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The Tetrafluoroborate Salt of 4-Methoxybenzyl N-2-(dimethylamino)ethyl-N-nitrosocarbamate: Synthesis, Crystal Structure and DFT Calculations

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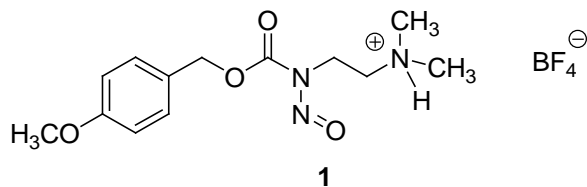
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Index abstract

The Tetrafluoroborate Salt of 4-Methoxybenzyl N-2-(dimethylamino)ethyl-N-nitrosocarbamate:
Synthesis, Crystal Structure and DFT Calculations

Helene Hedian and Vladimir Benin*

This article describes the preparation, crystal structure and theoretical analysis of the tetrafluoroborate salt of 4-methoxybenzyl N-2-(dimethylamino)ethyl-N-nitrosocarbamate, the first reported N-nitrosocarbamate salt.



The tetrafluoroborate salt of 4-methoxybenzyl N-2-(dimethylamino)ethyl-N-nitrosocarbamate:
Synthesis, crystal structure and DFT calculations

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Abstract: The tetrafluoroborate salt of 4-methoxybenzyl N-2-(dimethylamino)ethyl-N-nitrosocarbamate was prepared in two steps, *via* the corresponding carbamate. Its crystal structure is monoclinic, space group $P2_1/c$. The unit cell dimensions are: $a = 19.499(8) \text{ \AA}$, $b = 5.877(3) \text{ \AA}$, $c = 15.757(7) \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 110.019(7)^\circ$, $\gamma = 90^\circ$, $V = 1696.5(12) \text{ \AA}^3$, $Z = 4$. The structure exhibits an unexpected, pseudo-*gauche* conformation with respect to the C2 – C3 bond, due to a stabilizing hydrogen bond between the carbonyl oxygen (O1) and the hydrogen atom at the trialkylammonium center (H3n), with a distance between them of 2.37 \AA . DFT calculations on the cation ($B3LYP/6-31+G(d)$) confirm that the hydrogen bond stabilized *gauche* conformation is the global minimum structure.

Keywords: N-nitrosocarbamate, tetrafluoroborate salt, trialkylammonium salt, hydrogen bond, DFT, *gauche* conformation

N-2-(Dimethylamino)ethyl-N-nitrosocarbamate Salt

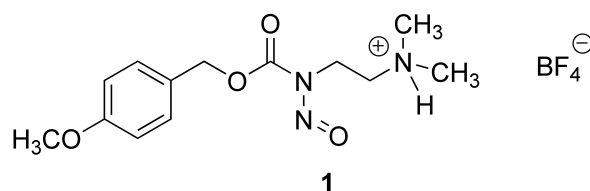
Introduction

In recent years considerable effort has been focused on the development of drugs designed to release their active species at the desired locality and/or conditions, and also on identifying structures with photosensitive groups that would cleave upon irradiation with near UV or visible light, yielding active intermediates for biological applications.¹ First reported by Barltrop and Schofield in 1962², photolabile protecting groups have found numerous applications in biology in the past decade.^{3,4} The protecting groups (also known as “caging” groups) can render a bioactive compound inert until they are removed by photolysis, thus releasing the compound rapidly. Some examples of commonly used photolabile caging groups include the *o*-nitrobenzyl⁵, desyl⁶ and 2-methoxy-5-nitrophenyl (MNP).⁷ However, the commonly employed 2-nitrobenzyl photosensitive protecting group has found limited use in compounds destined for biochemical systems, due to the release of a toxic by-product: 2-nitrobenzaldehyde.^{8,9}

