Models for potential dendritic nitric oxide donors: crystal structures of two 2-nitroanilino precursors and nitric oxide-release behavior of the nitrosated derivatives

Alec R. Badour,^a Corey J. Arnett-Butscher,^a Dillip K. Mohanty,^{a*} Philip J. Squattrito,^{a*} Kelly J. Lambright^b and Kristin Kirschbaum^b

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^aDepartment of Chemistry and Biochemistry, Central Michigan University, Mount Pleasant, Michigan 48859, USA, and

^bCollege of Natural Sciences and Mathematics, University of Toledo, Toledo, OH 43606, USA. *Correspondence e-mail: mohan1dk@cmich.edu, p.squattrito@cmich.edu

Two molecular precursors to dendrimeric materials that could serve as slow and sustained NO-releasing therapeutic agents have been synthesized and characterized. *N*¹,*N*⁴-Bis(2-nitrophenyl)butane-1,4-diamine, C₁₆H₁₈N₄O₄, (I), crystallizes in a lattice with equal populations of two molecules of different conformations, both of which possess inversion symmetry through the central C—C bond. One molecule has exclusively *anti* conformations along the butyl chain, while the other has a *gauche* conformation of the substituents on the first C—C bond. *N*²,*N*²-Bis[2-(2-nitroanilino)ethyl]-*N*¹-(2-nitrophenyl)ethane-1,2-diamine, C₂₄H₂₇N₇O₆, (II), crystallizes with one unique molecule in the asymmetric unit. Neighboring pairs of molecules are linked into dimers *via* N—H...O amine–nitro hydrogen bonds. The dimers are assembled into layers that stack in an *A*–*B*–*A*–*B* sequence such that the repeat distance in the stacking direction is over 46 Å. Molecular NO-release agents *N*¹,*N*⁴-bis(2-nitrophenyl)-*N*¹,*N*⁴-dinitrosobutane-1,4-diamine, C₁₆H₁₆N₆O₆, (III), and *N*¹-(2-nitrophenyl)-*N*²,*N*²-bis[2-[(2-nitrophenyl)(nitroso)amino]ethyl]-*N*¹-nitrosoethane-1,2-diamine, C₂₄H₂₄N₁₀O₉, (IV), were prepared *via* treatment of (I) and (II), respectively, with NaNO₂ and acetic acid. The release of NO from solid-phase samples of (III) and (IV) suspended in phosphate buffer was monitored spectroscopically over a period of 21 days. Although (IV) released a greater amount of NO, as expected due to it having three NO moieties for every two in (III), the (IV):(III) ratio of the rate and extent of NO release was significantly less than 1.5:1, suggesting that some combination of electronic, chemical, and/or steric factors may be affecting the release process.

1. Introduction

Nitric oxide (NO) has been widely studied as a gasotransmitter involved in a variety of biological processes. It is produced *in vivo* from L-arginine by a family of enzymes called NO synthases (NOS), which require molecular oxygen and a host of cofactors for their activity (Szabo, 2016). Structurally simple NO is a highly reactive radical that is consumed quickly and exhibits complex chemistry (Lundberg *et al.*, 2015). It plays beneficial roles in the functioning of the nervous, cardiovascular, respiratory and immune systems at a very low concentration (Ignarro, 2010). High levels of NO are known to cause apoptosis and other maladies, including septic shock, neurodegenerative diseases, ulcerative colitis, and cancer (Kroncke *et al.*, 1997). Thus, it is of critical importance to regulate NO levels within appropriate ranges. One way to accomplish this is through the development of agents that are capable of gradually releasing NO during therapeutic use in the body.

We have reported a series of NO donors which release NO in a slow, sustained, and rate-tunable fashion (Curtis *et al.*, 2013, 2014; Yu *et al.*, 2011; Lagoda *et al.*, 2014). In addition, we have shown that the released NO can inhibit the proliferation of human aortic smooth muscle cells, a contributing factor to the progression of atherosclerosis (Curtis *et al.*, 2013; Yu *et al.*, 2011). The reported NO donors were prepared from *N*-nitrosated aryl–alkyl secondary diamines. The resulting nitrosated diamines can donate a maximum of two moles of NO.

The ability to precisely control molecular architecture during synthesis has created interest in employing dendritic materials in the development of controlled drug delivery systems (Seabra *et al.*, 2015). Furthermore, the electronic environment, physical properties, including pK_a (depending on the nature of the dendrimer), and steric hindrance vary throughout the molecule depending on its proximity to the periphery (Yamamoto & Takanashi, 2008). As a result, it can be envisioned that a dendritic molecule containing NO-donating groups linked to the repeat unit will exhibit unique generation-dependent NO-releasing capabilities. For example, with increasing generation, the number of NO-donating sites increases exponentially. It is of interest to see if the amounts of released NO reflect the statistical generation-dependence alone or if other factors, including solubility, hydrophilicity, and steric hindrance, also contribute to the observed NO concentrations. Therefore, the ability to fine-tune NO-release tendencies through the manipulation of dendrimeric structure and generation number is of great therapeutic interest. Prior to attempting the creation of NO-donating dendrimeric molecules, it was desirable to synthesize and study the NO-release behavior of low molecular weight compounds that are able to act as structural models for the future preparation of dendritic NO donors.

This investigation reports the synthesis and X-ray crystal structures of two compounds, namely N^1,N^4 -bis(2-nitrophenyl)butane-1,4-diamine, (I), and N^2,N^2 -bis[2-(2-nitroanilino)ethyl]- N^1 -(2-nitrophenyl)ethane-1,2-diamine, (II), containing two and three secondary amine moieties, as precursors to NO-donating compounds (Scheme 1). The preparation of (I) was accomplished by the reaction of two equivalents of

2-fluoronitrobenzene with 1,4-diaminobutane, while (II) was synthesized by the reaction of three equivalents of 2-fluoronitrobenzene with tris(2-aminoethyl)amine. The nitrosation of (I) and (II) was then carried out *via* treatment with NaNO_2 and the release of NO was measured over time in order to be able to see how the extent of release correlates with the number of donor sites.

2. Experimental

2.1. Synthesis and crystallization

2-Fluoronitrobenzene (3.2834 g, 23.27 mmol) was dissolved in 10 ml of *N,N*-dimethylacetamide (DMAC) in a one-necked 50 ml round-bottomed flask fitted with a magnetic stirrer bar. K_2CO_3 (12.8642 g, 93.08 mmol) was added, creating a heterogeneous mixture, followed by addition of 1,4-diaminobutane (1.0256 g, 11.63 mmol), which promptly resulted in the formation of an intense red color. The reaction was allowed to proceed for 10 h at room temperature while stirring. Upon completion of the reaction, the reaction mixture was diluted with methylene chloride (20 ml) and filtered over a Celite bed under vacuum. The methylene chloride component of the filtrate was removed under reduced pressure using a rotary evaporator. DMAC and excess 2-fluoronitrobenzene were subsequently removed *via* vacuum distillation using a short-path distillation apparatus. The crude product was diluted with methylene chloride (20 ml) and placed in a separatory funnel. The organic layer was washed with deionized water (20 ml). Following removal of the aqueous layer, the methylene chloride layer was washed with saturated sodium chloride solution (20 ml) and again with additional deionized water (20 ml). The organic layer was removed from the separatory funnel, dried over anhydrous magnesium sulfate, and filtered *via* gravity filtration. The solvent was removed under reduced pressure. The solid orange crude product was recrystallized from a methylene chloride–hexane mixture (100:1 *v/v*) to yield orange crystals suitable for X-ray diffraction (yield 82%; m.p. 426–428 K). ^1H NMR (300 MHz, CDCl_3): δ 1.86 (*m*, 4H), 3.40 (*q*, 4H), 6.66 (*m*, 2H), 6.85 (*d*, 2H), 7.45 (*m*, 2H), 8.08 (*s br*, 2H), 8.17 (*m*, 2H); FT-IR (ν , cm^{-1}): 3367, 2935, 2856, 1618, 1577, 1507, 1417, 1353, 1334, 1276, 1250, 1226, 1148, 1038, 738; ESI-MS (m/z) calculated for $[M + \text{H}]^+$ 331.35, found 331.15.

