J. Am. Chem. Soc. 1984, 106, 239–243

argon pressure with a stainless-steel cannula. The solution assayed for 2.85 mmol of NADP$^+$, corresponding to an 84% yield based on NAD$^+$. The NADP was not isolated.

**Registry No. 1a**, 53-84-9; **1b**, 53-59-8; **2a**, 58-68-4; **2b**, 53-57-6; **3**, 56-65-5; **4**, 1094-61-7; **5**, 4300-28-1; **5**·2Na, 18265-46-8; **6**, 14050-66-9; **7**, 53406-00-1; NADPP, 9032-70-6; NAD kinase, 9032-66-0; AdK, 9013-02-9; 5′-AMP, 61-19-8; nicotinamide, 98-92-0; ribose 5-phosphate bis(cyclohexylammonium) salt, 87763-86-8; PP$_i$ase, 9024-82-2; 2-chloro-2,4-dinitrobenzene, 97-00-7.

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# Structure of *N*-Methyl-*N*′-nitro-*N*-nitrosoguanidine

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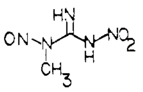
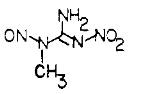
**Abstract:** *N*-Methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG, $C_2H_5N_5O_3$) has been shown to be a nitrimine, $ONN(CH_3)C(NH_2)NNO_2$, by crystallographic methods in the solid and by $^{15}N$ NMR in $Me_2SO$-$d_6$ solution. MNNG crystallizes in the space group $P2_1/c$ with $a = 11.673$ (2) Å, $b = 11.260$ (3) Å, $c = 9.892$ (3) Å, $\beta = 114.56$ (2)°, $V = 1178.9$ (5) Å$^3$, $\rho = 1.64$ (1) g cm$^{-3}$ by flotation in a bromoform and 1-bromohexane mixture, $M_r = 147.09$, and $Z = 8$. The structure was determined by direct methods and was refined with 1019 reflections by full-matrix least-squares procedures to $R_1 = 0.075$ and $R_2 = 0.060$. MNNG is nearly planar, indicative of a highly but not fully delocalized electronic structure. An intramolecular amino-to-nitro hydrogen bond is seen. Rapid proton exchange in $Me_2SO$-$d_6$ and $CDCl_3$, probably the result of intramolecular hydrogen bonding, is indicated by the uncoupled $^{15}N$ and proton spins of the amino group and by the presence of only a single resonance signal for the two amino protons despite restrictions to the rotation of the amino group.

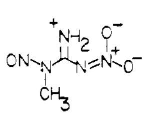
The routine use of *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG) as a mutagen and animal carcinogen has made this compound one of the most widely studied molecules in cancer research.[1] McKay and Wright (1947)[2] first synthesized MNNG by reacting methylamine with nitroguanidine followed by treatment of the resulting methylnitroguanidine with nitrous acid. Without presenting supporting data, they assigned the nitramine structure, A, to the product. Subsequent investigations of the structure of nitroguanidine and related compounds using dipole moment and dissociation constant data,[3-5] as well as ultraviolet[3,6] and infrared spectroscopy,[7] suggested that MNNG should have the tautomeric nitrimine structure, B (see B-I). Ioki and coworkers[8] used EPR spectroscopy to investigate the structure of a nitroxide radical resulting from the photolysis of MNNG. Bond lengths reported for the crystal structures of compounds with bonds similar to those in MNNG were used to calculate the coupling constants expected for various possible nitroxides, and it was concluded that this MNNG-derived nitroxide radical is a nitrimine. Indeed, nitroguanidine was found by crystallographic methods to be a nitrimine, with a highly delocalized electronic structure that could be represented as a resonance hybrid of at least eight different forms.[9] Even though it has been shown that nitroguanidine and probably many of its derivatives exist in the nitrimine form, the use of the nitramine, A, to represent MNNG dominates in the literature.[10-13] It thus appears that the controversy over the correct structure of MNNG has remained unresolved.



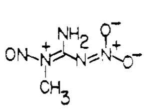
A



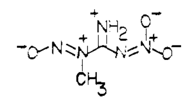
B-I



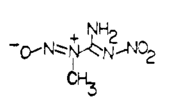
B-II



B-III



B-IV



B-V

Realizing the widespread application of MNNG as a model carcinogenic N-nitroso compound, it seemed imperative to confirm its structure in order to evaluate structure–activity relationships in this and related molecules. In particular, we have been employing MNNG as a model compound for determining the structure of nitrosocimetidine, which is similar to MNNG in mutagenic activity and structure.[14-16]

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[†] Department of Chemistry.
[‡] Department of Biochemistry and Biophysics.
[§] Cancer Center of Hawaii.