Zimmerman first demonstrated the efficient photosolvolysis of benzyl acetate in 50% aqueous dioxane.¹⁰ His studies showed that the process occurred in a homolytic fashion and led to radical-derived products: 4,4'-dimethoxybibenzyl and 4-methoxybenzyl dioxane. However, a more recent study of Toscano *et al.* on the photocleavage of substituted benzyl diazeniumdiolates demonstrated that the nature of the cleavage process depended on the pattern of substitution in the benzylic group.¹¹ It was found that compounds with π -donor substituent groups at the 3- and 5-positions of the benzene ring tended to decompose *via* heterolytic, rather than homolytic bond cleavage, and generate resonance stabilized (in the excited state) benzylic carbocations.

Based on the demonstrated potential of substituted benzylic moieties as photolabile protecting groups, we have recently prepared several classes of substituted benzyl N-nitrosocarbamates, containing an N-2-(dimethylamino)ethyl or an N-2-(methylthio)ethyl group.

Our longer term goal is to develop a new class of anticancer agents, capable of releasing the active substance photolytically, in controlled conditions. In the current report we describe the synthesis, crystal structure and theoretical studies on one interesting structure: 4-Methoxybenzyl N-2-(dimethylamino)ethyl-N-nitrosocarbamate, as a tetrafluoroborate salt (Structure **1**). To the best of our knowledge, this is the first reported structure of an N-nitrosocarbamate salt.



Experimental Section

A. *Synthesis.* ^1H NMR and ^{13}C NMR spectra of all compounds were recorded at 300 MHz and 75 MHz respectively, and referenced to the solvent (CDCl_3 : 7.27 ppm and 77.0 ppm; $\text{DMSO}-d_6$: 2.49 ppm and 39.5 ppm). Elemental analysis was provided by Atlantic Microlab, Norcross, GA. 4-Methoxybenzyl phenyl carbonate was prepared following a literature protocol.¹² Nitrosonium tetrafluoroborate (NOBF_4) was purchased from Fluka. Solvents for synthesis or purification were used as purchased.

4-Methoxybenzyl N-2-(dimethylamino)ethylcarbamate (2). 4-Methoxybenzyl phenyl carbonate (1.40 g, 5.42 mmol) was dissolved in benzene (20 mL). N,N-(Dimethylamino)ethylamine (0.43 g, 4.88 mmol, 0.54 mL) was added and the mixture was refluxed overnight at 80 °C. The resultant solution was washed with 1 M aq. NaOH (4 x 25 mL), the organic layer was dried (Na_2SO_4), and the solvent removed under reduced pressure. The product was collected as 1.03 g of yellow oil (83% yield). ^1H NMR (CDCl_3) δ 7.22 (d, J =

8.6 Hz, 2H), 6.79 (d, $J = 8.6$ Hz, 2H), 5.35 (bs, 1H), 4.94 (s, 2H), 3.71 (s, 3H), 3.17 (m, 2H), 2.30 (t, $J = 6.0$ Hz, 2H), 2.11 (s, 6H); ^{13}C NMR (CDCl_3) δ 159.5, 156.5, 129.9, 128.8, 113.9, 77.3, 66.4, 58.2, 55.3, 45.1. Anal. Calcd. for $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}_3$: C, 61.88; H, 7.99; N, 11.10. Found: C, 61.64; H, 8.27; N, 10.95.