To produce (II), tris(2-aminoethyl)amine (1.025 g, 7.007 mmol), 2-fluoronitrobenzene (2.976 g, 21.09 mmol), K_2CO_3 (8.715 g, 63.1 mmol), and DMAC (30 ml) were combined in a 50 ml round-bottomed flask and stirred for 20 h at room temperature. A work-up analogous to that utilized in the procedure for (I) was followed. The crude product was recrystallized from a methylene chloride–hexane mixture (100:1 *v/v*) to yield bright-orange crystals suitable for X-ray diffraction (yield 66%; m.p. 376–378 K). ^1H NMR (300 MHz, CDCl_3): δ 2.95 (*t*, 6H), 3.43 (*q*, 6H), 6.57 (*t*, 3H), 6.77 (*d*, 3H), 7.34 (*t*, 3H), 8.06 (*d*, 3H), 8.18 (*t*, 3H); FT-IR (ν , cm^{-1}): 3373, 3084, 2957, 2905, 2861, 1616, 1570, 1509, 1473, 1441, 1417, 1352, 1317, 1260, 1229, 1151, 1037, 740; ESI-MS (m/z) calculated for $[M + \text{H}]^+$ 510.53, found 510.20.

2.2. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 1. For (I), C—H hydrogens were included as riding atoms with fixed distances of 0.95 (aryl) or 0.99 Å (methylene), and with $U_{eq}(H) = 1.2U_{iso}(C)$. N—H hydrogens were located from difference Fourier syntheses and were refined isotropically without any restraints (bond lengths can be found in Table 2). For (II), both C—H and N—H hydrogens were refined isotropically without restraints [C—H = 0.978 (13)–1.014 (14) (methylene) and 0.930 (15)–0.994 (17) Å (aryl); N—H bond lengths can be found in Table 3].

2.3. Nitric oxide release studies

For the nitrosation of (I) and (II) at the amine N atoms, (I) (0.213 g, 0.644 mmol) or (II) (0.456 g, 0.890 mmol) was completely dissolved in 5 ml of dry tetrahydrofuran (THF) in a single-necked 50 ml round-bottomed flask. Glacial acetic acid (0.1 ml, 105 mmol) was added and the reaction solution was cooled in an ice water bath for 15 min. Upon cooling, solid NaNO₂ was added [0.887 g, 12.9 mmol to (I); 1.23 g, 17.8 mmol to (II)] yielding a heterogeneous mixture. The flask was immediately capped, sealed, and removed from the ice bath. The reaction was allowed to warm to room temperature (295 K) and proceed for 30 min. Upon completion, the mixture was partitioned into three separate test tubes containing ice and deionized water, yielding a yellow precipitate in each. The tubes were centrifuged and the liquid phase

was decanted. This process was repeated once with fresh ice water, and then with cold saturated sodium bicarbonate. Additional washes with ice water were performed until a neutral pH was reached. The solid material in each tube was dissolved in cold (283 K) methylene chloride, and the three fractions were combined and then dried over solid magnesium sulfate. Following removal of the magnesium sulfate *via* gravity filtration, the methylene chloride was removed under reduced pressure using a rotary evaporator to yield the nitrosated products. Once synthesized, the products were stored in sealed containers at 273 K for later use in NO-release studies. Analytical data for (III), C₁₆H₁₆N₆O₆, yield 72%; FT-IR (ν , cm⁻¹): 3109, 2953, 2877, 1606, 1584, 1531, 1447, 1355, 1132, 1070. Analytical data for (IV), C₂₄H₂₄N₁₀O₉, yield 82%; FT-IR (ν , cm⁻¹): 3112, 2960, 2859, 1606, 1530, 1464, 1446, 1353, 1129, 1085. The completeness of nitrosation was verified by the disappearance of the N—H stretch at *ca* 3370 cm⁻¹ in the spectra of (I) and (II).

Nitric oxide release was studied by adding a measured amount of (III) (0.0319 g) or (IV) (0.185 g) to a 25 ml round-bottomed flask equipped with a magnetic stirrer bar. Two cadmium pellets were rinsed with 1 ml of 0.1 M HCl followed by 1 ml of 0.1 M NH₄OH and then added to the flask. Next, 20 ml of phosphate buffer saline (PBS) solution was added and stirring was initiated creating a suspension of (III) or (IV) in the aqueous medium. The flask was sealed with a glass stopper and covered with aluminum foil to exclude sunlight. Aliquots (200 μ l) were removed over the course of the reaction to monitor the amount of NO released. Each aliquot was

Table 1
Experimental details.

	(I)	(II)
Crystal data		
Chemical formula	C ₁₆ H ₁₈ N ₄ O ₄	C ₂₄ H ₂₇ N ₇ O ₆
M_r	330.34	509.52
Crystal system, space group	Triclinic, $P\bar{1}$	Orthorhombic, $Pbca$
Temperature (K)	120	120
a, b, c (Å)	6.7032 (4), 8.1646 (5), 15.1177 (9)	7.5749 (2), 13.4138 (4), 46.3793 (14)
α, β, γ (°)	81.099 (2), 79.555 (2), 67.488 (2)	90, 90, 90
V (Å ³)	748.34 (8)	4712.5 (2)
Z	2	8
Radiation type	Cu $K\alpha$	Cu $K\alpha$
μ (mm ⁻¹)	0.90	0.89
Crystal size (mm)	0.08 × 0.07 × 0.03	0.21 × 0.13 × 0.06
Data collection		
Diffractometer	Bruker APEXII CCD	Bruker APEXII CCD
Absorption correction	Multi-scan (SADABS; Sheldrick, 1996)	Multi-scan (SADABS; Sheldrick, 1996)
T_{min}, T_{max}	0.689, 0.753	0.655, 0.753
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	2595, 2595, 2314	50384, 4413, 4182
R_{int}	0.027	0.026
$(\sin \theta/\lambda)_{max}$ (Å ⁻¹)	0.609	0.609
Refinement		
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.043, 0.138, 1.10	0.031, 0.079, 1.06
No. of reflections	2595	4413
No. of parameters	226	442
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement	All H-atom parameters refined
$\Delta\rho_{max}, \Delta\rho_{min}$ (e Å ⁻³)	0.25, -0.34	0.22, -0.24

Computer programs: APEX3 (Bruker, 2015), SAINT (Bruker, 2015), SHELXS97 (Sheldrick 2008), SHELXL2016 (Sheldrick, 2015) and CrystalMaker (Palmer, 2014).

transferred to a 1.5 ml plastic Eppendorf micro centrifuge tube (Fisher) and centrifuged at 2000 rpm for 2 min. Two 50 μ l aliquots of the supernatant were transferred to separate wells of a 96-well plate and combined with 50 μ l of PBS solution. To another two wells were added 100 μ l of PBS as controls. Greiss reagent (100 μ l) was added to each of the four wells and, following incubation for 5 min at room temperature, the absorbance of each well was determined at 550 nm using a Molecular Devices SpectraMax M2 micro plate reader and *SoftMax Pro 5* software (Molecular Devices, 2005). The NO release rate was determined by plotting absorbance *versus* time.

3. Results and discussion

N^1,N^4 -Bis(2-nitrophenyl)-1,4-butanediamine, (I), crystallizes in the triclinic space group $P\bar{1}$ with halves of two independent molecules in the asymmetric unit (Fig. 1). Each molecule has inversion symmetry through the central C—C bond of the butyl chain, but the two molecules differ in the conformation across the first two C atoms in the chain. One molecule shows a *gauche* conformation, as indicated by the N1—C1—C2—C2ⁱ torsion angle of $-68.4(2)^\circ$ [symmetry code: (i) $-x, -y + 2, -z$], while the other is *anti* across the analogous bond [torsion angle N11—C11—C12—C12ⁱⁱ = $-174.65(17)^\circ$; symmetry code: (ii) $-x + 1, -y + 2, -z + 1$]. As a result, although both molecules have their arene rings parallel due to the inversion symmetry, the planes of the rings in the molecules with the *gauche* conformation are several Å apart, while those with the *anti* conformation are nearly coplanar. The structure is thus composed of step-shaped molecules and essentially flat molecules. Both molecules show intramolecular N—H...O hydrogen bonding between the *ortho* amine and nitro groups (Table 2) to form a six-membered ring that is typically observed in molecules with these functional groups adjacent to each other (Badour *et al.*, 2016; Helttunen *et al.*, 2013). The arene ring in the *gauche* molecule is rotated modestly relative to the butyl chain [torsion angle C8—C3—N1—C1 = $8.0(2)^\circ$], while the ring in the *anti* molecule is almost perfectly aligned with the chain [torsion angle C18—C13—N11—C11 = $-0.4(2)^\circ$], further contributing to the flatness of the latter. *N*-Arylbutanediamides (succinamides) provide a useful point of comparison for the conformations of the molecules in (I) as they offer a four-carbon chain terminated at both ends by an aryl-substituted N—H group. Four such molecules, namely *N,N'*-bis(2-chlorophenyl)succinamide (Saraswathi *et al.*, 2011a), *N,N'*-bis(3-chlorophenyl)succinamide (Saraswathi *et al.*, 2011b), *N,N'*-bis(3-methylphenyl)succinamide (Saraswathi *et al.*, 2011c), and *N,N'*-bis(2-hydroxyphenyl)butanediamide (Crass *et al.*, 1996), all show *anti* conformations along the length of the carbon chain and crystallize on centers of inversion with $Z' = \frac{1}{2}$. In the 2-chlorophenyl, 3-chlorophenyl, and 2-hydroxyphenyl derivatives, the arene rings are rotated significantly (*ca* 48, 35, and 35° , respectively) out of the plane of the butane chain, while the methylphenyl rings are only rotated by about 5° . This variation is understandable since none of these molecules have the constraining driving force of