(1) Gichner, T.; Veleminsky, J. *Mutat. Res.* **1982**, *99*, 129.
(2) McKay, A. F.; Wright, G. *J. Am. Chem. Soc.* **1947**, *69*, 3028.
(3) Kumler, W. D.; Sah, P. P. T. *J. Org. Chem.* **1953**, *18*, 669.
(4) Kumler, W. D. *Ibid.*, 676.
(5) Barton, S. S.; Hall, R. H.; Wright, G. F. *J. Am. Chem. Soc.* **1951**, *73*, 2201.
(6) McKay, A. F.; Picard, J. P.; Brunet, P. E. *Can. J. Chem.* **1951**, *29*, 746.
(7) Kumler, W. D. *J. Am. Chem. Soc.* **1954**, *76*, 814.
(8) Ioki, Y.; Imamura, A.; Nagata, C.; Nakadate, M. *Photochem. Photobiol.* **1975**, *21*, 387.
(9) Bryden, J. H.; Burkhardt, L. A.; Hughes, E. W.; Donohue, J. *Acta Crystallogr.* **1956**, *9*, 573–578.
(10) Lawley, P. D. *Nature* (*London*) **1968**, *218*, 580–581.
(11) Nagata, C.; Yoshikazu, I.; Kodama, M.; Tagashira, Y.; Nakadate, M. *Ann. N.Y. Acad. Sci.* **1973**, *222*, 1031.
(12) "Aldrich Catalog"; Aldrich Chemical Co.: Milwaukee, WI, 1982–1983 p 807.
(13) Montgomery, J. A. In "Nitrosoureas in Cancer Treatment"; Serrou, B., Schein, P. S.; Imbach, J.-L., Eds.; Elsevier: New York, 1981, p 13.
(14) Pool, B. L.; Eisenbrand, G.; Schmaehl, D. *Toxicology* **1979**, *15*, 69.
(15) Henderson, E. E.; Basilio, M.; Davis, R. M. *Chem.-Biol. Interact.* **1981**, *38*, 87.
(16) Ichinotsubo, D.; McKinnon, E.; Liu, C.; Rice, S.; Mower, H. *Carcinogenesis* **1981**, *2*, 261.

0002-7863/84/1506-0239$01.50/0

Table I. Atomic Positional Parameters

(a) Non-Hydrogen Atoms ($\times 10^4$)[a]

| | $x$ | $y$ | $z$ | $B_{eq}$, Å$^2$ |
|---|---|---|---|---|
| C(1) | 11143 (9) | 43 (10) | 12776 (13) | 3.8 (3) |
| N(2) | 9956 (5) | −341 (5) | 12780 (6) | 2.5 (1) |
| C(3) | 9865 (6) | −1182 (6) | 13783 (7) | 2.6 (2) |
| N(4) | 10967 (5) | −1361 (5) | 14910 (6) | 2.9 (1) |
| N(5) | 11012 (6) | −2144 (5) | 15971 (6) | 3.1 (2) |
| O(6) | 10067 (5) | −2520 (5) | 16081 (6) | 4.5 (2) |
| O(7) | 12084 (5) | −2423 (5) | 16873 (5) | 4.5 (1) |
| O(8) | 8930 (5) | 753 (5) | 10865 (5) | 4.2 (1) |
| N(9) | 8833 (6) | 39 (5) | 11760 (7) | 3.5 (2) |
| N(10) | 8763 (6) | −1647 (6) | 13492 (7) | 3.3 (2) |
| C(11) | 3929 (9) | −137 (10) | 6746 (11) | 4.5 (3) |
| N(12) | 5084 (6) | 329 (5) | 7884 (7) | 3.1 (2) |
| C(13) | 5150 (7) | 1158 (6) | 8958 (8) | 3.0 (2) |
| N(14) | 4003 (5) | 1386 (5) | 8923 (6) | 2.8 (1) |
| N(15) | 3928 (6) | 2124 (6) | 9962 (7) | 3.6 (2) |
| O(16) | 4853 (5) | 2535 (5) | 11011 (6) | 5.5 (2) |
| O(17) | 2849 (5) | 2346 (5) | 9799 (6) | 4.8 (2) |
| O(18) | 6112 (6) | −681 (6) | 6851 (7) | 6.4 (2) |
| N(19) | 6209 (7) | 20 (7) | 7877 (9) | 5.6 (2) |
| N(20) | 6251 (6) | 1579 (7) | 9854 (8) | 4.2 (2) |

(b) Hydrogen Atoms ($\times 10^3$)

| | $x$ | $y$ | $z$ | $B$, Å$^2$ |
|---|---|---|---|---|
| H(1A) | 1184 (7) | −44 (7) | 1335 (8) | 5 (2) |
| H(1B) | 1123 (9) | 78 (9) | 1302 (9) | 9 (3) |
| H(1C) | 1102 (9) | 19 (8) | 1190 (10) | 7 (3) |
| H(10A) | 811 (5) | −147 (6) | 1272 (6) | 2 (2) |
| H(10B) | 872 (7) | −220 (7) | 1451 (9) | 7 (2) |
| H(11A) | 449 (5) | −64 (5) | 596 (6) | 2 (1) |
| H(11B) | 357 (8) | −51 (8) | 716 (9) | 6 (3) |
| H(11C) | 355 (7) | 38 (7) | 607 (8) | 6 (2) |
| H(20A) | 698 (8) | 136 (7) | 951 (8) | 7 (2) |
| H(20B) | 628 (7) | 213 (7) | 1066 (8) | 5 (2) |

