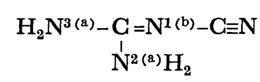
Cyanamide Derivatives. Part 106.* The Preparation of ^{15}N-Labeled Cyanoguanidines

Akira OMURA,** Tsutomu NONAKA, Toshio FUCHIGAMI, Eiichi ICHIKAWA, and Keijiro ODO
Department of Electronic Chemistry, The Graduate School, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152

(Received July 12, 1976)

Methods for labeling the chemically non-equivalent nitrogen atoms of cyanoguanidine with ^{15}N were established. 1-Cyanoguanidine-1-^{15}N and 1-cyano-^{15}N-guanidine were prepared, and their labeled positions were also confirmed by mass spectroscopic analysis. ^{15}N FT-NMR spectra of cyanoguanidine enriched with ^{15}N were measured.

Cyanoguanidine (**1**), also called dicyandiamide, is one of the useful starting compounds for the synthesis of C–N alternating compounds. However, no reliable mechanisms of many reactions of **1** and its related compounds have been established because of the ambiguity in the correlation between the arrangement of nitrogen atoms in a product molecule and that in a reactant. Such a problem would be solved by using a ^{15}N tracer. The authors had already prepared a labeled **1**, 1-cyanoguanidine-2,3-^{15}N$_2$, and put it to use for clarification of the mechanism of cathodic crossed hydrocoupling of acetone with **1**.[1]



$$\underset{\textstyle N^{2(a)}H_2}{H_2N^{3(a)}\text{–}\underset{|}{C}=N^{1(b)}\text{–}C\equiv N^{(c)}}$$

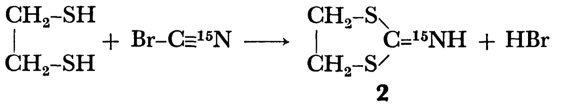
1

In this work, methods for labeling the non-equivalent nitrogen atoms (N^b and N^c) other than N^a and for enriching all nitrogen atoms with ^{15}N were developed. It is required in preparation of a labeled compound that its formation mechanism has been established, at least reliably. And also, the labeled position should be reconfirmed in some way. Such requirements were satisfied in this work.

Results and Discussion

A procedure for labeling the N^b was newly designed because there was no earlier literature which could be used for the preparation of 1-cyanoguanidine-1-^{15}N. At the first stage, 2-imino-1,3-dithiolane-^{15}N (**2**) was synthesized in a 98% yield from 1,2-ethanedithiol and cyanogen bromide-^{15}N.[2] Cyanogen bromide-^{15}N was prepared by the bromination of potassium cyanide-^{15}N (^{15}N abundance, 2.7 atom %).[3]

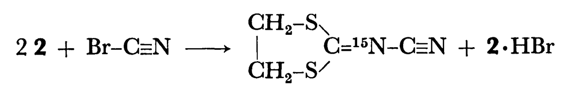
$$KC\equiv{}^{15}N + Br_2 \longrightarrow Br\text{–}C\equiv{}^{15}N + KBr$$



$$\begin{matrix}CH_2\text{–}SH\\ |\\ CH_2\text{–}SH\end{matrix} + Br\text{–}C\equiv{}^{15}N \longrightarrow \begin{matrix}CH_2\text{–}S\diagdown\\ |\qquad C={}^{15}NH\\ CH_2\text{–}S\diagup\end{matrix} + HBr$$

2

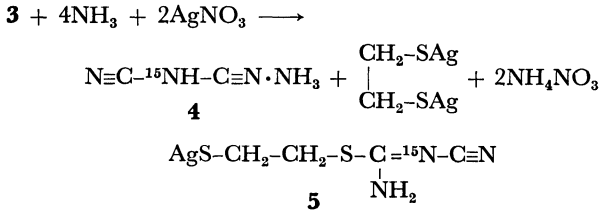
And then the free base of **2** was also treated with ordinary cyanogen bromide in acetone so as to be converted into 2-[(cyano)imino-^{15}N]-1,3-dithiolane (**3**) in an 80% yield. The compound, **3**, was identified with an independently synthesized authentic sample by an IR spectrum and a mixed melting test.[4] The hydrobromide, which was inevitably produced, of **2** could be repeatedly used.