4-Methoxybenzyl N-2-(dimethylamino)ethyl-N-nitrosocarbamate, tetrafluoroborate salt (1). 4-Methoxybenzyl N-2-(dimethylamino)ethylcarbamate (**2**: 0.78 g, 3.09 mmol) was dissolved in anhydrous acetonitrile (25 mL) at -15 °C, under nitrogen atmosphere. NOBF_4 (0.40 g, 3.42 mmol) was added in one portion, and the resultant mixture was kept at -15 °C for 15 min, followed by 3 h at 0 °C. The solvent was removed under reduced pressure at 0 °C, yielding the product as a yellow solid (0.70 g, 59% yield). Additional purification was achieved *via* recrystallization from acetonitrile at -30 °C, which yielded the product as pale yellow crystals. Mp 88 – 90 °C (dec). ^1H NMR ($\text{DMSO}-d_6$) δ 9.20 (bs, 1H), 7.45 (d, $J = 8.8$ Hz, 2H), 6.98 (d, $J = 8.8$ Hz, 2H), 5.44 (s, 2H), 4.02 (t, $J = 6.3$ Hz, 2H), 3.76 (s, 3H), 3.10 (t, $J = 6.3$ Hz, 2H), 2.76 (s, 6H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 159.7, 152.9, 130.7, 126.5, 114.0, 69.7, 55.2, 53.0, 42.5, 36.0. Anal. Calcd. for $\text{C}_{13}\text{H}_{20}\text{BF}_4\text{N}_3\text{O}_4$: C, 42.30; H, 5.46; N, 11.38. Found: C, 42.46; H, 5.52; N, 11.25.

B. Crystal Structure. A crystal (approximate dimensions 0.60 x 0.15 x 0.05 mm³) was placed onto the tip of a 0.1 mm diameter glass capillary and mounted on a Bruker SMART Platform CCD diffractometer for data collection at 173(2) K.¹³ A preliminary set of cell parameters was calculated from reflections harvested from three sets of 20 frames. These initial sets of frames were oriented such that orthogonal wedges of reciprocal space were surveyed. This produced initial orientation matrices determined from 19 reflections. The data collection was carried out using $\text{MoK}\alpha$ radiation (graphite monochromator) with a frame time of 90

seconds and a detector distance of 4.990 cm. A randomly oriented region of reciprocal space was surveyed to the extent of one sphere and to a resolution of 0.84 Å. Three major sections of frames were collected with 0.30° steps in ω at three different ϕ settings and a detector position of -28° in 2θ . The intensity data were corrected for absorption and decay (SADABS).¹⁴ Final cell parameters were calculated from the xyz centroids of 3136 strong reflections from the actual data collection after integration (SAINT).¹⁵

The structure was solved using SHELXS-97 and refined using SHELXL-97.¹⁶ The space group $P2_1/c$ was determined based on systematic absences and intensity statistics. A direct-methods solution was calculated which provided most non-hydrogen atoms from the E-map. Full-matrix least squares/difference Fourier cycles were performed which located the remaining non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters. The proton on N3 was placed from the difference map and was refined as a riding atom with relative isotropic displacement parameters. All remaining hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. The final full matrix least squares refinement converged to $R1 = 0.0784$ and $wR2 = 0.2490$ (F^2 , all data).

Table 1. Crystal data and structure refinement.

CCDC submission number	704631
Empirical formula	$C_{13}H_{20}BF_4N_3O_4$
Formula weight	369.13
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	$a = 19.499(8)$ Å $b = 5.877(3)$ Å $c = 15.757(7)$ Å $\alpha = 90^\circ$

	$\beta = 110.019(7)^\circ$
	$\gamma = 90^\circ$
Volume	1696.5(12) Å ³
Z	4
Density (calculated)	1.445 Mg/m ³
Absorption coefficient	0.133 mm ⁻¹
<i>F</i> (000)	768
Crystal color, morphology	yellow, needle
Crystal size	0.60 x 0.15 x 0.05 mm ³
Theta range for data collection	1.11 to 25.14°
Index ranges	-22 ≤ <i>h</i> ≤ 23, -6 ≤ <i>k</i> ≤ 6, -18 ≤ <i>l</i> ≤ 18
Reflections collected	12111
Independent reflections	2987 [<i>R</i> (int) = 0.0622]
Observed reflections	2040
Completeness to theta = 25.14°	98.6%
Absorption correction	Multi-scan
Max. and min. transmission	0.9934 and 0.9245
Refinement method	Full-matrix least-squares on <i>F</i> ²
Data / restraints / parameters	2987 / 49 / 265
Goodness-of-fit on <i>F</i> ²	1.054
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> 1 = 0.0784, <i>wR</i> 2 = 0.2139
<i>R</i> indices (all data)	<i>R</i> 1 = 0.1123, <i>wR</i> 2 = 0.2490
Largest diff. peak and hole	0.761 and -0.709 e.Å ⁻³

