

1,1'-Dimethoxy-3,3'-dimethyl-3,3'-(hexane-1,6-diyl)bis(triazen-2-ium-2-olate): a nitric oxide donor

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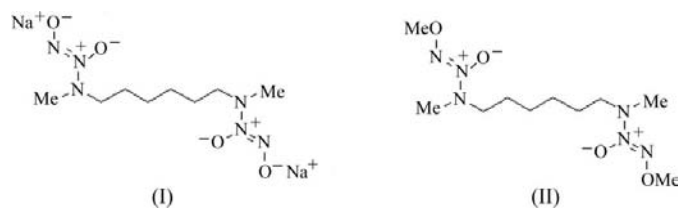
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The title compound, $C_{10}H_{24}N_6O_4$, is the most stable type of nitric oxide (NO) donor among the broad category of discrete *N*-diazoniumdiolates (NO adducts of nucleophilic small molecule amines). Sitting astride a crystallographic inversion center, the molecule contains a symmetric dimethylhexane-1,6-diamine structure bearing two planar O^2 -methylated *N*-diazoniumdiolate functional groups [N(O)=NOMe]. These two groups are parallel to each other and have the potential to release four molecules of NO. The methylated diazeniumdiolate substituent removes the negative charge from the typical N(O)=NO⁻ group, thereby increasing the stability of the diazeniumdiolate structure. The crystal was nonmerohedrally twinned by a 180° rotation about the real [101] axis. This is the first *N*-based bis-diazoniumdiolate compound with a flexible aliphatic main unit to have its structure analyzed and this work demonstrates the utility of stabilizing the *N*-diazoniumdiolate functional group by methylation.

Comment

Nitric oxide (NO) is an extremely reactive free radical and an important physiological gas molecule. Among a host of organic NO donor species reported to date, *N*-diazoniumdiolates have emerged as attractive candidates for direct use as pharmacological agents (Keefer *et al.*, 2003) as well as dopants within polymeric materials to create more biocompatible NO release polymers (Frost *et al.*, 2005). Discrete *N*-diazoniumdiolates [$R'R''N-N(O)=NOR$, NO adducts of nucleophilic small molecule amines] have been developed and can be classified within three broad categories: intramolecularly stabilized (*R* is an intramolecularly protonated amine), anionic (*R* = cation, *i.e.* Na⁺) and protected species (*R* is a substituent group, *e.g.* Me). O^2 -Methylated bis-diazoniumdiolates are the most stable type of NO donors (protected species), with half-lives at physiological conditions on the order of days–months (Saavedra *et al.*, 2002). Under similar

conditions, anionic diazeniumdiolates have much shorter half-lives, ranging from only 2 s to a few minutes (Saavedra *et al.*, 2002). Stability variation is attributed to the structural differences among the three diazeniumdiolate species.



Recently, we reported the synthesis and NO release properties of a series of bis-sodium salt *N*-diazoniumdiolates, one of the most useful NO donors that provides doubled NO delivery capability compared to their zwitterionic counterparts (Reynolds *et al.*, 2005). Bis-sodium 1,1-(1-*N*,6-*N*-dimethylhexamethylenediaminyl)diazene-1-ium-1,2-diolate, (I), is one molecule in that series. Although various analytical data strongly suggested that the bis-diazoniumdiolates were formed within the molecule, exact confirmation of its structural authenticity proved to be extremely difficult due to the labile nature of such an NO donor. We therefore derivatized the compound *via* methylation at the O^2 position of the $N_2O_2^-$ group. The resulting, more stable, O^2 -methyl protected form, bis- O^2 -methyl 1,1-(1-*N*,6-*N*-dimethylhexamethylenediaminyl)diazene-1-ium-1,2-diolate [systematic name: 1,1'-dimethoxy-3,3'-dimethyl-3,3'-(hexane-1,6-diyl)bis(triazen-2-ium-2-olate)], (II), enabled full characterization. The resulting data strongly supported the identification of its precursor, the bis-sodium diazeniumdiolate species, (I).

For the first time, a representative single crystal of the *N*-based O^2 -methylated bis-diazoniumdiolate compound with a flexible dimethylhexanediamine main unit, (II), has been grown and the structure analyzed. This work demonstrates the utility of stabilizing the *N*-diazoniumdiolate functional group by methylation. The single-crystal X-ray diffraction data (Fig. 1

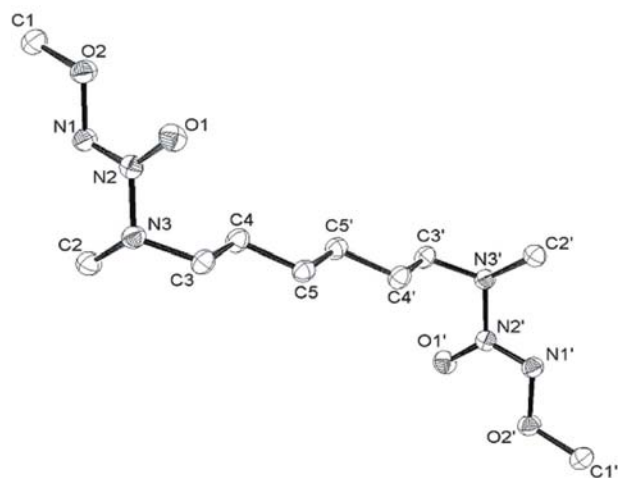


Figure 1

A view of the molecule of (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms have been omitted for clarity [symmetry code: (') $-x, 1 - y, 2 - z$].