[a] The equivalent isotropic temperature factors, $B_{eq}$, have been calculated by $B_{eq} = (4/3)(\beta_{11}a^2 + \cdots + \beta_{23}bc \cos \alpha)$. $\sigma(B_{eq}) = [(8/9)a^4\sigma^2(\beta_{11}) + \cdots + (8/9)b^2c^2 \cos^2 \alpha\, \sigma^2(\beta_{23})]^{1/2}$. See ref 24.

## Experimental Section

**Material.** The title compound, MNNG, was obtained from Aldrich Chemical Co. and was used without further purification or recrystallization.

**Crystallography.** A single crystal 0.14 × 0.14 × 0.13 mm in size was mounted on a glass fiber. An automated four-circle Syntex diffractometer with graphite-monochromatized Mo K$\alpha$ radiation (K$\alpha_1$ $\lambda$ = 0.70930 Å, K$\alpha_2$ $\lambda$ = 0.71359 Å) was used for the measurement of all diffraction intensities. The cell constants and their standard deviations were determined by a least-squares treatment of the angular coordinates of 15 independent reflections with 2Θ values between 24° and 32°. The space group $P2_1/c$ was assigned on the basis of the systematic absences, $l$ odd for $h0l$ and $k$ odd for $0k0$. The Θ − 2Θ scan mode was used with a variable scan rate ($\omega$) with most reflections being collected at the slowest rate, $\omega$ = 0.5°2Θ min$^{-1}$. The intensities of three check reflections were remeasured after every 100 reflections initially and after every 50 for the later and greater part of the data set. Some instrumental instability was noted. During the course of data collection, a 32% decrease in intensity due to decay was observed, and the appropriate correction was made.

Standard deviations were assigned according to the formula $\sigma(I) = [(CT + B_1 + B_2)\omega^2 + (pI)^2]^{1/2}$ where CT is the total integrated count, $B_1$ and $B_2$ are the background counts, and the intensity is $I = \omega(CT - B_1 - B_2)$. A value of 0.02 was assigned to the empirical parameter $p$. The weights ($w$) used in least-squares refinement of the structural parameters were the reciprocal squares of $\sigma(F_o)$. Of the 2326 unique reflections measured, only the 1019 for which $I > 2\sigma(I)$ were used. These were corrected for Lorentz and polarization effects.[17] The monochromator crystal was assumed to be half-perfect and half-mosaic in character in the polarization correction. A correction for the effect of absorption ($\mu$ = 1.4 cm$^{-1}$) was not made. The atomic scattering factors[18] for C$^0$, N$^0$, O$^0$ and H (bonded)[19] were used; the first three were modified to include the real part of the anomalous dispersion correction.[20]

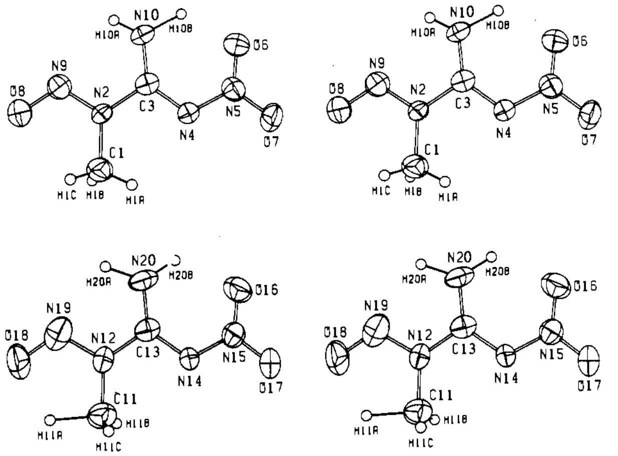

**Figure 1.** The two unique MNNG molecules oriented for ease of comparison. Ellipsoids of 50% probability are shown. Hydrogen B's have all been reset to 0.6 Å$^2$ in these figures.

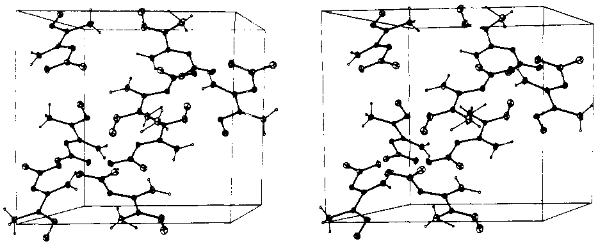

**Figure 2.** A stereoview of the packing of molecules in a unit cell. +$a$ is horizontal to the right; +$b$ extends upward in the plane of the page; +$c$ points up out of the page toward the reader. Ellipsoids of 10% probability are used.