Table 2

Hydrogen-bond geometry (Å, $^\circ$) for (I).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
N1—H1N...O1	0.88 (2)	1.95 (2)	2.6273 (18)	132.2 (19)
N1—H1N...O1 ⁱ	0.88 (2)	2.34 (2)	3.0388 (19)	136.8 (19)
N11—H11N...O11	0.84 (2)	1.97 (2)	2.6221 (19)	133 (2)

Symmetry code: (i) $-x + 1, -y + 1, -z$.

the N—H...O amine–nitro hydrogen bonding, which requires the ring twist to be kept to a minimum. A related molecule, diphenylsuccinate (Brisse *et al.*, 1979), shows a similar behavior. When derivatives with different ring substituents at opposite ends of the molecule were studied, the results were mixed. *N*-(2-Chlorophenyl)-*N'*-(2-methylphenyl)succinamide (Saraswathi *et al.*, 2011d) crystallizes in the *anti* conformation with $Z' = \frac{1}{2}$ and disorder between the methyl and chloro groups. Of this series of molecules, only *N*-(4-methylphenyl)-*N'*-phenylbutanediamide (Saraswathi *et al.*, 2011e) shows *gauche* conformations across the carbon chain and no internal symmetry. From this small sample it would appear that the *gauche* conformation is significantly less common than the *anti* conformation, so having equal populations of both conformers in the crystal of (I) is unexpected.

The packing diagram for (I) is shown in Fig. 2. While it is unusual that the structure is composed of two molecules of differing conformations, having both molecules on inversion centers is the most likely arrangement for this situation (Brock & Dunitz, 1994; Pidcock *et al.*, 2003). The *gauche* molecules are located on the centers of inversion at the corners of the unit cell. Adjacent pairs along the *a* axis are linked into dimers through weak intermolecular N—H...O hydrogen bonds (Table 2) across the inversion center in the *ab* face of the unit cell at $\frac{1}{2}, \frac{1}{2}, 0$. The intermolecular H...O distance of 2.34 (2) Å is consistent with what is typically observed for this type of

Figure 1

The two independent molecules of (I) are shown with atom labels and 70% probability displacement ellipsoids for the non-H atoms. The intramolecular hydrogen bonds are shown as dashed lines. The molecule on the left has a *gauche* conformation about the C1—C2 bond, while the molecule on the right has an *anti* conformation about the C11—C12 bond. [Symmetry codes: (i) $-x, -y + 2, -z$; (ii) $-x + 1, -y + 2, -z + 1$.]

Table 3

Hydrogen-bond geometry ($\text{\AA}$, $^\circ$) for (II).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
$N2-H2N\cdots O1$	0.884 (17)	1.939 (16)	2.6214 (13)	132.9 (14)
$N2-H2N\cdots O1^i$	0.884 (17)	2.399 (16)	3.0715 (14)	133.1 (13)
$N4-H4N\cdots O3$	0.868 (16)	1.942 (16)	2.6265 (13)	134.7 (13)
$N6-H6N\cdots O5$	0.849 (15)	2.013 (15)	2.6320 (13)	129.1 (12)

Symmetry code: (i) $-x, -y + 2, -z$.

interaction (Panunto *et al.*, 1987). The *anti* molecules are located on the centers of inversion in the *ac* faces of the unit cell at $\frac{1}{2}, 0, \frac{1}{2}$, where they are unable to self-dimerize. The principal interactions between the two independent molecules appear to be the close face-to-face (dihedral angle *ca* 3.8°) contacts of the arene rings that are stacked in the approximate *a* direction. The separations between the C atoms in neighboring rings (3.3–3.4 $\text{\AA}$) are similar to those in graphite indicating some appreciable π – π interactions. The simultaneous presence of intermolecular hydrogen bonds between the *gauche* molecules and the π – π interactions between *gauche* and *anti* molecules would appear to be important in explaining why both molecules appear in the same crystal.

N^1 -(2-Nitrophenyl)- N^2,N^2 -bis[2-(2-nitroanilino)ethyl]ethane-1,2-diamine, (II), crystallizes in the orthorhombic space group *Pbca* with one independent molecule lacking any internal symmetry in the asymmetric unit (Fig. 3). The three amine H atoms participate in the expected intramolecular hydrogen bonds with O atoms of the *ortho* nitro groups (Table 3). The three 2-(2-nitroanilino)ethyl groups all have different conformations. The N atoms on the C1–C2 bond are approximately *anti* [$N1-C1-C2-N2$ torsion angle = $171.0 (1)^\circ$], while those attached to C9–C10 are about 23° short of being *anti* [$N1-C9-C10-N4$ torsion angle = $157.56 (9)^\circ$], and those on C17–C18 are closest to being *gauche* [$N1-C17-C18-N6$ torsion angle = $46.8 (1)^\circ$]. The aryl rings are rotated about the C3–N2, C18–N6, and C10–N4 bonds by *ca* 8, 10, and 1° , respectively. The three rings, *i.e.*

Figure 3

The molecular structure of (II), showing atom labels and 70% probability displacement ellipsoids for the non-H atoms. The intramolecular hydrogen bonds are shown as dashed lines.

A (C3–C8), *B* (C11–C16) and *C* (C19–C24), have dihedral angles of $A-B = 68.00 (3)^\circ$, $A-C = 37.30 (4)^\circ$, and $B-C = 78.70 (3)^\circ$. All three rings are positioned moderately towards the apex side of the N1 trigonal pyramid, giving the overall molecule more of a spread-out propeller than a compact tripodal shape. A similar overall arrangement to (II) is seen in the related molecule tris[2-(2,6-dimethylanilino)ethyl]amine (Moroz *et al.*, 2011). By contrast, the ethyl C–C bonds in tris[2-(benzoylamino)ethyl]amine all have *anti* conformations of the appended N atoms and the aryl rings form a pronounced tripod, though on the apical side of the central trigonal pyramid (Goldcamp *et al.*, 2000). In another related molecule, nitrilotriacetanilide [tris(2-aminoethyl)amine], one ring is directed below the basal side of the trigonal pyramid, one is strongly to the apical side, and one is slightly to the apical side [*i.e.* spread out more like those in (II)] (Rowland *et al.*, 2001). This conformational diversity is attributable, in part,

Figure 2

Packing diagram of (I) with the outline of the unit cell. The view is onto the (010) plane. The *gauche* molecules at the corners of the unit cell are linked into dimers across centers of inversion by weak $N-H\cdots O$ amine–nitro hydrogen bonds (dashed), while the *anti* molecules in the center of each cell do not participate in such interactions. [Symmetry code: (#) $-x + 1, -y + 1, -z$.]

Figure 4

Partial packing diagram of (II), showing molecules linked into dimers across a center of inversion by weak $N-H\cdots O$ amine–nitro hydrogen bonds (dashed). Only one of the three amine groups participates in these intermolecular interactions. The view is approximately onto the (010) plane. [Symmetry code: (#) $-x, -y + 2, -z$.] Displacement ellipsoids are drawn at the 70% probability level.

Figure 5

Full packing diagram of (II) with the outline of the unit cell. The view is onto the (100) plane. The dominant packing motif is double layers of molecules linked through intermolecular hydrogen bonds that are stacked in the c direction. Displacement ellipsoids are drawn at the 70% probability level.

to differences in intramolecular hydrogen-bonding opportunities between the pendant groups, with the presence of such interactions favoring the compact tripodal shape. In (II), there are no $\text{N}-\text{H}\cdots\text{O}$ hydrogen bonds between an amine of one arm and a nitro O atom of another arm.