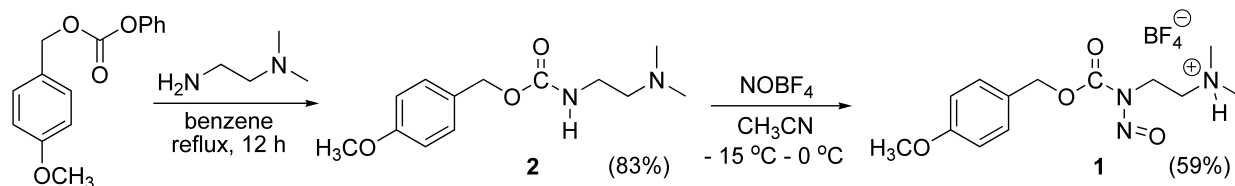
C. Theoretical Studies. All calculations were performed using the *Gaussian03/GaussView* software package¹⁷, on a *Linux*-operated *QuantumCube QS4-2400C* by Parallel Quantum Solutions.¹⁸ Calculations were conducted using DFT at the *B3LYP* level with the *6-31+G(d)* basis set¹⁹⁻²¹, taking into account the fact that for charged species (especially anions) the use of diffuse functions is recommended.²²⁻²⁵ All minima were validated by subsequent frequency calculations at the same level of theory, and had sets of only positive second derivatives. Values of free energy changes were obtained after frequency calculations and zero-point energy corrections. ZPE corrections were not scaled.

Results and Discussion

A. Synthesis. The target structure **1** was prepared using a two-step synthetic protocol (Scheme 1). 4-Methoxybenzyl phenyl carbonate¹² was reacted with N,N-

dimethylethylenediamine in refluxing benzene, to yield the corresponding carbamate **2**. The latter was nitrosated using NOBF₄, in anhydrous acetonitrile. Interestingly, the use of external base (e.g. pyridine) led to complications and mixtures that were difficult to resolve. We propose the main reason to be the inherent competition of the trialkylamine substructure, contained in **2**, with any external base, especially amine bases. Thus, a clean and high yield nitrosation could be conducted only in the absence of added base. In such conditions the deprotonation, necessary to complete the N-nitrosation process, is accomplished by the second nitrogen center in carbamate **2**, which ends up in the form of a trialkylammonium salt.

Scheme 1



B. Crystal structure analysis. The structure is the one suggested and an *ORTEP* drawing is presented in Figure 1. The BF₄⁻ anion was modeled as disordered over three positions (67:25:8), and only one major component is shown in Figure 1, for greater clarity. The structure demonstrates the typical planar geometry for the core N-nitrosocarbamate moiety. The dihedral angles O1 – C1 – N1 – N2 and C1 – N1 – N2 – O3 have values of 178.5° and 178.0° correspondingly.

What is interesting about this structure is the unexpected conformational preference with respect to the C2 – C3 bond. The non-hydrogen groups at both C2 and C3 are sterically demanding, leading to an anticipated *anti* conformation, while in reality the dihedral angle N3 –

C3 – C2 – N1 has a value of 78.3°, much closer to a *gauche* conformation. The major factor stabilizing such arrangement seems to be the close contact and favorable hydrogen bonding interaction of the hydrogen atom at the ammonium center (H3n) and the carbonyl oxygen (O1). The distance O1 – H3n is 2.37 Å and the donor – acceptor distance O1 – N3 is 2.94 Å. These distances are longer than the values typical for a hydrogen bond (typical acceptor – H distance is 1.6 – 2.0 Å, the average for water is 1.97 Å), but are both shorter than the sum of the van der Waals radii in each case. The interaction O1 – H3n leads to the formation of a seven-membered ring, with a nonlinear arrangement for the hydrogen bond donor and acceptor sites (N3 – H3n --- O1 angle of 125.8°).