The structure was solved by direct methods with MULTAN80[21] using the 280 reflections with $|E| > 1.41$. The solution with the maximum possible CFOM, 3.00, indicated the positions of all 20 non-hydrogen atoms of the two unique molecules per asymmetric unit. After anisotropic refinement[22] of the non-hydrogen positions (see paragraph at end of paper regarding supplementary material), all 10 hydrogen positions were unambiguously located on a difference Fourier function.[23] A careful search of the regions around N(4) and N(14) was done to see if any support for the hydrogen placement in tautomer A could be found; it failed to show any electron density that could be attributed to hydrogen atoms bound to these nitrogens, affirming that the tautomer A structure is incorrect for both molecules. Several cycles of full-matrix least-squares refinement with anisotropic thermal parameters for the non-hydrogens and isotropic ones for the hydrogens yielded $R_1 = \Sigma(|F_o - |F_c||)/\Sigma F_o = 0.075$ and $R_2 = [\Sigma w(F_o - |F_c|)^2/\Sigma wF_o^2]^{1/2} = 0.060$. The "goodness of fit", $[\Sigma w(F_o - |F_c|)^2/(m - s)]^{1/2}$, is 2.25, where $m$ (1019) is the number of observations used in least-squares refinement, and $s$ (221) is the number of parameters.

The final positional coordinates, together with their standard deviations, are presented in Table I. Bond distances and angles[25] are given in Table II.

**Nuclear Magnetic Resonance.** Natural abundance $^{15}$N NMR data were acquired at 50.68 MHz on a Bruker WM-500 spectrometer. Approximately 500 mg of MNNG was dissolved in 2 mL of Me$_2$SO-$d_6$, and the resulting solution was analyzed immediately since significant decomposition of this compound in Me$_2$SO is observable within 24 h.

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(17) Ottersen, T. "LP-76"; University of Hawaii: Honolulu, HI, 1976.

(18) "International Tables for X-ray Crystallography"; Kynoch Press: Birmingham, AL, 1974; Vol. IV, pp 72–98.

(19) *Ibid.*, p 71.

(20) *Ibid.*, pp 140–150.

(21) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J.-P.; Woolfson, M. M. "MULTAN80, a System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data"; University of York, England, 1980.

(22) Gantzel, P. K.; Sparks, R. A.; Trueblood, K. N. UCLALS4, 1964, American Crystallographic Association Library (old) No. 317, modified by T. Ottersen and K. Seff (1976).

(23) Hubbard, C. R.; Quicksall, C. O.; Jacobson, R. A., Ames Laboratory Fast Fourier, Iowa State University, 1971.

(24) Cheng, M. Y.; Larson, H. O.; Seff, K. *Acta Crystallogr., Sect. B* **1982**, *B38*, 1335–1337.

(25) Wood, J. S. "MOLGE"; M.I.T.: Cambridge, MA, 1964. The torsion angle convention used is that of Klyne, W.; Prelog, V. *Experientia* **1960**, *16*, 521.

Table II. Interatomic Distances and Angles

(a) Bond Lengths, Å

| | | | |
|---|---|---|---|
| C(1)-N(2) | 1.450 (11) | C(11)-N(12) | 1.446 (12) |
| N(2)-C(3) | 1.407 (9) | N(12)-C(13) | 1.391 (9) |
| N(2)-N(9) | 1.346 (8) | N(12)-N(19) | 1.358 (10) |
| C(3)-N(4) | 1.319 (9) | C(13)-N(14) | 1.346 (9) |
| C(3)-N(10) | 1.302 (9) | C(13)-N(20) | 1.307 (10) |
| N(4)-N(5) | 1.355 (8) | N(14)-N(15) | 1.352 (8) |
| N(5)-O(6) | 1.225 (8) | N(15)-O(16) | 1.233 (8) |
| N(5)-O(7) | 1.235 (8) | N(15)-O(17) | 1.223 (9) |
| O(8)-N(9) | 1.235 (8) | O(18)-N(19) | 1.252 (10) |
| C(1)-H(1A) | 0.95 (8) | C(11)-H(11A) | 1.34 (6) |
| C(1)-H(1B) | 0.86 (11) | C(11)-H(11B) | 0.81 (9) |
| C(1)-H(1C) | 0.84 (9) | C(11)-H(11C) | 0.86 (8) |
| N(10)-H(10A) | 0.85 (6) | N(20)-H(20A) | 1.06 (9) |
| N(10)-H(10B) | 1.21 (8) | N(20)-H(20B) | 1.00 (7) |