Scheme 2

Molecules of (II) are linked into dimers across centers of inversion through $\text{N}-\text{H}\cdots\text{O}$ amine–nitro hydrogen bonds similar to those seen in (I) (Fig. 4). The $\text{H}\cdots\text{O}$ distance of

2.40 (2) Å (Table 3) is a bit longer than that observed in (I) but still within the range normally seen in this type of three-center hydrogen bond (Panunto *et al.*, 1987). Although there are three amine groups in (II), this linkage occurs through only one of them. As shown in the full packing diagram (Fig. 5) rows of molecules are linked into double layers with the hydrogen bonds in the center and arene rings on the exterior sides of the layer. These layers are then stacked in the c direction in an $A-B-A-B$ sequence which accounts for the eight molecules in the unit cell. The relatively smaller role played by intermolecular hydrogen bonding in (II) *versus* that in (I) together with the absence in (II) of the efficient $\pi-\pi$ interactions seen in (I) appear to correlate with the lower melting point of (II) (376 K) compared to (I) (426 K).

Figure 6

Moles of NO released per 100 moles of release agent for (III), (IV), and *N*-(2-nitroanilino)-*N*-nitrosobutane, (V), *versus* time. (V), (III), and (IV) carry one, two, and three NO moieties per molecule, respectively.

Scheme 3

Precursors (I) and (II) were converted into NO-releasing agents (III) and (IV) *via* nitrosation of the amine groups (Schemes 2 and 3). In their present form (*i.e.* prior to

dendrimerization), (III) and (IV) contain two and three NO moieties capable of release, respectively. The NO-release data for (III), (IV), and *N*-(2-nitroanilino)-*N*-nitrosobutane, (V), which carries only one NO moiety, are shown in Fig. 6. As the number of NO-donating sites increases from 1 in (V) to 2 in (III) to 3 in (IV), the molecules of NO released per unit amount of compound increases but not in direct correlation with the number of release sites. This result confirms that the number of NO release sites is an important factor in the rate of release, but it is not the only factor. The similarity of the NMR chemical shifts (8.0–8.2 ppm) of the amine protons in (I) and (II) indicate that the electronic environments at the amine N atoms are quite similar, at least in solution. The photo and thermal sensitivity of the nitrosated products make obtaining good-quality NMR spectra difficult, but if the electronic similarity holds in (III) and (IV), then the lower than expected correlation may be due to another factor, such as steric effects within the solid materials. In this case, the replacement of an N–H bond with an N–NO bond might well result in significant changes in both the molecular and packing structure due to the elimination of intramolecular and intermolecular N–H...O hydrogen bonds, as well as the size difference between H and NO. Consequently, one would prefer to have the crystal structures of (III) and (IV) to make meaningful steric arguments, however, the same instabilities present challenges to this task and so far we have not successfully crystallized either compound. Still other factors may also be influencing the rate and extent of NO release. Noting that the rate of release of (III) is actually higher than that of (IV) in the first *ca* 30 h, it may be possible that the release of the first NO molecule may have an effect on the liberation of subsequent molecules. In addition, the relative hydrophobicity of these compounds could have a role in influencing NO release as the tests are conducted in aqueous solutions that are meant to mimic *in vivo* environments. The results of this study show that factors other than the number of N–NO groups have measurable effects on NO release rates.

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Models for potential dendritic nitric oxide donors: crystal structures of two 2-nitroanilino precursors and nitric oxide-release behavior of the nitrosated derivatives

Alec R. Badour, Corey J. Arnett-Butscher, Dillip K. Mohanty, Philip J. Squattrito, Kelly J. Lambright and Kristin Kirschbaum

Computing details

For both structures, data collection: *APEX3* (Bruker, 2015); cell refinement: *SAINT* (Bruker, 2015); data reduction: *SAINT* (Bruker, 2015); program(s) used to solve structure: *SHELXS97* (Sheldrick 2008); program(s) used to refine structure: *SHELXL2016* (Sheldrick, 2015); molecular graphics: *CrystalMaker* (Palmer, 2014); software used to prepare material for publication: *SHELXL2016* (Sheldrick, 2015).

*N*¹,*N*⁴-Bis(2-nitrophenyl)butane-1,4-diamine (C₁₆H₁₈N₄O₄)

Crystal data

C₁₆H₁₈N₄O₄

M_r = 330.34

Triclinic, *P* $\bar{1}$

a = 6.7032 (4) Å

b = 8.1646 (5) Å

c = 15.1177 (9) Å

α = 81.099 (2)°

β = 79.555 (2)°

γ = 67.488 (2)°

V = 748.34 (8) Å³

Z = 2

F(000) = 348

D_x = 1.466 Mg m^{−3}

Melting point: 426 K

Cu *Kα* radiation, λ = 1.54178 Å

Cell parameters from 8641 reflections

θ = 3.0–69.8°

μ = 0.90 mm^{−1}

T = 120 K

Plate, orange

0.08 × 0.07 × 0.03 mm

Data collection

Bruker APEXII CCD
diffractometer

Radiation source: ImuS

Multi-layer optics monochromator

φ and ω scans

Absorption correction: multi-scan
(SADABS; Sheldrick, 1996)

T_{min} = 0.689, *T_{max}* = 0.753

2595 measured reflections

2595 independent reflections

2314 reflections with *I* > 2σ(*I*)

R_{int} = 0.027

$\theta_{\max}$ = 69.9°, $\theta_{\min}$ = 3.0°

h = −7→8

k = −9→9

l = 0→18

Refinement

Refinement on *F*²

Least-squares matrix: full

R [*F*² > 2σ(*F*²)] = 0.043

wR(*F*²) = 0.138

S = 1.10

2595 reflections

226 parameters

0 restraints

Primary atom site location: structure-invariant
direct methods
Secondary atom site location: difference Fourier
map
Hydrogen site location: mixed

H atoms treated by a mixture of independent
and constrained refinement

$$w = 1/[\sigma^2(F_o^2) + (0.0905P)^2 + 0.1858P]$$

$$\text{where } P = (F_o^2 + 2F_c^2)/3$$

$$(\Delta/\sigma)_{\max} < 0.001$$

$$\Delta\rho_{\max} = 0.25 \text{ e } \text{\AA}^{-3}$$

$$\Delta\rho_{\min} = -0.34 \text{ e } \text{\AA}^{-3}$$

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. Refined as a 2-component twin.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($\text{\AA}^2$)

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
O1	0.3995 (2)	0.39294 (16)	0.06812 (8)	0.0234 (3)
O2	0.4336 (2)	0.18683 (17)	0.17903 (9)	0.0328 (4)
N1	0.2731 (2)	0.72853 (19)	0.09832 (10)	0.0184 (3)
N2	0.3819 (2)	0.34646 (18)	0.15066 (10)	0.0193 (3)
C1	0.2477 (3)	0.9133 (2)	0.06805 (11)	0.0197 (4)
H1A	0.358057	0.915574	0.015071	0.024*
H1B	0.275780	0.966550	0.116822	0.024*
C2	0.0214 (3)	1.0264 (2)	0.04247 (11)	0.0189 (4)
H2A	−0.089810	1.014268	0.093221	0.023*
H2B	0.006300	1.153139	0.032834	0.023*
C3	0.2460 (3)	0.6631 (2)	0.18512 (11)	0.0170 (4)
C4	0.3000 (3)	0.4780 (2)	0.21374 (11)	0.0175 (4)
C5	0.2769 (3)	0.4156 (2)	0.30547 (12)	0.0200 (4)
H5	0.315419	0.291392	0.322189	0.024*
C6	0.1996 (3)	0.5310 (2)	0.37113 (11)	0.0212 (4)
H6	0.185322	0.487901	0.433117	0.025*
C7	0.1418 (3)	0.7143 (2)	0.34535 (11)	0.0204 (4)
H7	0.088022	0.795481	0.390472	0.025*
C8	0.1618 (3)	0.7780 (2)	0.25606 (11)	0.0192 (4)
H8	0.117980	0.902940	0.240922	0.023*
H1N	0.335 (4)	0.649 (3)	0.0588 (15)	0.031 (6)*
O11	0.7626 (2)	0.35662 (16)	0.43988 (8)	0.0264 (3)
O12	0.9038 (3)	0.15051 (17)	0.34842 (9)	0.0364 (4)
N11	0.6419 (2)	0.69358 (19)	0.37783 (10)	0.0191 (3)
N12	0.8198 (2)	0.30994 (19)	0.36156 (10)	0.0213 (3)
C11	0.5565 (3)	0.8826 (2)	0.39118 (11)	0.0202 (4)
H11A	0.407060	0.939507	0.374695	0.024*
H11B	0.649339	0.941833	0.352011	0.024*
C12	0.5537 (3)	0.9028 (2)	0.48948 (11)	0.0208 (4)
H12A	0.705134	0.854587	0.503870	0.025*
H12B	0.473649	0.832488	0.528306	0.025*