$$2\,\mathbf{2} + Br\text{–}C\equiv N \longrightarrow \begin{matrix}CH_2\text{–}S\diagdown\\ |\qquad C={}^{15}N\text{–}C\equiv N\\ CH_2\text{–}S\diagup\end{matrix} + \mathbf{2}\cdot HBr$$

3

An attempt to obtain directly 1-cyanoguanidine-1-^{15}N by the ammonolysis of **3** was unsuccessful. The ammonolysis in the presence of silver nitrate afforded the ammonium salt of dicyanoamine-^{15}N (**4**) in a 47% yield. The compound, **4**, was converted into the potassium salt[5] and identified with an authentic sample by an IR spectrum. The by-product seemed to be mainly a compound, **5**. But **5** could not be purely isolated from the coprecipitated silver salt of 1,2-ethanedithiol.

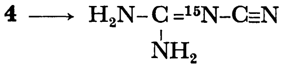


$$\mathbf{3} + 4NH_3 + 2AgNO_3 \longrightarrow$$

$$\underset{\mathbf{4}}{N\equiv C\text{–}{}^{15}NH\text{–}C\equiv N\cdot NH_3} + \begin{matrix}CH_2\text{–}SAg\\ |\\ CH_2\text{–}SAg\end{matrix} + 2NH_4NO_3$$

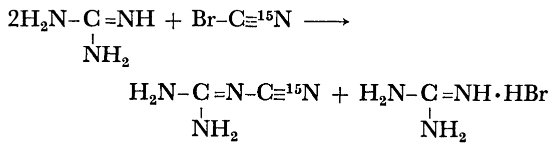
$$\underset{\mathbf{5}}{AgS\text{–}CH_2\text{–}CH_2\text{–}S\text{–}\underset{\underset{\textstyle NH_2}{|}}{C}={}^{15}N\text{–}C\equiv N}$$

The compound, **4**, was converted into 1-cyanoguanidine-1-^{15}N in a 49% yield by reflux in 1-butanol.[6]



$$\mathbf{4} \longrightarrow H_2N\text{–}\underset{\underset{\textstyle NH_2}{|}}{C}={}^{15}N\text{–}C\equiv N$$

1-Cyano-^{15}N-guanidine labeled at the N^c was prepared in an 84% yield from guanidine and cyanogen bromide-^{15}N (^{15}N abundance, 5.0 atom %) in DMF.



$$2H_2N\text{–}\underset{\underset{\textstyle NH_2}{|}}{C}=NH + Br\text{–}C\equiv{}^{15}N \longrightarrow$$

$$H_2N\text{–}\underset{\underset{\textstyle NH_2}{|}}{C}=N\text{–}C\equiv{}^{15}N + H_2N\text{–}\underset{\underset{\textstyle NH_2}{|}}{C}=NH\cdot HBr$$

Also, **1** enriched at all the nitrogen atoms with ^{15}N was prepared in order to supply a sample to ^{15}N FT-NMR spectroscopy. After cyanamide-^{15}N prepared from cyanogen bromide and ammonia-^{15}N (^{15}N abundance, 10.3 atom %) was dissolved in dilute hydrochloric acid to disperse completely ^{15}N to the two nitrogen atoms by the formation of a carbodiimido form,[7] it was dimerized in an alkaline solution.[8] Yields of cyanamide and cyanoguanidine were 100 and 85%, respectively.

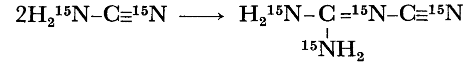
---

* Part 105: T. Fuchigami and K. Odo, *Bull. Chem. Soc, Jpn.*, **49**, 3607 (1976).

