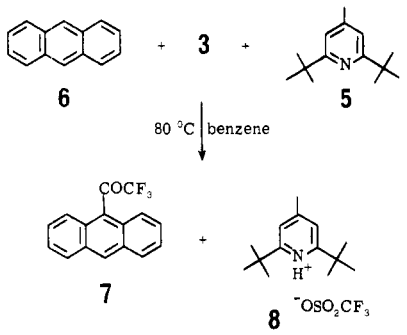
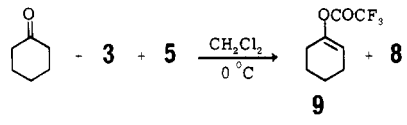
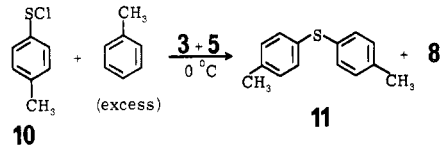
than carbon also promises to be of synthetic utility, as in the reaction with some covalent chlorides at chlorine. When 1.05



equiv of **3** is added to 1 equiv of *p*-toluenesulfenyl chloride (**10**) in 8 equiv of toluene with 1 equiv of **5** at 0 °C, 36%[12] of sulfide **11** is formed. When trityl chloride (**12**) is mixed with an excess of **3** at 25 °C, it is quantitatively converted to trityl triflate (**13**).[13]



One driving force for these reactions at chlorine stems from the high volatility of the trifluoroacetyl chloride (**14**) (bp −18 °C), which is evolved from the reaction medium.



The reactions cited above are simply illustrations of some of the types of reactions which have been observed. Details of other reactions will be reported in a later publication.

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(6) ^{19}F NMR spectrum of TFAT ($CHCl_3$) δ 72.90 (3 F, s), 74.45 (3 F, s); IR ($CHCl_3$): 1845 cm^{-1} (s). Anal. $C_3F_6O_4S$: C.
(7) A. G. Anderson and P. J. Stang, *J. Org. Chem.*, **41**, 3034 (1976).
(8) The base can be recovered from these reactions as the triflate salt (**8**) and regenerated.
(9) The yield of **7** was determined by NMR. The identity of **7** was confirmed by comparisons of its spectra with ^1H and ^{19}F spectra of an authentic sample.[10]
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(12) Determined by GLC of the isolated product. The identity of **11** was confirmed by comparison (^1H NMR and GLPC retention time) with an authentic sample (R. J. Maner, Ph.D. Dissertation, University of Iowa, 1967).
(13) ^1H NMR of **13** (CF_3CO_2H) δ 8.26 (3 H, tt, J = 7.5 and ~1 Hz), 7.90 (6 H, tt, J = 7.5 and ~1 Hz), 7.78 (6 H, tt, J = 7.5 and ~1 Hz).

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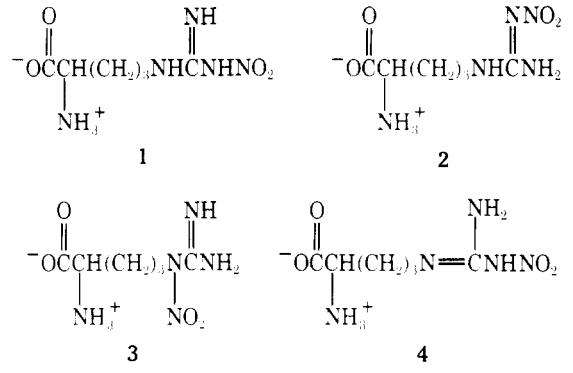
Structure of Nitroarginine. A Nitrogen-15 Nuclear Magnetic Resonance Study

Summary: The methyl ester hydrochloride of N^G-nitroarginine exists in the nitrimine form in aqueous solution, as determined by ^{15}N and ^1H nuclear magnetic resonance studies.