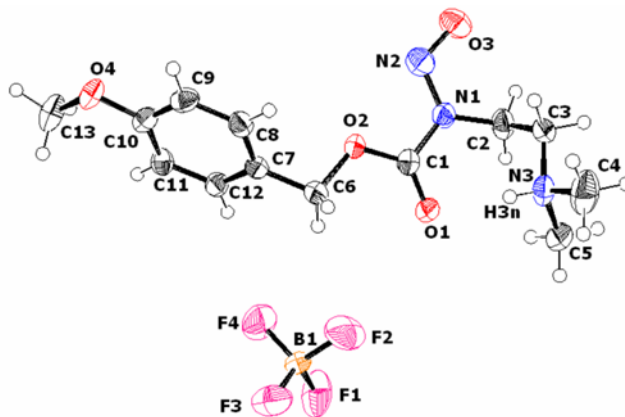


Figure 1. ORTEP drawing of the X-ray structure of compound **1**. Thermal ellipsoids are drawn at 50% probability. Hydrogen atoms are given arbitrary radii. Only one component of the disordered BF₄⁻ anion is shown.

Selected experimental bond lengths and angles are reported in Table 2, together with the theoretical values of the same parameters, based on the global minimum structure **1-g-CO** as optimized at the *B3LYP/6-31+G(d)* level. The DFT calculations reproduce fairly accurately the values of most structural parameters. One notable exception is the degree of planarity of the N-nitrosocarbamate substructure. It is virtually flat, according to the experimental structure, while

the theoretical result points at about 15° deviation from planarity. The theoretical and experimental structures also differ in the conformation at the benzene ring – benzylic carbon bond (C6 – C7 bond). The calculated structure exhibits a nearly perfect staggered conformation, with a dihedral angle C8 – C7 – C6 – O2 = – 87.7°, while in the experimental geometry the conformation is close to eclipsed, with the same dihedral angle having the value of – 68.8°. The hydrogen bond distance H3n – O1 in the calculated structure is 1.70 Å.

Table 2. Selected experimental and theoretical bond lengths (Å) and angles (deg) for structure **1**. Theoretical data are for the global minimum structure **1-g-CO**, optimized at the *B3LYP/6-31+G(d)* level.

Parameter ^a	Experimental value	Theoretical value
O1 – C1	1.199(5)	1.237
O2 – C1	1.310(5)	1.301
O3 – N2	1.241(5)	1.201
N1 – N2	1.368(5)	1.413
N1 – C1	1.398(5)	1.408
C2 – C3	1.502(6)	1.533
C1 – N1 – N2 – O3	178.0(3)	179.6
C2 – N1 – N2 – O3	-3.4(5)	-3.6
C6 – O2 – C1 – O1	10.7(6)	3.5
C6 – O2 – C1 – N1	-169.8(3)	-176.6
N2 – N1 – C1 – O1	-178.4(4)	-165.5
N2 – N1 – C1 – O2	2.1(5)	14.7
N1 – C2 – C3 – N3	78.3(5)	78.9
C8 – C7 – C6 – O2	- 68.8(4)	- 87.7

^a Atom labels in accordance with the crystallographic designation for compound **1**.

Crystal packing for structure **1** is shown in Figure 2. The individual molecules are arranged back-to-back, with association realized *via* interactions of the N-nitrosocarbamate substructures with the tetrafluoroborate anions. The molecules are located in two sets of parallel planes, which are at an approximate angle of 62°.