(b) Bond Angles, deg

| | | | |
|---|---|---|---|
| C(1)-N(2)-C(3) | 123.7 (6) | C(11)-N(12)-C(13) | 125.2 (7) |
| C(1)-N(2)-N(9) | 122.2 (6) | C(11)-N(12)-N(19) | 119.3 (7) |
| N(2)-C(3)-N(4) | 111.5 (6) | N(12)-C(13)-N(14) | 111.7 (6) |
| N(2)-C(3)-N(10) | 118.1 (6) | N(12)-C(13)-N(20) | 119.3 (7) |
| C(3)-N(4)-N(5) | 117.7 (5) | C(13)-N(14)-N(15) | 118.4 (6) |
| N(4)-C(3)-N(10) | 130.4 (7) | N(14)-C(13)-N(20) | 129.1 (7) |
| N(4)-N(5)-O(6) | 123.1 (6) | N(14)-N(15)-O(16) | 124.1 (6) |
| N(4)-N(5)-O(7) | 115.3 (6) | N(14)-N(15)-O(17) | 114.3 (6) |
| O(6)-N(5)-O(7) | 121.5 (6) | O(16)-N(15)-O(17) | 121.6 (6) |
| O(8)-N(9)-N(2) | 113.3 (6) | O(18)-N(19)-N(12) | 113.8 (7) |
| N(9)-N(2)-C(3) | 114.1 (5) | N(19)-N(12)-C(13) | 115.4 (6) |
| H(1A)-C(1)-N(2) | 114 (5) | H(11A)-C(11)-N(12) | 95 (2) |
| H(1B)-C(1)-N(2) | 106 (6) | H(11B)-C(11)-N(12) | 108 (6) |
| H(1C)-C(1)-N(2) | 108 (6) | H(11C)-C(11)-N(12) | 112 (5) |
| H(1A)-C(1)-H(1B) | 115 (8) | H(11A)-C(11)-H(11B) | 124 (7) |
| H(1A)-C(1)-H(1C) | 118 (8) | H(11A)-C(11)-H(11C) | 93 (6) |
| H(1B)-C(1)-H(1C) | 93 (9) | H(11B)-C(11)-H(11C) | 123 (8) |
| H(10A)-N(10)-C(3) | 122 (4) | H(20A)-N(20)-C(13) | 113 (4) |
| H(10B)-N(10)-C(3) | 114 (4) | H(20B)-N(20)-C(13) | 118 (4) |
| H(10A)-N(10)-H(10B) | 123 (5) | H(20A)-N(20)-H(20B) | 129 (6) |

(c) Selected Torsion Angles, deg[a]

| | |
|---|---|
| O(8)-N(9)-N(2)-C(3) | 178 |
| N(9)-N(2)-C(3)-N(4) | 168 |
| N(2)-C(3)-N(4)-N(5) | 181 |
| C(3)-N(4)-N(5)-O(7) | 191 |
| O(18)-N(19)-N(12)-C(13) | 177 |
| N(19)-N(12)-C(13)-N(14) | 178 |
| N(12)-C(13)-N(14)-N(15) | 184 |
| C(13)-N(14)-N(15)-O(17) | 184 |

[a] See ref 25 for the torsion angle convention used. esd's are about 1°.

Table III. Hydrogen Bonds, A-H···B

| A | H | B | equiv position for B | H···B, Å | A-B, Å | A-H-B, deg |
|---|---|---|---|---|---|---|
| N(10) | H(10B) | O(6) | $x, y, z$ | 1.72 (8) | 2.569 (8) | 122 (6) |
| N(20) | H(20A) | O(8) | $x, y, z$ | 2.11 (9) | 2.998 (8) | 129 (6) |
| N(20) | H(20B) | O(16) | $x, y, z$ | 1.87 (7) | 2.582 (9) | 124 (6) |
| N(10) | H(10A) | O(17) | $1-x, -y, 2-z$ | 2.47 (6) | 3.107 (8) | 133 (5) |
| N(10) | H(10A) | N(14) | $1-x, -y, 2-z$ | 2.32 (6) | 3.124 (8) | 159 (5) |

Chemical shifts are reported on the $\delta$ scale and are calculated relative to an external standard of liquid ammonia at 0 ppm. A possible error of ±1 ppm is present for reported shift values. Spectra were acquired in both the proton-coupled and undecoupled modes.

The $^1H$ NMR data for MNNG were acquired at 100 MHz by using a Varian XL-100 NMR spectrometer interfaced with a Nicolet 1180 data system. Solutions of approximately 5 mg/mL MNNG in $Me_2SO$-$d_6$ and $CDCl_3$ were prepared and analyzed immediately. Chemical shifts are reported on the $\delta$ scale and are calculated relative to the solvent offset value of 7.24 ppm for $CHCl_3$ and 2.49 ppm for $Me_2SO$.