and Table 1) provide the strongest evidence to date verifying the proposed structures of the bis-sodium *N*-diazoniumdiolate (I) in an indirect but valid way. The bis-diazoniumdiolate molecule (II) sits on a crystallographic center of symmetry, which bisects the bond between C5 and C5' (symmetry code: $-x, 1 - y, 2 - z$). The two methylated diazeniumdiolate moieties of the molecule, bonded with two amine N atoms, are equivalent by symmetry. The *anti* disposition of the two $N_2O_2^-$ groups of the molecule accompanies the symmetry element (Fig. 1). The methylation occurs at the O^2 position of the diazeniumdiolate group, as previously reported for a couple of mono-diazoniumdiolate species (Keefer *et al.*, 2001; Saavedra *et al.*, 2004). Furthermore, the $N_2O_2^-$ groups are nearly planar, with an O2–N1–N2–O1 torsion angle of only 3.9 (2)°. Within the $N_2O_2^-$ structure, the N1–N2 and N2–O1 bond distances are short (Table 1), indicating extensive charge and double-bond delocalization. The torsion angle and bond lengths are similar to those in other structurally characterized *N*- or *C*-diazoniumdiolates (Keefer *et al.*, 2001; Saavedra *et al.*, 1992, 2004; Arulsamy *et al.*, 2005, 2006). The substituted methyl group on O2 is believed to reduce the negative character from the planar N(O)=NO⁻ group, which prevents protonation, thereby increasing the half-life of the diazeniumdiolate structure under physiological conditions (Saavedra *et al.*, 1992). In addition, as a consequence of the crystallographic inversion center, the two diazeniumdiolate groups are parallel to each other, with a distance between the two planes of 7.331 Å.

Experimental

Compound (II) was synthesized by reacting dimethyl sulfate and the bis-sodium diazeniumdiolate of dimethylhexane-1,6-diamine, (I), which was prepared by the addition of nitric oxide to *N,N'*-dimethylhexane-1,6-diamine under elevated pressure (Reynolds *et al.*, 2005) in the presence of anhydrous sodium carbonate in anhydrous methanol at 273–298 K for about 6 h. After work-up, the crude product was purified by flash chromatography with dichloromethane/ethyl acetate (3:1) to obtain a clear oil (yield 59%). Large colorless plate-like crystals of the bis- O^2 -methylated diazeniumdiolate of dimethylhexane-1,6-diamine were grown by diffusion of petroleum ether into an ethyl acetate solution of the compound at 277 K (m.p. 330 K). Analysis calculated for $C_{10}H_{24}N_6O_4$: C 41.09, H 8.27, N 28.75%; found: C 40.98, H 8.62, N 28.56%.

Crystal data

$C_{10}H_{24}N_6O_4$	$V = 756.50$ (19) Å ³
$M_r = 292.35$	$Z = 2$
Monoclinic, $P2_1/n$	Mo $K\alpha$ radiation
$a = 6.7115$ (15) Å	$\mu = 0.10$ mm ⁻¹
$b = 9.4207$ (8) Å	$T = 123$ (2) K
$c = 12.1863$ (11) Å	$0.40 \times 0.36 \times 0.28$ mm
$\beta = 100.942$ (2)°	

Data collection

Bruker SMART CCD area-detector diffractometer	4787 measured reflections
Absorption correction: multi-scan (Blessing, 1995; Sheldrick, 2003)	3692 independent reflections
$T_{min} = 0.774$, $T_{max} = 0.973$	3020 reflections with $I > 2\sigma(I)$
	$R_{int} = 0.040$

Table 1

Selected geometric parameters (Å, °).

O2–N1	1.3930 (13)	N2–N3	1.4047 (15)
O2–C1	1.4393 (16)	N3–C2	1.4700 (17)
O1–N2	1.2503 (15)	N3–C3	1.4795 (17)
N1–N2	1.2825 (16)		
N1–O2–C1	107.72 (10)	N1–N2–N3	114.85 (10)
N2–N1–O2	106.79 (10)	N2–N3–C2	113.88 (10)
O1–N2–N1	127.01 (11)	N2–N3–C3	111.53 (10)
O1–N2–N3	118.01 (11)	C2–N3–C3	115.45 (11)

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.036$	94 parameters
$wR(F^2) = 0.118$	H-atom parameters constrained
$S = 1.10$	$\Delta\rho_{max} = 0.27$ e Å ⁻³
26771 reflections	$\Delta\rho_{min} = -0.21$ e Å ⁻³

The crystal was found to be a nonmerohedral twin with the twin components related by a 180° rotation about the real [101] axis and a twin fraction ratio of 0.603 (1):0.397 (1). *TWINABS* (Sheldrick, 2003) was used to apply postcollection corrections. Data were merged according to Laue group $2/m$ with the contributions of both twin components as well as overlaps used in corrections and in preparing the HKLF 5 file used in the refinement. For the calculation of the quality-of-fit and variance/covariance values, the number of observations was taken to be the number of unique data from the dominant component rather than the total number in the twin-separated data set. There were 3692 total data and 1889 unique data after merging for Fourier. H atoms were placed at calculated positions (methyl C–H = 0.98 Å and methine CH₂ = 0.99 Å) and refined as riding atoms, with $U_{iso}(H) = 1.5U_{eq}(C)$ or $1.2U_{eq}(C)$, respectively.

Data collection: *SMART* (Bruker, 2001); cell refinement: *CELL_NOW* (Sheldrick, 2003); data reduction, program used to solve and refine structure, molecular graphics and preparation of material for publication: *SHELXTL* (Sheldrick, 2008).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FA3166). Services for accessing these data are described at the back of the journal.

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