Sir: The N^G-nitro protecting group for arginine was first employed in 1934[1] and has since found broad application in syntheses of arginine-containing peptides.[2] However, the structure of nitroarginine has eluded unambiguous assignment. Four isomeric structures are conceivable for the guanidino portion of nitroarginine (**1**–**4**). Structure **1**, a nitramine,



was proposed when the first synthesis of nitroarginine was described by Kossel and Kennaway.[3] But the nitrimine structure **2** and nitramines **3** and **4** were not excluded. Other early reports[1,4] also favored nitroarginine structure **1**. Later studies[5] of nitroguanidine and its derivatives based on dipole moment, ultraviolet absorption, and pK_a measurements indicated a nitrimine-type structure (cf. **2**). Subsequently, both structures **1**[6] and **2**[7] for nitroarginine began to appear in the literature, and the confusion persists today.[8]

Nitrogen-15 NMR at the natural abundance level has become a practical structure elucidation technique, and was applied to the nitroarginine structural problem. This technique is unambiguous, and unlike earlier studies[5] does not rely heavily on arguments concerning the relative contributions of various zwitterionic and resonance forms.

Figure 1a shows the proton broad band decoupled natural abundance ^{15}N FT NMR spectrum at 9.12 MHz of a 58 wt % solution of N^G-nitroarginine methyl ester monohydrochloride[2b] in water. The spectrum was obtained in a 10-mm sample tube using a repetition time of 10 s. Chemical shifts are reported in ppm upfield from external 1.0 M $Na^{15}NO_3$ in D_2O. Five resonances were observed. Since the chemical shifts of nitro groups generally fall in the range −30 to +60 ppm,[9] the peak at 8.4 ppm arises from this group. The resonance at 138.5 ppm is due to the imino nitrogen atom. This rather unusual chemical shift value will be discussed below. The three upfield resonances are characteristic of amine-type nitrogen nuclei.[9] The resonance at 335.6 ppm is readily assigned to the α-amino group and is in good agreement with the value of 332.5 ppm reported[10] for the hydrochloride of arginine methyl ester itself. The resonances at 281.0 and 293.1 ppm must then arise from the two amine-type nitrogen atoms of the nitroguanidino group.

Additional information concerning the structure of nitroarginine was obtained from the proton-coupled ^{15}N NMR spectrum. Figure 1c was obtained under conditions similar to those employed for Figure 1a, with the exception that a gated decoupling scheme was employed. The decoupler was turned off only during the pulse and acquisition period in order to obtain a coupled spectrum which retains the (negative) nuclear Overhauser effect. The resonance at 281.0 ppm was split

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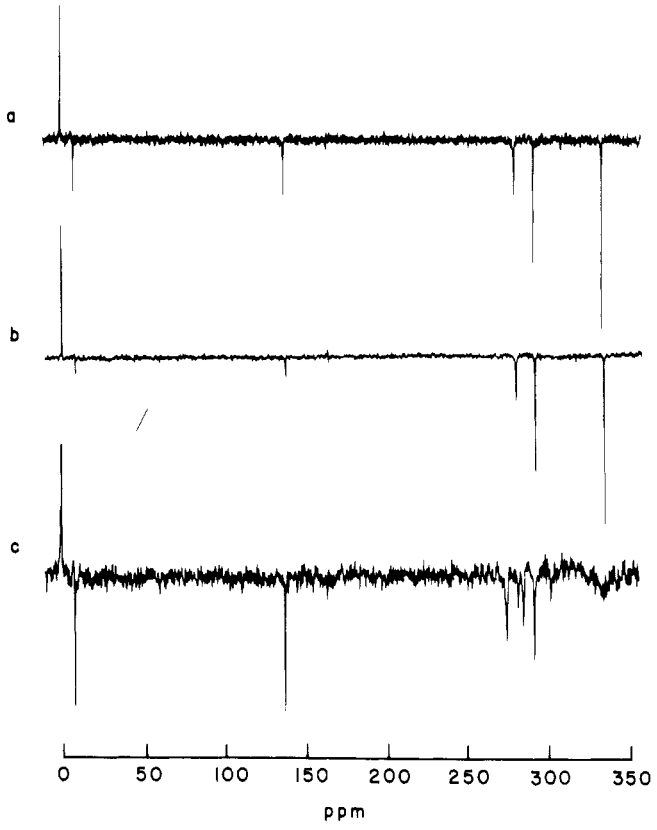