C13	0.7037 (3)	0.6276 (2)	0.29682 (11)	0.0172 (4)
C14	0.7889 (3)	0.4419 (2)	0.28573 (11)	0.0178 (4)
C15	0.8498 (3)	0.3795 (2)	0.19956 (12)	0.0204 (4)
H15	0.905061	0.255025	0.194199	0.024*
C16	0.8301 (3)	0.4963 (2)	0.12335 (12)	0.0214 (4)
H16	0.870755	0.453865	0.065180	0.026*
C17	0.7489 (3)	0.6794 (2)	0.13241 (12)	0.0202 (4)
H17	0.736216	0.761044	0.079733	0.024*
C18	0.6876 (3)	0.7431 (2)	0.21577 (11)	0.0188 (4)
H18	0.632815	0.868101	0.219405	0.023*
H11N	0.641 (4)	0.619 (3)	0.4231 (17)	0.039 (7)*

Atomic displacement parameters ($\text{\AA}^2$)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0346 (7)	0.0198 (6)	0.0138 (6)	−0.0083 (5)	−0.0017 (5)	−0.0023 (5)
O2	0.0529 (9)	0.0136 (6)	0.0270 (7)	−0.0071 (6)	−0.0057 (6)	−0.0007 (5)
N1	0.0244 (7)	0.0135 (7)	0.0155 (7)	−0.0047 (6)	−0.0036 (6)	−0.0012 (6)
N2	0.0248 (7)	0.0134 (7)	0.0187 (8)	−0.0056 (6)	−0.0039 (6)	−0.0005 (6)
C1	0.0263 (9)	0.0148 (8)	0.0184 (8)	−0.0079 (7)	−0.0041 (7)	0.0000 (6)
C2	0.0251 (9)	0.0133 (8)	0.0161 (8)	−0.0052 (7)	−0.0024 (6)	−0.0001 (6)
C3	0.0175 (8)	0.0164 (8)	0.0168 (8)	−0.0048 (7)	−0.0051 (6)	−0.0009 (6)
C4	0.0193 (8)	0.0167 (8)	0.0161 (9)	−0.0051 (7)	−0.0030 (6)	−0.0035 (7)
C5	0.0238 (8)	0.0169 (8)	0.0190 (9)	−0.0069 (7)	−0.0055 (7)	0.0011 (7)
C6	0.0251 (9)	0.0243 (9)	0.0146 (8)	−0.0093 (7)	−0.0047 (7)	0.0003 (7)
C7	0.0210 (8)	0.0214 (9)	0.0190 (9)	−0.0064 (7)	−0.0025 (6)	−0.0059 (7)
C8	0.0210 (8)	0.0162 (8)	0.0198 (9)	−0.0050 (7)	−0.0027 (7)	−0.0045 (7)
O11	0.0447 (8)	0.0199 (6)	0.0150 (6)	−0.0119 (6)	−0.0040 (5)	−0.0026 (5)
O12	0.0613 (10)	0.0126 (6)	0.0270 (8)	−0.0057 (6)	−0.0022 (7)	−0.0024 (5)
N11	0.0270 (8)	0.0153 (7)	0.0148 (7)	−0.0074 (6)	−0.0017 (6)	−0.0030 (6)
N12	0.0299 (8)	0.0147 (7)	0.0189 (8)	−0.0075 (6)	−0.0027 (6)	−0.0029 (6)
C11	0.0264 (9)	0.0152 (8)	0.0190 (9)	−0.0066 (7)	−0.0024 (7)	−0.0042 (7)
C12	0.0278 (9)	0.0161 (9)	0.0182 (9)	−0.0077 (7)	−0.0005 (7)	−0.0043 (7)
C13	0.0170 (8)	0.0173 (8)	0.0177 (8)	−0.0060 (7)	−0.0018 (6)	−0.0037 (7)
C14	0.0212 (8)	0.0160 (8)	0.0165 (9)	−0.0067 (7)	−0.0030 (6)	−0.0019 (7)
C15	0.0227 (8)	0.0178 (8)	0.0206 (9)	−0.0065 (7)	−0.0008 (7)	−0.0067 (7)
C16	0.0227 (8)	0.0253 (9)	0.0173 (9)	−0.0087 (7)	−0.0022 (7)	−0.0057 (7)
C17	0.0204 (8)	0.0234 (9)	0.0175 (9)	−0.0090 (7)	−0.0034 (6)	−0.0002 (7)
C18	0.0216 (8)	0.0153 (8)	0.0197 (9)	−0.0065 (7)	−0.0041 (6)	−0.0015 (7)

Geometric parameters ($\text{\AA}$, $^\circ$)

O1—N2	1.2448 (18)	O11—N12	1.2480 (19)
O2—N2	1.2400 (19)	O12—N12	1.2365 (19)
N1—C3	1.346 (2)	N11—C13	1.346 (2)
N1—C1	1.460 (2)	N11—C11	1.459 (2)
N1—H11N	0.88 (2)	N11—H11N	0.84 (2)
N2—C4	1.428 (2)	N12—C14	1.432 (2)

C1—C2	1.527 (2)	C11—C12	1.516 (2)
C1—H1A	0.9900	C11—H11A	0.9900
C1—H1B	0.9900	C11—H11B	0.9900
C2—C2 ⁱ	1.523 (3)	C12—C12 ⁱⁱ	1.528 (3)
C2—H2A	0.9900	C12—H12A	0.9900
C2—H2B	0.9900	C12—H12B	0.9900
C3—C8	1.426 (2)	C13—C18	1.420 (2)
C3—C4	1.428 (2)	C13—C14	1.426 (2)
C4—C5	1.404 (2)	C14—C15	1.406 (2)
C5—C6	1.368 (2)	C15—C16	1.369 (2)
C5—H5	0.9500	C15—H15	0.9500
C6—C7	1.404 (2)	C16—C17	1.401 (2)
C6—H6	0.9500	C16—H16	0.9500
C7—C8	1.371 (2)	C17—C18	1.371 (2)
C7—H7	0.9500	C17—H17	0.9500
C8—H8	0.9500	C18—H18	0.9500
C3—N1—C1	124.99 (14)	C13—N11—C11	124.79 (15)
C3—N1—H1N	115.9 (14)	C13—N11—H11N	115.9 (17)
C1—N1—H1N	118.0 (14)	C11—N11—H11N	119.0 (17)
O2—N2—O1	120.78 (14)	O12—N12—O11	120.77 (14)
O2—N2—C4	119.36 (14)	O12—N12—C14	119.34 (14)
O1—N2—C4	119.86 (14)	O11—N12—C14	119.88 (14)
N1—C1—C2	113.07 (14)	N11—C11—C12	109.10 (14)
N1—C1—H1A	109.0	N11—C11—H11A	109.9
C2—C1—H1A	109.0	C12—C11—H11A	109.9
N1—C1—H1B	109.0	N11—C11—H11B	109.9
C2—C1—H1B	109.0	C12—C11—H11B	109.9
H1A—C1—H1B	107.8	H11A—C11—H11B	108.3
C2 ⁱ —C2—C1	112.72 (17)	C11—C12—C12 ⁱⁱ	112.04 (18)
C2 ⁱ —C2—H2A	109.0	C11—C12—H12A	109.2
C1—C2—H2A	109.0	C12 ⁱⁱ —C12—H12A	109.2
C2 ⁱ —C2—H2B	109.0	C11—C12—H12B	109.2
C1—C2—H2B	109.0	C12 ⁱⁱ —C12—H12B	109.2
H2A—C2—H2B	107.8	H12A—C12—H12B	107.9
N1—C3—C8	121.09 (15)	N11—C13—C18	120.68 (15)
N1—C3—C4	123.83 (15)	N11—C13—C14	123.62 (15)
C8—C3—C4	115.07 (15)	C18—C13—C14	115.70 (15)
C5—C4—C3	121.72 (15)	C15—C14—C13	121.51 (16)
C5—C4—N2	116.48 (15)	C15—C14—N12	116.71 (15)
C3—C4—N2	121.80 (15)	C13—C14—N12	121.77 (15)
C6—C5—C4	120.95 (16)	C16—C15—C14	120.61 (16)
C6—C5—H5	119.5	C16—C15—H15	119.7
C4—C5—H5	119.5	C14—C15—H15	119.7
C5—C6—C7	118.87 (16)	C15—C16—C17	118.99 (15)
C5—C6—H6	120.6	C15—C16—H16	120.5
C7—C6—H6	120.6	C17—C16—H16	120.5
C8—C7—C6	121.04 (16)	C18—C17—C16	121.31 (16)

