61	1.258 (7)
C33—C34	1.447 (8)	C6—O62	1.259 (7)
C34—N37	1.359 (7)		
O11—C1—O12	120.6 (7)	O61—C6—O62	126.3 (6)
O51—C5—O52	119.9 (7)		

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

D—H···A	D—H	H···A	D···A	D—H···A
N14—H14···O3	0.93	1.88	2.764 (6)	159
N14—H14···O62	0.93	2.30	2.911 (6)	123
N32—H32···O27	0.88	1.94	2.622 (6)	134
O12—H12···N38^{i}	0.84	1.98	2.771 (7)	157
O3—H3···O61^{ii}	0.84	1.77	2.605 (5)	173
O52—H52···O62^{ii}	0.84	1.73	2.490 (6)	149
O1*W*—H1*WA*···O1^{iii}	0.84	2.11	2.946 (13)	179
O1*W*—H1*WB*···O51	0.84	1.84	2.678 (16)	179

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

H atoms were located in a difference map, positioned geometrically and refined with fixed individual displacement parameters [set to 1.2 times U_{eq} value of the parent atom (1.5 for methyl groups)] using a riding model, with N—H = 0.88 Å, O—H = 0.84 Å and C—H distances ranging from 0.93 to 0.99 Å. In addition, the torsion angles about the hydroxyl groups and the methyl group at the pyrazolopyrimidone ring system were refined.

Data collection: *X-AREA* (Stoe & Cie, 2001); cell refinement: *X-AREA*; data reduction: *X-AREA*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *XP* in *SHELXTL-Plus* (Sheldrick, 1991); software used to prepare material for publication: *SHELXL97*.

One of the authors (PN) is grateful to CIPLA, Mumbai, for a gift sample of sildenafil citrate and HSY thanks C.Shivakumar (IISc) and K. M. L. Rai (UOM) for spectral studies.

References

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.
Blessing, R. H. (1995). *Acta Cryst.* A**51**, 33–38.
El-Abadelah, M. M., Sabri, S. S., Khanfar, M. A., Voelter, W. & Maichle-Mössmer, C. (1999). *Z. Naturforsch. Teil B*, **54**, 1323–1326.
McCullough, A. R. (2002). *Rev. Urol.* **4**, 26–38.
Melnikov, P., Corbi, P. P., Cuin, A., Cavicchioli, M. & Guimares, W. R. (2003). *J. Pharm. Sci.* **92**, 2140–2143.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Sheldrick, G. M. (1991). *SHELXTL-Plus.* Release 4.1. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Sheldrick, G. M. (1997). *SHELXL97*. University of Göttingen, Germany.
Stoe & Cie (2001). *X-AREA*. Stoe & Cie, Darmstadt, Germany.
Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
Terrett, N. K., Bell, A. S., Brown, D. & Ellis, P. (1996). *Bioorg. Med. Chem. Lett.* **6**, 1819–1824.