Figure 1. Natural abundance ^{15}N FT NMR spectra of N^G-nitroarginine methyl ester hydrochloride in water. (a) Proton broad band decoupled spectrum (6640 accumulations) with a repetition time of 10 s. (b) Proton broad band decoupled spectrum (24 540 accumulations) with a repetition time of 2.1 s. (c) Gated decoupling experiment (15 235 accumulations) showing coupled spectrum with nuclear Overhauser effect retained. The small spike in the center of each spectrum (165 ppm) is an instrumental artifact. Some peaks in the spectra are inverted due to a negative nuclear Overhauser effect.

into a doublet ($^1J_{NH}$ = 97 Hz) which arises from a nitrogen atom bearing one hydrogen atom, and the resonance at 293.1 ppm appeared as a triplet ($^1J_{NH}$ = 94 Hz) which indicated two directly attached protons. The α-amino nitrogen resonance was split into an unresolved multiplet. Proton exchange may play a role in the appearance of this peak.

The nitro and imino nitrogen resonances at 8.4 and 138.5 ppm still appear as singlets in Figure 1c and thus lack directly attached protons. This conclusion is further verified by the results of a crude relaxation time study. Figure 1b shows the proton-decoupled ^{15}N NMR spectrum determined under the same conditions as Figure 1a, with the exception that the pulse repetition time was shortened to 2.1 s. The nitro and imino resonances are greatly reduced in intensity relative to the three upfield resonances, indicating that these nuclei have considerably longer spin–lattice relaxation times than do the nuclei that absorb upfield. Since dipole–dipole relaxation from directly attached protons is usually the most efficient relaxation mechanism for ^{15}N nuclei, the longer spin–lattice relaxation times for the nitro and imino nitrogen nuclei are consistent with a lack of directly bound protons.

The experimental results allow the structure of N^G-nitroarginine methyl ester hydrochloride to be elucidated. Structures of types **1**, **3**, and **4** all contain both a nitramine group and a guanidino-type imino nitrogen. The amino nitrogen resonance of nitromethylamine appears at 208 ± 8 ppm.[11] Similarly, the imino nitrogen resonance of *N,N,N',N'*-tetramethylguanidine appears at 209 ± 3 ppm.[9,12] Thus, the spectra of structures of type **1**, **3**, and **4** should feature two resonances in the 200-ppm region. However, Figure 1a shows no resonances at all in this region. On the other hand, a structure similar to **2** would have a spectrum containing two amine-type nitrogen resonances in the region of 300 ppm and an imino resonance which has been shifted downfield from its position in tetramethylguanidine due to delocalization of electron density into the nitro group.[9] Indeed that was observed, and the chemical shifts strongly support a structure similar to **2**. The coupled spectrum in Figure 1c and the relaxation time study show that the imino nitrogen atom does not bear a directly attached proton. These results also serve to rule out structures of type **1** and **3**.

It will be noted that the ^{15}N NMR spectra show no evidence for geometric (syn–anti) isomerism about the carbon–nitrogen double bond. This could in principal be due to accidental isochrony, the presence of only one isomer, or rapid isomerization. Studies of related molecules[13] suggest that rapid interconversion of isomers is the most likely explanation.

Additional evidence for a type **2** structure is provided by the ^1H NMR spectrum. The 90-MHz ^1H NMR spectrum of nitroarginine methyl ester hydrochloride in dimethyl-d_6 sulfoxide at ~60 °C displayed what appeared to be four resonances for the protons on the δ carbon atom at 280, 286, 292, and 298 Hz downfield from Me_4Si in the approximate ratio of intensities of 1:2.3:2.3:1. Analysis of this spectral pattern revealed that the δ protons are split into a triplet by the γ protons ($^3J_{HH}$ = 6.5 Hz, see below) and that each line of the triplet is further split by a single proton on the nitrogen atom attached to the δ carbon atom ($^3J_{HH}$ = 6.0 Hz). This interpretation is confirmed by the fact that irradiation of the guanidino protons at 8 ppm decoupled these protons and resulted in the collapse of the pattern at δ 3.2 to a singlet triplet. Addition of 2 drops of D_2O to the sample also led to collapse to a triplet ($^3J_{HH}$ = 6.5 Hz), due to replacement of the exchangeable protons by deuterons. These experiments provide additional evidence excluding structures of types **3** and **4**, which lack protons on the appropriate nitrogen atoms.

Thus, in aqueous solution, N^G-nitroarginine methyl ester hydrochloride has the nitrimine structure similar to **2**.

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