** Present address: Nippon (Japan) Carbide Industries Inc., Uozu, Toyama.

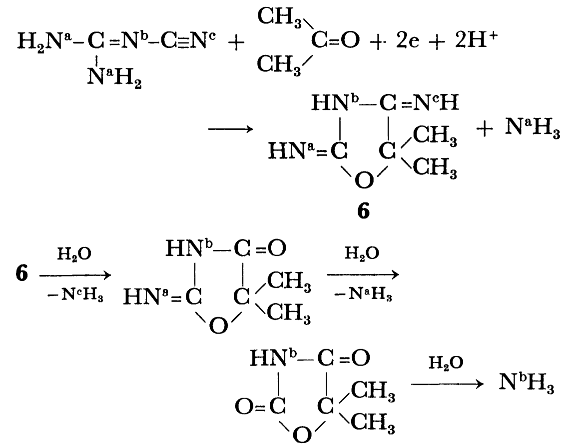
$$\mathrm{Br{-}C{\equiv}N} + 2\,{}^{15}\mathrm{NH_3} \longrightarrow \mathrm{H_2{}^{15}N{-}C{\equiv}N} + {}^{15}\mathrm{NH_4Br}$$

$$\mathrm{H_2{}^{15}N{-}C{\equiv}N} \xrightarrow{\mathrm{H^+}} [\mathrm{H_2{}^{15}N^+{=}C{=}NH} \longleftrightarrow \mathrm{H^{15}N{=}C{=}\overset{+}{N}H_2}] \xrightarrow{-\mathrm{H^+}} \mathrm{H_2{}^{15}N{-}C{\equiv}{}^{15}N}$$

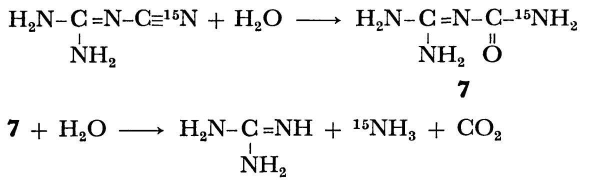


$$2\mathrm{H_2{}^{15}N{-}C{\equiv}{}^{15}N} \longrightarrow \mathrm{H_2{}^{15}N{-}\underset{{}^{15}NH_2}{C}{=}{}^{15}N{-}C{\equiv}{}^{15}N}$$

The labeled position was confirmed by the measurement of ^{15}N abundance of ammonia generated in the hydrolytic decomposition of 2,4-diimino-5,5-dimethyl-1,3-oxazolidine (**6**), which was formed by the electrolytic reduction of a mixture of labeled cyanoguanidine and acetone.[1,9]



The labeled position in 1-cyano-^{15}N-guanidine was further confirmed by the following procedure. Cyanoguanidine was converted into carbamoylguanidine (**7**) by reflux in dilute hydrochloric acid and then **7** was hydrolyzed to give guanidine and ammonia (yield, 93%) in a hot aqueous sodium hydroxide solution.[10] The guanidine was also decomposed quantitatively to ammonia by the Kjeldahl method.



$$\mathrm{H_2N{-}\underset{NH_2}{C}{=}N{-}C{\equiv}{}^{15}N} + \mathrm{H_2O} \longrightarrow \mathrm{H_2N{-}\underset{NH_2}{C}{=}N{-}\underset{O}{\overset{}{C}}{-}{}^{15}NH_2}$$

7

$$\mathbf{7} + \mathrm{H_2O} \longrightarrow \mathrm{H_2N{-}\underset{NH_2}{C}{=}NH} + {}^{15}\mathrm{NH_3} + \mathrm{CO_2}$$

As shown in Table 1, ^{15}N abundances in the samples of ammonia agreed with the calculated values.

^{15}N FT-NMR spectra of the enriched cyanoguanidine were measured in DMF to obtain some preliminary data. These exhibited three resonance peaks under the condition of proton decoupling at a long pulse interval (180 s). The peak at a lower magnetic field split into a triplet set in non-decoupling, while the peaks at a higher magnetic field did not split. In the measurement using a shorter pulse interval (1 s), no signal was observed at such a higher magnetic field even when accumulated ten thousand times. The peak at the lower magnetic field was also assigned to N^a by a spectrum of 1-cyanoguanidine-2,3-^{15}N$_2$.[1] These facts suggest that the two N^a nitrogen atoms are also magnetically equivalent to each other. The singlet peaks at the higher magnetic field would be assigned to N^b and N^c with no hydrogen atom. Some ambiguities in the assignment might be taken away by measuring spectra of labeled cyanoguanidines other than 1-cyanoguanidine-2,3-^{15}N$_2$, but those were not measured in this work because an extremely long time would be required for measurement. Some spectra are schematically shown in Fig. 1.