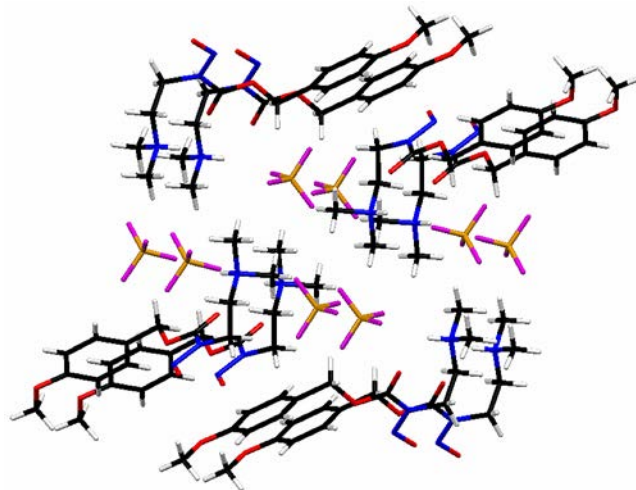


Figure 2. Crystal packing plot for structure **1**. Only one component of the disordered BF_4^- anion is shown.

C. Theoretical Studies. The stationary point searches were conducted on the cation solely, in an attempt to analyze its inherent conformational preferences, irrespective of interactions with the BF_4^- anion. Conformational analysis was conducted with respect to rotations around the C2 – C3 and the C3 – N3 bonds. Several minima structures were identified, at the *B3LYP/6-31+G(d)* level, and they are shown in Figure 3, together with their relative Gibbs free energies. The optimized species **1-g-CO**, which is the analog of the experimental structure, is the global minimum. Interestingly, the other *gauche* conformation is also stabilized by hydrogen bonding, this time to the oxygen atom of the nitroso group (structure **1-g'-NO**). The role of hydrogen bonding is demonstrated by the higher energies of the *gauche* conformations **1-g** and **1-g'**, in which the H3n – O interaction is prevented by rotation around the C3 – N bond that precludes close contact of H3n with either the carbonyl or nitroso oxygen center. The *anti* conformation (structure **1-a**) is at least 6.5 kcal/mol higher in energy than any of the hydrogen bond – stabilized *gauche* conformations.

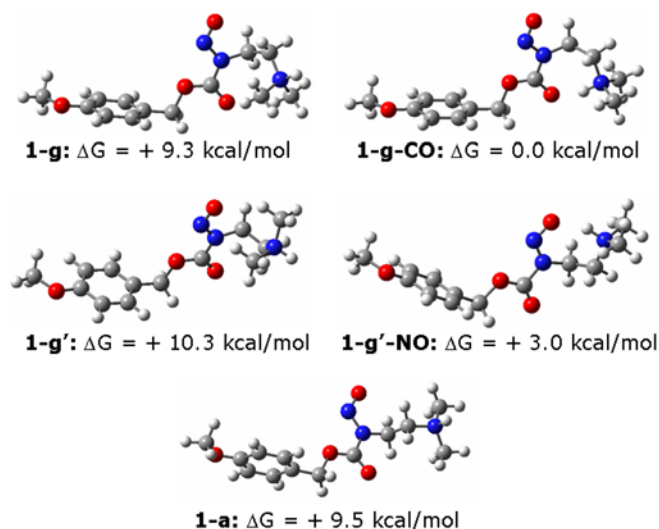


Figure 3. Optimized structures of several conformations of compound **1** (cation only), together with their relative Gibbs free energies, referenced to the global minimum **1-g-CO**. Results from *B3LYP/6-31+G(d)* calculations.

Supplementary Material

Crystallographic data (excluding structure factors) for the structure reported in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number **CCDC 704631**. Copies of the data can be obtained free of charge at <http://www.ccdc.cam.ac.uk/conts/depositing.html>, or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). Calculated energies and thermodynamic parameters of the conformational minima of compound **1** (cation) are summarized in Table S1.

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