C8—C7—H7	119.5	C18—C17—H17	119.3
C6—C7—H7	119.5	C16—C17—H17	119.3
C7—C8—C3	122.31 (16)	C17—C18—C13	121.87 (16)
C7—C8—H8	118.8	C17—C18—H18	119.1
C3—C8—H8	118.8	C13—C18—H18	119.1
C4—C3—N1—C1	−171.20 (15)	C3—N1—C1—C2	−95.43 (19)
C14—C13—N11—C11	179.27 (15)	C13—N11—C11—C12	−167.33 (15)
C8—C3—N1—C1	8.0 (2)	N1—C1—C2—C2 ⁱ	−68.4 (2)
C18—C13—N11—C11	−0.4 (2)	N11—C11—C12—C12 ⁱⁱ	−174.65 (17)

Symmetry codes: (i) $-x, -y+2, -z$; (ii) $-x+1, -y+2, -z+1$.

Hydrogen-bond geometry ($\text{\AA}$, $^\circ$)

$D\cdots A$	$D\cdots H$	$H\cdots A$	$D\cdots A$	$D\cdots H\cdots A$
N1—H1N $\cdots$ O1	0.88 (2)	1.95 (2)	2.6273 (18)	132.2 (19)
N1—H1N $\cdots$ O1 ⁱⁱⁱ	0.88 (2)	2.34 (2)	3.0388 (19)	136.8 (19)
C8—H8 $\cdots$ O12 ^{iv}	0.95	2.60	3.256 (2)	127
N11—H11N $\cdots$ O11	0.84 (2)	1.97 (2)	2.6221 (19)	133 (2)
C12—H12B $\cdots$ O11 ^v	0.99	2.55	3.470 (2)	155
C18—H18 $\cdots$ O2 ^{vi}	0.95	2.46	3.366 (2)	159

Symmetry codes: (iii) $-x+1, -y+1, -z$; (iv) $x-1, y+1, z$; (v) $-x+1, -y+1, -z+1$; (vi) $x, y+1, z$.

*N*¹-(2-Nitrophenyl)-*N*²,*N*²-bis[2-[(2-nitroanilino)ethyl]ethane-1,2-diamine (C₂₄H₂₇N₇O₆)

Crystal data

C₂₄H₂₇N₇O₆
 $M_r = 509.52$
 Orthorhombic, *Pbca*
 $a = 7.5749$ (2) $\text{\AA}$
 $b = 13.4138$ (4) $\text{\AA}$
 $c = 46.3793$ (14) $\text{\AA}$
 $V = 4712.5$ (2) $\text{\AA}^3$
 $Z = 8$
 $F(000) = 2144$

$D_x = 1.436$ Mg m^{−3}
 Melting point: 376 K
 Cu $K\alpha$ radiation, $\lambda = 1.54178$ $\text{\AA}$
 Cell parameters from 9785 reflections
 $\theta = 3.8\text{--}70.0^\circ$
 $\mu = 0.89$ mm^{−1}
 $T = 120$ K
 Triangular prism, yellow
 $0.21 \times 0.13 \times 0.06$ mm

Data collection

Bruker APEXII CCD
 diffractometer
 Radiation source: ImuS
 Multi-layer optics monochromator
 φ and ω scans
 Absorption correction: multi-scan
 (SADABS; Sheldrick, 1996)
 $T_{\min} = 0.655$, $T_{\max} = 0.753$

50384 measured reflections
 4413 independent reflections
 4182 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.026$
 $\theta_{\text{max}} = 70.0^\circ$, $\theta_{\text{min}} = 1.9^\circ$
 $h = -9 \rightarrow 8$
 $k = -16 \rightarrow 16$
 $l = -55 \rightarrow 56$

*Refinement*Refinement on F^2

Least-squares matrix: full

 $R[F^2 > 2\sigma(F^2)] = 0.031$ $wR(F^2) = 0.079$ $S = 1.06$

4413 reflections

442 parameters

0 restraints

Primary atom site location: structure-invariant
direct methodsSecondary atom site location: difference Fourier
map

Hydrogen site location: difference Fourier map

All H-atom parameters refined

 $w = 1/[\sigma^2(F_o^2) + (0.0343P)^2 + 2.0708P]$ where $P = (F_o^2 + 2F_c^2)/3$ $(\Delta/\sigma)_{\max} = 0.001$ $\Delta\rho_{\max} = 0.22 \text{ e } \text{\AA}^{-3}$ $\Delta\rho_{\min} = -0.24 \text{ e } \text{\AA}^{-3}$ *Special details*

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($\text{\AA}^2$)

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
O1	0.10378 (12)	1.08863 (7)	−0.01246 (2)	0.0308 (2)
O2	0.30627 (13)	1.14180 (7)	−0.04137 (2)	0.0323 (2)
O3	0.78758 (13)	0.54020 (7)	0.12028 (2)	0.0343 (2)
O4	0.84429 (12)	0.46457 (6)	0.16032 (2)	0.0306 (2)
O5	0.29091 (12)	1.04871 (6)	0.14961 (2)	0.0296 (2)
O6	0.39256 (12)	1.11208 (7)	0.18916 (2)	0.0375 (2)
N1	0.18245 (12)	0.84159 (7)	0.09745 (2)	0.0173 (2)
N2	0.17842 (14)	1.04263 (7)	0.04110 (2)	0.0236 (2)
N3	0.25888 (14)	1.11500 (7)	−0.01723 (2)	0.0230 (2)
N4	0.58206 (13)	0.69789 (8)	0.11960 (2)	0.0216 (2)
N5	0.77672 (13)	0.53401 (7)	0.14699 (2)	0.0242 (2)
N6	0.06877 (13)	0.89790 (7)	0.15092 (2)	0.0188 (2)
N7	0.30044 (13)	1.05048 (7)	0.17636 (2)	0.0253 (2)
C1	0.20183 (16)	0.88416 (8)	0.06863 (2)	0.0199 (2)
C2	0.13671 (18)	0.99193 (9)	0.06804 (3)	0.0255 (3)
C3	0.34148 (16)	1.07529 (8)	0.03378 (2)	0.0203 (2)
C4	0.38489 (16)	1.11365 (8)	0.00601 (2)	0.0206 (2)
C5	0.55501 (17)	1.14786 (9)	−0.00052 (3)	0.0258 (3)
C6	0.68709 (18)	1.14413 (9)	0.01954 (3)	0.0308 (3)
C7	0.64809 (18)	1.10657 (9)	0.04694 (3)	0.0300 (3)
C8	0.48243 (17)	1.07365 (9)	0.05396 (3)	0.0254 (3)
C9	0.29142 (15)	0.75279 (8)	0.10129 (2)	0.0194 (2)
C10	0.48761 (16)	0.77778 (9)	0.10495 (2)	0.0225 (2)
C11	0.58330 (14)	0.68520 (8)	0.14861 (2)	0.0179 (2)
C12	0.68072 (14)	0.60927 (8)	0.16288 (2)	0.0194 (2)
C13	0.68717 (16)	0.60277 (9)	0.19294 (3)	0.0232 (3)
C14	0.59608 (17)	0.66913 (9)	0.20977 (3)	0.0253 (3)
C15	0.49346 (16)	0.74231 (9)	0.19626 (3)	0.0238 (2)