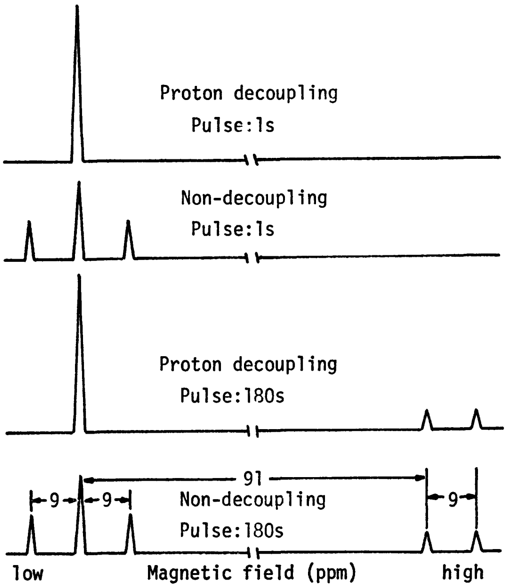


Fig. 1. Schematic ^{15}N FT-NMR spectra of enriched cyanoguanidine.

Experimental

Heavy Nitrogen Reagents. Ammonium chloride-^{15}N(^{15}N abundance, 10.3 atom %) and potassium cyanide-^{15}N(^{15}N abundance, 98.0 atom %) were supplied from the Japan Iso-

Table 1. Confirmation of labeled position

Method	^{15}N Abundance, atom %								
	1-Cyanoguanidine-1-^{15}N			1-Cyano(-^{15}N)guanidine			Enriched cyanoguanidine		
	N^a	N^b	N^c	N^a	N^b	N^c	N^a	N^b	N^c
Calculation[1]	0.7	2.7	0.7	0.7	0.7	5.0	5.5	5.5	5.5
Measurement[2]	0.8	2.5	0.8	0.7	0.7	5.0	5.6	5.5	5.7
Measurement[3]	—	—	—	0.9[4]		4.7	5.3[4]		5.4

[1]: 0.7 atom % of the natural abundance of ^{15}N is counted in.
[2]: The decomposition of 2,4-diimino-5,5-dimethyloxazolidine (**6**).
[3]: The direct decomposition of cyanoguanidine.
[4]: A mixture of N^{a}H$_3$ and N^{b}H$_3$.

tope Association.

Preparation of Labeled Cyanoguanidines. 1-Cyanoguanidine-1-^{15}N: A solution of potassium cyanide-^{15}N(^{15}N abundance, 2.7 atom %, 11 g, 0.17 mol) in water (24 ml) was slowly added to an ice-cooled mixture of 27 g (0.17 mol) of bromine and 27 ml of water. Wet cyanogen bromide-^{15}N was first distilled from the reaction mixture, then redistilled after being dried with anhydrous calcium chloride: bp 60—62 °C; yield, 72%.

Into 21 ml of toluene containing small amounts of ethanol and hydrogen chloride as catalysts was dissolved 10.4 g (0.11 mol) of 1,2-ethanedithiol, and 10.9 g (0.10 mol) of cyanogen bromide-^{15}N in 50 ml of toluene was added dropwise into the solution. After three hours, 20.5 g of the hydrobromide of 2-imino-1,3-dithiolane-^{15}N (**2**) were crystallized out of the reaction mixture: mp 183—187 °C, dec.; yield, 98%. The hydrobromide was converted into the free base by sodium hydrogencarbonate in a mixture of ether and water as a suspension: yield, 86%; mp 64—65 °C (lit[2]) 63.8—64.8 °C); and *m/e* 119 (M$^+$).

To an acetone solution containing 5.0 g (0.047 mol) of ordinary cyanogen bromide was added a solution of **2** (10.3 g, 0.087 mol) in acetone, dropwise. The hydrobromide of **2** was filtered off, then the solvent was evaporated to leave 4.5 g (yield, 80%) of 2-[(cyano)imino-^{15}N]-1,3-dithiolane (**3**) as a residue: mp 79—81 °C (an authentic sample,[4]) 79—81 °C).