## Results and Discussion

The crystallographic results clearly show that both molecules of MNNG exist as tautomer B (see B-I) in the solid state; two hydrogen atoms are bound to N(10) and two to N(20), as shown in Figure 1.[26] This is consistent with the recent observation[27] that this tautomer is generally preferred by guanidine groups with electron-withdrawing substituents.

In Figure 2,[26] it can be seen that various intermolecular forces (hydrogen bonding (Table III[28]), electrostatic or charge transfer, and packing) act on the two nonequivalent molecules. It is interesting to see how much and how differently those forces have affected their planarity [Figure 1, Table II (c), and Table IV[25]].

In Table II (a), it can be seen that the C(1)-N(2) bond is single as would be expected. [This discussion of the first molecule, C(1)-N(10), applies to the second molecule, C(11)-N(20), as well.] However, all three C(3)-N bonds are significantly shorter, implying some multiple bond character for C(3)-N(2), and even more and nearly equal multiple bond character for C(3)-N(4) and C(3)-N(10). The N-N distances N(2)-N(9) and N(4)-N(5) are nearly equal and shorter than expected for a N-N single bond. Furthermore, the angles around atoms N(5), C(3), and N(2) all

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[26] Johnson, C. K. "ORTEP"; Oak Ridge National Laboratory: Oak Ridge, TN, 1965; Report ORNL-3794.

[27] Boyar, A.; Marsh, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 1995-1998.

[28] Trueblood, K. N. "ALDIST"; U.C.L.A.: Los Angeles, CA, 1962.

Table IV. Deviations of Atoms from Least-Squares Planes

| plane 1 | | plane 2 | |
|---|---|---|---|
| atom | dev, Å | atom | dev, Å |
| N(2) | 0.001* | N(12) | 0.002* |
| C(3) | -0.002* | C(13) | -0.009* |
| N(4) | 0.001* | N(14) | 0.002* |
| N(10) | 0.001* | N(20) | 0.004* |
| C(1) | -0.304 | C(11) | -0.119 |
| N(5) | 0.011 | N(15) | 0.073 |
| O(6) | 0.264 | O(16) | 0.228 |
| O(7) | -0.198 | O(17) | -0.008 |
| O(8) | 0.209 | O(18) | -0.023 |
| N(9) | 0.244 | N(19) | 0.036 |
| H(1A) | -0.70 | H(11A) | -0.32 |
| H(1B) | 0.42 | H(11B) | 0.53 |
| H(1C) | -0.68 | H(11C) | -0.92 |
| H(10A) | -0.01 | H(20A) | -0.18 |
| H(10B) | 0.22 | H(20B) | 0.06 |

[a] Indicates atoms used to define planes.

add to 360 (1)° as would be expected if $\pi$ delocalization were extensive. Further evidence for widespread delocalization is the near planarity of the entire molecule as seen in Table IV and Figures 1 and 2. The electronic structure may be described as B-I with significant contributions from resonance forms B-II to B-V.

The structure consists of charge-transfer dimer pairs of molecules at inversion centers. The interplanar spacing for molecules 1 is 3.38 Å, based on N(2), C(3), N(4), and the corresponding spacing for dimers of molecule 2 is 3.35 Å. Dimers of molecule 1 join to form chains by 2.97-Å interdimer interactions between N(2) and O(6), as do dimers of molecule 2 [N(12) to O(16) = 2.98 Å]. These interactions can be seen in Figure 2, although the second half of a dimer of molecule 1 must be generated mentally, by inversion at 0, $^1/_2$, 0, for example. These short interactions are electrostatic, between the central guanidine nitrogens, N(2) and N(12), which resonance forms B-III, B-IV, and B-V indicate are positive, and O(6) and O(16), which are negative according to resonance forms B-II, B-III, and B-IV.

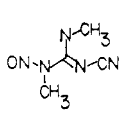
Various considerations suggest that an intramolecular hydrogen-bond-like interaction occurs between C(11)-H(11A) and O(18) [C(11)-O(18) = 2.57 (1) Å; H(11A) - O(18) = 1.72 (6) Å; C(11)-H(11A)-O(18) = 114 (3)°]. The methyl group in the second conformer is rotated 60° from its position in molecule 1 to allow such an interaction. The oxygen corresponding to O(18) in molecule 1, namely, O(8), participates in a hydrogen bond, but O(18) otherwise does not. The thermal ellipsoid at O(18) is elongated toward H(11A), whose electron density is in turn displaced toward O(18) (see Figure 1) as indicated by the long C(11)-H(11A) bond and small N(12)-C(11)-H(11A) angle (those latter are only of marginal significance, however). Also favoring this proposal is the marginally smaller C(11)-N(12)-N(19) angle of the second molecule [see Table II (b)] as compared to the first.