C16	0.48690 (15)	0.75010 (8)	0.16682 (2)	0.0204 (2)
C17	−0.00235 (15)	0.82235 (9)	0.10512 (2)	0.0196 (2)
C18	−0.02435 (16)	0.81483 (8)	0.13772 (2)	0.0198 (2)
C19	0.08961 (14)	0.90749 (8)	0.17968 (2)	0.0180 (2)
C20	0.20124 (15)	0.97899 (8)	0.19303 (3)	0.0214 (2)
C21	0.21675 (17)	0.98492 (10)	0.22306 (3)	0.0291 (3)
C22	0.12409 (18)	0.92142 (11)	0.24059 (3)	0.0322 (3)
C23	0.01299 (17)	0.85070 (10)	0.22796 (3)	0.0274 (3)
C24	−0.00427 (15)	0.84361 (9)	0.19865 (2)	0.0214 (2)
H2N	0.103 (2)	1.0378 (12)	0.0267 (3)	0.036 (4)*
H4N	0.648 (2)	0.6565 (12)	0.1101 (3)	0.031 (4)*
H6N	0.139 (2)	0.9301 (11)	0.1401 (3)	0.025 (4)*
H1A	0.1409 (18)	0.8448 (10)	0.0537 (3)	0.025 (3)*
H1B	0.3274 (18)	0.8833 (9)	0.0637 (3)	0.017 (3)*
H2A	0.005 (2)	0.9948 (11)	0.0697 (3)	0.032 (4)*
H2B	0.1903 (19)	1.0281 (11)	0.0848 (3)	0.028 (4)*
H5	0.572 (2)	1.1733 (11)	−0.0196 (3)	0.030 (4)*
H6	0.804 (2)	1.1655 (12)	0.0147 (3)	0.037 (4)*
H7	0.740 (2)	1.1021 (11)	0.0615 (3)	0.034 (4)*
H8	0.461 (2)	1.0464 (11)	0.0726 (3)	0.031 (4)*
H9A	0.2767 (18)	0.7064 (10)	0.0854 (3)	0.025 (3)*
H9B	0.2520 (17)	0.7198 (9)	0.1188 (3)	0.017 (3)*
H10A	0.5474 (18)	0.7857 (10)	0.0861 (3)	0.024 (3)*
H10B	0.5010 (18)	0.8401 (11)	0.1163 (3)	0.026 (4)*
H13	0.758 (2)	0.5507 (11)	0.2014 (3)	0.032 (4)*
H14	0.600 (2)	0.6643 (11)	0.2305 (3)	0.033 (4)*
H15	0.4245 (19)	0.7886 (11)	0.2077 (3)	0.027 (4)*
H16	0.4179 (19)	0.7999 (11)	0.1586 (3)	0.025 (3)*
H17A	−0.0486 (18)	0.7592 (10)	0.0961 (3)	0.022 (3)*
H17B	−0.0755 (18)	0.8780 (10)	0.0982 (3)	0.020 (3)*
H18A	0.0214 (18)	0.7488 (10)	0.1453 (3)	0.022 (3)*
H18B	−0.1512 (18)	0.8185 (10)	0.1423 (3)	0.021 (3)*
H21	0.293 (2)	1.0352 (12)	0.2308 (3)	0.040 (4)*
H22	0.134 (2)	0.9250 (13)	0.2619 (4)	0.046 (5)*
H23	−0.054 (2)	0.8052 (11)	0.2402 (3)	0.031 (4)*
H24	−0.0815 (19)	0.7948 (11)	0.1908 (3)	0.023 (3)*

Atomic displacement parameters ($\text{\AA}^2$)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0283 (5)	0.0345 (5)	0.0297 (5)	−0.0039 (4)	−0.0047 (4)	0.0102 (4)
O2	0.0478 (6)	0.0311 (5)	0.0180 (4)	0.0027 (4)	0.0064 (4)	0.0050 (3)
O3	0.0355 (5)	0.0365 (5)	0.0308 (5)	0.0114 (4)	0.0050 (4)	−0.0041 (4)
O4	0.0252 (5)	0.0192 (4)	0.0475 (5)	0.0049 (4)	−0.0046 (4)	0.0028 (4)
O5	0.0262 (5)	0.0261 (4)	0.0365 (5)	−0.0055 (4)	−0.0007 (4)	0.0064 (4)
O6	0.0272 (5)	0.0276 (5)	0.0577 (6)	−0.0077 (4)	−0.0061 (4)	−0.0115 (4)
N1	0.0196 (5)	0.0178 (4)	0.0147 (4)	−0.0002 (4)	0.0014 (3)	0.0024 (3)
N2	0.0258 (5)	0.0236 (5)	0.0214 (5)	0.0018 (4)	0.0019 (4)	0.0073 (4)

N3	0.0326 (6)	0.0171 (5)	0.0194 (5)	0.0022 (4)	0.0022 (4)	0.0020 (4)
N4	0.0201 (5)	0.0245 (5)	0.0201 (5)	0.0025 (4)	0.0011 (4)	0.0015 (4)
N5	0.0184 (5)	0.0209 (5)	0.0332 (6)	0.0010 (4)	−0.0006 (4)	−0.0006 (4)
N6	0.0197 (5)	0.0191 (5)	0.0178 (5)	−0.0046 (4)	0.0030 (4)	0.0001 (4)
N7	0.0173 (5)	0.0191 (5)	0.0395 (6)	0.0006 (4)	−0.0029 (4)	−0.0036 (4)
C1	0.0249 (6)	0.0199 (6)	0.0149 (5)	0.0019 (5)	0.0022 (4)	0.0012 (4)
C2	0.0326 (7)	0.0214 (6)	0.0225 (6)	0.0047 (5)	0.0080 (5)	0.0054 (5)
C3	0.0260 (6)	0.0135 (5)	0.0214 (5)	0.0041 (4)	0.0020 (5)	−0.0008 (4)
C4	0.0263 (6)	0.0153 (5)	0.0201 (5)	0.0014 (4)	0.0025 (5)	−0.0016 (4)
C5	0.0312 (7)	0.0179 (6)	0.0283 (6)	−0.0006 (5)	0.0099 (5)	−0.0039 (5)
C6	0.0251 (6)	0.0221 (6)	0.0451 (8)	−0.0017 (5)	0.0056 (6)	−0.0095 (5)
C7	0.0296 (7)	0.0231 (6)	0.0372 (7)	0.0047 (5)	−0.0082 (6)	−0.0098 (5)
C8	0.0329 (7)	0.0204 (6)	0.0229 (6)	0.0051 (5)	−0.0027 (5)	−0.0029 (5)
C9	0.0222 (6)	0.0170 (5)	0.0189 (5)	−0.0012 (4)	−0.0015 (4)	0.0013 (4)
C10	0.0221 (6)	0.0247 (6)	0.0208 (6)	−0.0024 (5)	−0.0001 (5)	0.0061 (5)
C11	0.0136 (5)	0.0176 (5)	0.0226 (5)	−0.0041 (4)	−0.0006 (4)	0.0013 (4)
C12	0.0151 (5)	0.0172 (5)	0.0260 (6)	−0.0015 (4)	0.0000 (4)	0.0005 (4)
C13	0.0208 (6)	0.0205 (6)	0.0281 (6)	−0.0033 (5)	−0.0037 (5)	0.0062 (5)
C14	0.0277 (6)	0.0279 (6)	0.0201 (6)	−0.0047 (5)	−0.0020 (5)	0.0023 (5)
C15	0.0226 (6)	0.0240 (6)	0.0248 (6)	−0.0012 (5)	0.0010 (5)	−0.0043 (5)
C16	0.0185 (5)	0.0175 (5)	0.0252 (6)	0.0004 (4)	−0.0022 (4)	0.0007 (4)
C17	0.0192 (6)	0.0211 (6)	0.0184 (5)	−0.0022 (5)	−0.0008 (4)	0.0008 (4)
C18	0.0208 (6)	0.0199 (6)	0.0188 (5)	−0.0040 (5)	0.0018 (4)	−0.0006 (4)
C19	0.0156 (5)	0.0183 (5)	0.0200 (5)	0.0046 (4)	0.0008 (4)	−0.0009 (4)
C20	0.0166 (5)	0.0195 (5)	0.0281 (6)	0.0042 (4)	−0.0012 (4)	−0.0031 (4)
C21	0.0240 (6)	0.0323 (7)	0.0310 (7)	0.0065 (5)	−0.0076 (5)	−0.0109 (5)
C22	0.0327 (7)	0.0442 (8)	0.0198 (6)	0.0097 (6)	−0.0039 (5)	−0.0051 (5)
C23	0.0285 (7)	0.0331 (7)	0.0206 (6)	0.0071 (5)	0.0034 (5)	0.0029 (5)
C24	0.0212 (6)	0.0225 (6)	0.0205 (5)	0.0017 (5)	0.0021 (4)	0.0000 (4)

Geometric parameters (Å, °)