Concentrated ammonia water containing 3.5 g (0.024 mol) of **3** and 8.2 g (0.048 mol) of silver nitrate was heated in a sealed tube at 100 °C for 3 h. After cooling, the resultant precipitate was filtered off and the mother liquor was concentrated to dryness. Extraction of the solids with acetone gave 0.95 g of the ammonium salt of dicyanoamine-^{15}N (**4**): yield, 47%.

The ammonium salt was then heated in 1-butanol under reflux for 20 h. The solvent was evaporated to dryness and the residue was extracted with warm ethanol. Concentration of the extract afforded 0.49 g (yield, 49%) of 1-cyanoguanidine-1-^{15}N.

1-Cyano-^{15}N-guanidine: A mixture of 12.5 g (0.21 mol) of guanidine and 11.2 g (0.11 mol) of cyanogen bromide-^{15}N (^{15}N abundance, 5.0 atom %) in 50 ml of DMF was stirred at 5 °C for 2 h. After evaporation of the solvent under reduced pressure and treatment of the residue with a small amount of water, 3.5 g of the titled compound were left as an insoluble part: yield, 84%.

Enriched Cyanoguanidine: Ammonia generated from 13.9 g (0.26 mol) of ammonium chloride-^{15}N (^{15}N abundance, 10.3 atom %) was introduced into an ethereal solution of 14.2 g (0.13 mol) of cyanogen bromide with a nitrogen stream. Ammonium bromide was filtered off and ether was evaporated to dryness. Cyanamide-^{15}N (4.1 g) was left as a residue in 76% yield.

The above cyanamide was dissolved in 30 ml of water containing several drops of concentrated hydrochloric acid, and then the pH of the solution was adjusted to 8.5 with sodium hydroxide. After a few days, the solution was concentrated to 10 ml and 3.5 g (yield, 85%) of the titled compound was collected on a filter paper.

Confirmation of Labeled Position. Procedures for the preparation of **6**, its hydrolysis, and the determination of ^{15}N abundance were similar to those reported in the previous works.[1,9])

Decomposition of 1-Cyano-^{15}N-guanidine: A mixture of 0.42 g (0.005 mol) of cyanoguanidine in 6.7 ml of 1.5 M hydrochloric acid was heated at 100 °C for 2 h, then 6.7 ml of 1.5 M sodium hydroxide was added to the solution. The ammonia thus generated was introduced into dilute hydrochloric acid with a nitrogen stream, giving 0.25 g of ammonium chloride in 93% yield. On the other hand, the above solution was acidified with hydrochloric acid again, then the solvent was evaporated to dryness. Extraction of the residue with ethanol gave 0.47 g of guanidine hydrochloride (yield, 98%). The guanidine was strongly heated with sulfuric acid and potassium and copper(II) sulfates in a Kjeldahl flask to decompose completely to ammonia.

The authors wish to thank Dr. M. Itagaki, JEOL Ltd., for the measurement of the ^{15}N FT-NMR spectra and also for his many helpful discussions on the spectra.

References

1) T. Nonaka, A. Omura, T. Fuchigami, and K. Odo, *Denki Kagaku*, **45**, 111 (1977).

2) R. W. Addor, *J. Org. Chem.*, **24**, 738 (1964).

3) W. W. Hartman and E. E. Dreger, *Org. Synth.*, Coll. Vol. II, 150 (1943).

4) R. J. Timmons and L. S. Wittenbrook, *J. Org. Chem.*, **32**, 1566 (1967).

5) K. Kubo, T. Nonaka, and K. Odo, *Bull. Chem. Soc. Jpn.*, **49**, 1339 (1976).

6) F. E. King, R. M. Acheson, and P. C. Spensly, *J. Chem. Soc.*, **1948**, 1336.

7) K. Bloch and R. Schoeneimer, *J. Biol. Chem.*, **138**, 167 (1941); and A. Bendich, J. F. Tinker, and G. B. Brown, *J. Am. Chem. Soc.*, **70**, 3109 (1948).

8) J. L. Osborn, U. S. Pat., 2416542 (1947); *Chem. Abstr.*, **41**, 3120 (1947).

9) T. Nonaka and K. Odo, *Denki Kagaku*, **40**, 66 (1972).

10) K. Sugino and M. Yamashita, *Kogyo Kagaku Zasshi*, **45**, 1 (1942).