A comparison of the crystal structures of MNNG (both molecules) and nitroguanidine[9] reveals that the C(3)-N(10) and perhaps the C(3)-N(4) bonds of MNNG are somewhat shorter than the corresonding bonds in nitroguanidine and that the C(3)-N(2) bond of MNNG is considerably longer than either of the corresponding bonds in nitroguanidine. The crystal structure of *N,N'*-dimethyl-*N''*-cyano-*N*-nitrosoguanidine[29] (DCNG, an analogue of the guanidine system in nitrosocimetidine) shows it to be a planar cyanimide, with a highly delocalized electronic structure like that of MNNG. In fact, in Table V it can be seen that the bond lengths in the C-N-N-O sequence are essentially identical in DCNG and MNNG. Recently, Prout and co-workers[30] reported the crystal structures of two nitrosoureas (N-methyl-*N*-nitrosourea and *N,N'*-dimethyl-*N*-nitrosourea) and two nitrosamides (2-nitroso-2-azabicyclo[2.2.2]octan-3-one and *N*-methyl-*N*-nitroso-*p*-nitrobenzamide). A comparison of these structures (MNU, DNU, NAO, and MNNB, respectively) to those of MNNG and DCNG (Table V) shows that the N-N and C-NNO bond lengths in the nitrosoguanidines are similar to those found in the nitrosamides but that the corresponding bonds in the nitrosoureas are significantly shorter and longer, respectively. Thus, it appears, from the comparison of related compounds, that nitrosation of *N*-methyl-*N'*-nitroguanidine and *N*-methyl-*N'*-cyanoguanidine modifies the electronic character of the guanidine system so that the C-N-N bonding system resembles that of a nitrosamide.

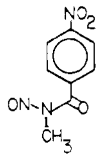
Table V. Bond Lengths (Å) in Several Nitrosoguanidines, Nitrosamides, and Nitrosoureas[c]

| | N-N | C-NNO |
|---|---|---|
| nitrosoguanidines | | |
| DCNG[a] | 1.343 (4) | 1.411 (4) |
| MNNG | 1.346 (8) | 1.407 (9) |
| | 1.358 (8) | 1.391 (9) |
| nitrosamides[b] | | |
| NAO | 1.353 (4) | 1.401 (5) |
| MNNB | 1.352 (5) | 1.405 (6) |
| nitrosoureas[b] | | |
| MNU | 1.326 (2) | 1.431 (2) |
| DNU | 1.332 (2) | 1.427 (2) |

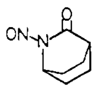
[a] Reference 29. [b] Reference 30. [c] DCNG = *N,N'*-dimethyl-*N''*-cyano-*N*-nitrosoguanidine; MNNG = *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine; NAO = 2-nitroso-2-azabicyclo[2.2.2]octan-3-one; MNNB = *N*-methyl-*N*-nitroso-*p*-nitrobenzamide; MNU = *N*-methyl-*N*-nitrosourea; DNU = *N,N'*-dimethyl-*N*-nitrosourea.



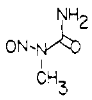
DCNG



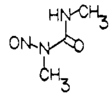
MNNB



NAO



MNU



DNU

The $^{15}$N NMR data acquired for MNNG are presented in Table VI, and an undecoupled spectrum that provides both nuclear Overhauser enhancement (NOE) and coupling information is shown in Figure 3. The assignment of $^{15}$N NMR signals was readily accomplished with excellent correlation by comparison with resonance signals observed for similar nitrogen atoms in other compounds.[31] The relative intensities of the coupled and undecoupled $^{15}$N NMR signals were all approximately the same except for the one at highest field (98.19 ppm), which changed sign to become negative in the undecoupled spectrum. Since the gyromagnetic ratio is negative for $^{15}$N, a negative NOE is expected for proton-bearing $^{15}$N atoms in the undecoupled spectrum.[32]

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(29) Cruz, W. V.; Seff, K. *Acta Crystallogr., Sect. C* **1983**, *C39*, 918-920.

(30) Prout, K.; Fail, J.; Hernandez-Cassou, S.; Miao, F. M. *Acta Crystallogr., Sect. B B* **1982**, *B38*, 2176-2181.

(31) Witanowski, M.; Stefaniak, L.; Januszewski, H. In "Nitrogen NMR"; Witanowski, M.; Webb, G., Eds.; Plenum: New York, 1973; pp 163-260.

(32) Martin, G. J.; Martin, M. L.; Gouesnard, J. P. "$^{15}$N-NMR Spectroscopy"; Springer-Verlag: New York, 1981; pp 29-33.