O1—N3	1.2467 (14)	C7—C8	1.3695 (19)
O2—N3	1.2294 (13)	C7—H7	0.970 (16)
O3—N5	1.2444 (13)	C8—H8	0.953 (15)
O4—N5	1.2296 (13)	C9—C10	1.5328 (16)
O5—N7	1.2432 (14)	C9—H9A	0.972 (14)
O6—N7	1.2337 (14)	C9—H9B	0.973 (13)
N1—C9	1.4602 (14)	C10—H10A	0.993 (14)
N1—C1	1.4608 (13)	C10—H10B	0.993 (14)
N1—C17	1.4672 (14)	C11—C16	1.4157 (16)
N2—C3	1.3539 (16)	C11—C12	1.4212 (16)
N2—C2	1.4571 (14)	C12—C13	1.3978 (16)
N2—H2N	0.884 (17)	C13—C14	1.3702 (18)
N3—C4	1.4400 (15)	C13—H13	0.963 (16)
N4—C11	1.3563 (14)	C14—C15	1.4000 (17)
N4—C10	1.4566 (15)	C14—H14	0.962 (15)
N4—H4N	0.868 (16)	C15—C16	1.3703 (16)

N5—C12	1.4460 (15)	C15—H15	0.970 (15)
N6—C19	1.3493 (14)	C16—H16	0.930 (15)
N6—C18	1.4539 (14)	C17—C18	1.5245 (15)
N6—H6N	0.849 (15)	C17—H17A	1.008 (14)
N7—C20	1.4427 (16)	C17—H17B	0.982 (14)
C1—C2	1.5276 (16)	C18—H18A	1.014 (14)
C1—H1A	0.987 (14)	C18—H18B	0.985 (14)
C1—H1B	0.978 (13)	C19—C24	1.4192 (16)
C2—H2A	0.999 (16)	C19—C20	1.4206 (16)
C2—H2B	1.004 (15)	C20—C21	1.4002 (17)
C3—C8	1.4200 (17)	C21—C22	1.371 (2)
C3—C4	1.4253 (16)	C21—H21	0.956 (17)
C4—C5	1.4011 (17)	C22—C23	1.397 (2)
C5—C6	1.367 (2)	C22—H22	0.994 (17)
C5—H5	0.958 (15)	C23—C24	1.3690 (16)
C6—C7	1.399 (2)	C23—H23	0.977 (15)
C6—H6	0.955 (17)	C24—H24	0.950 (15)
C9—N1—C1	111.96 (9)	H9A—C9—H9B	107.9 (11)
C9—N1—C17	111.48 (9)	N4—C10—C9	111.53 (9)
C1—N1—C17	112.73 (9)	N4—C10—H10A	105.4 (8)
C3—N2—C2	124.33 (11)	C9—C10—H10A	111.6 (8)
C3—N2—H2N	115.2 (10)	N4—C10—H10B	108.8 (8)
C2—N2—H2N	118.3 (10)	C9—C10—H10B	110.0 (8)
O2—N3—O1	121.32 (10)	H10A—C10—H10B	109.3 (11)
O2—N3—C4	119.46 (10)	N4—C11—C16	120.73 (10)
O1—N3—C4	119.22 (9)	N4—C11—C12	123.74 (10)
C11—N4—C10	123.95 (10)	C16—C11—C12	115.52 (10)
C11—N4—H4N	114.8 (10)	C13—C12—C11	121.82 (11)
C10—N4—H4N	121.1 (10)	C13—C12—N5	116.56 (10)
O4—N5—O3	121.58 (10)	C11—C12—N5	121.62 (10)
O4—N5—C12	118.82 (10)	C14—C13—C12	120.66 (11)
O3—N5—C12	119.60 (10)	C14—C13—H13	121.2 (9)
C19—N6—C18	123.09 (9)	C12—C13—H13	118.1 (9)
C19—N6—H6N	117.6 (10)	C13—C14—C15	118.71 (11)
C18—N6—H6N	116.4 (10)	C13—C14—H14	120.5 (9)
O6—N7—O5	121.72 (11)	C15—C14—H14	120.7 (9)
O6—N7—C20	118.82 (11)	C16—C15—C14	121.29 (11)
O5—N7—C20	119.46 (9)	C16—C15—H15	118.6 (8)
N1—C1—C2	110.72 (9)	C14—C15—H15	120.1 (8)
N1—C1—H1A	112.8 (8)	C15—C16—C11	121.92 (11)
C2—C1—H1A	110.0 (8)	C15—C16—H16	118.9 (9)
N1—C1—H1B	107.9 (7)	C11—C16—H16	119.1 (9)
C2—C1—H1B	108.7 (8)	N1—C17—C18	110.88 (9)
H1A—C1—H1B	106.5 (11)	N1—C17—H17A	112.3 (8)
N2—C2—C1	112.77 (10)	C18—C17—H17A	108.6 (7)
N2—C2—H2A	105.3 (8)	N1—C17—H17B	109.0 (8)
C1—C2—H2A	110.9 (9)	C18—C17—H17B	108.1 (7)

N2—C2—H2B	110.6 (8)	H17A—C17—H17B	107.9 (10)
C1—C2—H2B	108.2 (8)	N6—C18—C17	108.29 (9)
H2A—C2—H2B	108.9 (12)	N6—C18—H18A	110.9 (8)
N2—C3—C8	121.04 (11)	C17—C18—H18A	111.4 (7)
N2—C3—C4	123.65 (11)	N6—C18—H18B	110.1 (8)
C8—C3—C4	115.31 (11)	C17—C18—H18B	108.5 (8)
C5—C4—C3	121.73 (11)	H18A—C18—H18B	107.6 (11)
C5—C4—N3	116.34 (10)	N6—C19—C24	119.78 (10)
C3—C4—N3	121.87 (10)	N6—C19—C20	124.39 (10)
C6—C5—C4	120.92 (12)	C24—C19—C20	115.83 (10)
C6—C5—H5	122.9 (9)	C21—C20—C19	121.46 (11)
C4—C5—H5	116.2 (9)	C21—C20—N7	116.84 (11)
C5—C6—C7	118.49 (12)	C19—C20—N7	121.69 (10)
C5—C6—H6	120.5 (9)	C22—C21—C20	120.79 (12)
C7—C6—H6	121.0 (9)	C22—C21—H21	121.6 (9)
C8—C7—C6	121.70 (12)	C20—C21—H21	117.6 (9)
C8—C7—H7	118.1 (9)	C21—C22—C23	118.79 (12)
C6—C7—H7	120.2 (9)	C21—C22—H22	121.4 (10)
C7—C8—C3	121.84 (12)	C23—C22—H22	119.8 (10)
C7—C8—H8	119.7 (9)	C24—C23—C22	121.41 (12)
C3—C8—H8	118.5 (9)	C24—C23—H23	118.8 (9)
N1—C9—C10	112.53 (9)	C22—C23—H23	119.8 (9)
N1—C9—H9A	111.4 (8)	C23—C24—C19	121.72 (11)
C10—C9—H9A	109.6 (8)	C23—C24—H24	119.1 (8)
N1—C9—H9B	107.5 (8)	C19—C24—H24	119.2 (8)
C10—C9—H9B	107.7 (8)		

Hydrogen-bond geometry (Å, °)

<i>D</i> —H $\cdots$ <i>A</i>	<i>D</i> —H	H $\cdots$ <i>A</i>	<i>D</i> $\cdots$ <i>A</i>	<i>D</i> —H $\cdots$ <i>A</i>
N2—H2N $\cdots$ O1	0.884 (17)	1.939 (16)	2.6214 (13)	132.9 (14)
N2—H2N $\cdots$ O1 ⁱ	0.884 (17)	2.399 (16)	3.0715 (14)	133.1 (13)
N4—H4N $\cdots$ O3	0.868 (16)	1.942 (16)	2.6265 (13)	134.7 (13)
N6—H6N $\cdots$ O5	0.849 (15)	2.013 (15)	2.6320 (13)	129.1 (12)
C10—H10A $\cdots$ O2 ⁱⁱ	0.993 (14)	2.543 (14)	3.5068 (14)	163.6 (11)
C18—H18B $\cdots$ O4 ⁱⁱⁱ	0.985 (14)	2.584 (14)	3.3177 (15)	131.3 (10)

Symmetry codes: (i) $-x, -y+2, -z$; (ii) $-x+1, -y+2, -z$; (iii) $-x+1/2, y+1/2, z$.