Table **VI.** $^{15}$N NMR Data for MNNG in Me$_2$SO-$d_6$

| | | relative intensity, % | | | |
|---|---|---|---|---|---|
| nitrogen no. | resonance frequency, ppm | undecoupled spectrum | coupled spectrum | multiplicity | assignment |
| 1 | 98.19 | (−)90.6 | 70.8 | singlet | C-*N*-H$_2$ |
| 2 | 255.34 | 11.8 | 21.7 | singlet | C⟍*N*=NO$_2$ |
| 3 | 259.16 | 81.9 | 81.0 | singlet | C<br>>*N*-NO<br>C |
| 4 | 368.59 | 68.5 | 71.0 | singlet | N-*N*O$_2$ |
| 5 | 570.148 | 100 | 100 | singlet | N-*N*O |

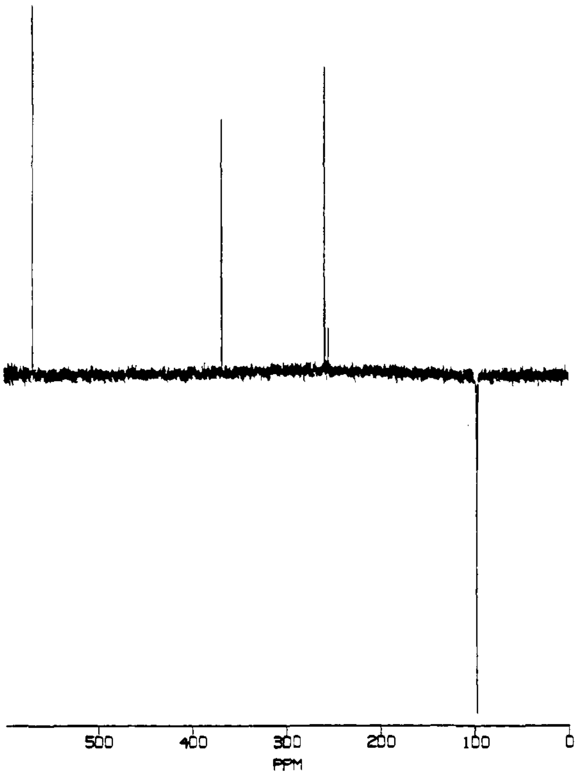

**Figure 3.** Undecoupled $^{15}$N NMR spectrum of MNNG in Me$_2$SO-$d_6$.

Thus, it can be seen in Figure 3 that only the signal for one nitrogen atom in MNNG exhibits a significant negative NOE and thus bears protons. The chemical shift of this signal makes it assignable to an amino group of a guanidine.[31] Thus, from $^{15}$N NMR studies it appears that MNNG possesses the nitrimine structure, B, in Me$_2$SO. Although the amino $^{15}$N signal is slightly broader than the others, there is no evidence of coupling between this nitrogen atom and the protons it bears. This is probably a result of rapid proton exchange, which would be facilitated by the intramolecular hydrogen bonding observed crystallographically (Table III) and by hydrogen bonding to the solvent.

The $^1$H NMR data for MNNG are presented in Table VII. It can be seen that MNNG in either CDCl$_3$ or Me$_2$SO-$d_6$ gives only two proton resonance signals, one for the methyl group and one for the amino group. Since the crystallographic results show the C–NH$_2$ bond of MNNG to have a high degree of double bond character [see C(3)–N(10) and C(13)–N(20) in Table II], restricted rotation about this bond should render the two amino protons nonequivalent. Thus, a separate signal for each amino proton would be expected in the $^1$H NMR spectrum of MNNG unless a rapid exchange process involving these protons is present to produce a time-averaged signal. This exchange process in a non-hydrogen-bonding solvent such as CDCl$_3$ probably involves MNNG's intramolecular hydrogen bond.

Table **VII.** $^1$H NMR Data for MNNG in Me$_2$SO-$d_6$ and CDCl$_3$

| | | resonance frequency, ppm | | | |
|---|---|---|---|---|---|
| proton no. | no. of protons | Me$_2$SO-$d_6$ | CDCl$_3$ | multiplicity | assignment |
| 1 | 3 | 3.14 | 3.27 | singlet | -CH$_3$ |
| 2 | 2 | 9.74 | 8.43 | broad singlet | -NH$_2$ |

Compared to other *N*-nitroso compounds, the intramolecular hydrogen bond in MNNG is unique and may contribute to its high mutagenic activity. This activity may also be enhanced by the electronic and structural flexibility of MNNG, which should allow it, within relatively broad limits, to adjust its $\pi$ densities and planarity to facilitate in vivo interactions with its host.

**Note Added in Proof.** This structure and that of an orthorhombic form of this compound were published[33] while this work was in progress. The first and second molecules here correspond closely to molecules (M)A and (M)B, respectively, there. Unfortunately, the atomic nomenclature, the choice of unit cell, and the description of torsion angles differ.

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**Registry No.** *N*-Methyl-*N'*-nitro-*N*-nitrosoguanidine, 70-25-7.

**Supplementary Material Available:** A table of anisotropic thermal parameters for the non-hydrogen atoms and a table of calculated and observed structure–factor amplitudes (6 pages). Ordering information is given on any current masthead page.

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(33) Nordenson, S.; Hvoslef, J. *Acta Crystallogr., Sect. B* **1981**, *B37*, 373–378.