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The Reaction of *N″*-Cyanoguanidine with Formaldehyde. IV. The Formation Pathway of 4-Cyanoimino-3-(methoxymethyl)perhydro-1,3,5-oxadiazine

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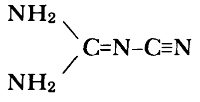
Synopsis. An investigation of reactions involving *N″*-cyanoguanidine (CG) and its methyl derivatives with formaldehyde as well as the consideration of the molecular structures of CG and 4-cyanoimino-3-(methoxymethyl)-perhydro-1,3,5-oxadiazine elucidated the formation pathway of the latter compound from CG: CG → *N*-hydroxymethyl-*N″*-cyanoguanidine → *N,N′*-bis(hydroxymethyl)-*N″*-cyanoguanidine → 4-(cyanoimino)perhydro-1,3,5-oxadiazine → 4-cyanoimino-3-(hydroxymethyl)perhydro-1,3,5-oxadiazine → 4-cyanoimino-3-(methoxymethyl)perhydro-1,3,5-oxadiazine.

The maximum number of formaldehyde molecules added to *N″*-cyanoguanidine (CG) can be anticipated to be 4 by analogy with urea, which has an analogous structure to that of CG, and is allowed to react with formaldehyde into 3,5-bis(methoxymethyl)perhydro-1,3,5-oxadiazin-4-one (**1**), tetrakis-substituted urea.[1-3] However, the exhaustive hydroxymethylation of CG with a large excess of formaldehyde provided no tetrakis-substituted CG but, rather, 4-cyanoimino-3-(methoxymethyl)perhydro-1,3,5-oxadiazine (**8**) as the major product.[4]

In our present report we wish to elucidate the reasons why the maximum number of formaldehyde molecules added to CG is not 4, but 3, and to propose a formation pathway for **8**.

Results and Discussion

Two possible molecular structures of CG (**I** and **II**) had previously been proposed.[5-6] A study[7] concerning the IR spectrum of CG suggested that structure **I** is more appropriate than structure **II**. Furthermore, our results concerning the ^{1}H NMR spectrum of CG have revealed that the structure CG is **I** over a wide pH range, including 7—10, since only one signal of the amino proton (δ=6.57 (s, 4H)) was observed. These facts exclude the possibility that the maximum number of formaldehyde molecules may be determined by three hydrogen atoms in the amino and imino groups in the structure of **II**.

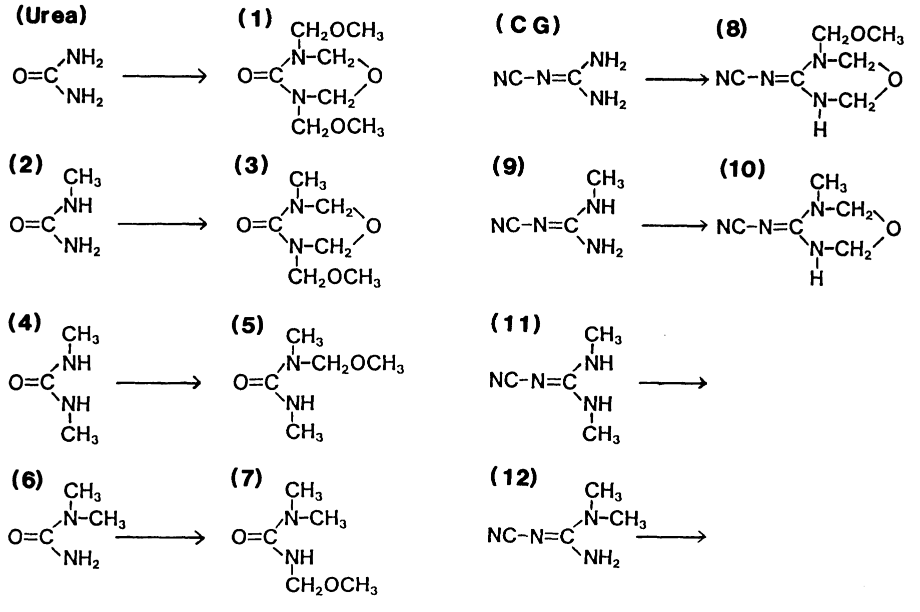


(**I**)

$$\overset{\textstyle NH}{\overset{\|}{NH_2\text{-}C}}\text{-}NH\text{-}C{\equiv}N$$

(**II**)

In a previous report,[3] we proposed a new formation pathway of **1** which was derived from urea and formaldehyde via tris(hydroxymethyl)urea and 3-(hydroxymethyl)perhydro-1,3,5-oxadiazin-4-one. The oxadiazine-ring formation may be a rate-determining



Scheme 1. The reactions of urea or *N″*-cyanoguanidine and its methyl derivatives with formaldehyde. Major products from the reactions of urea or *N″*-cyanoguanidine and its methyl derivatives with formaldehyde are shown and blank spaces represent that starting materials were recovered unchanged.

step in this formation, probably because the steric hindrance of the hydroxymethyl groups interferes with the addition of a fourth formaldehyde molecule to tris(hydroxymethyl)urea.

In order to examine the difference in the reactions of CG with formaldehyde and of urea with formaldehyde, CG and its methyl derivatives were allowed to react with a large excess of formaldehyde. The hydroxymethylated products were etherified by MeOH in order to isolate them. The major products from urea or CG and its methyl derivatives with formaldehyde are shown in Scheme 1 together with their reaction equations. Although the maximum number of formaldehyde molecules added to urea was 4, only one formaldehyde molecule was added to *N*,*N*′- or *N*,*N*-dimethylurea (**4** and **6**) into *N*-methoxymethyl-*N*,*N*′- or *N*-methoxymethyl-*N*′,*N*′-dimethylurea (**5** and **7**). On the other hand, 3-methoxymethyl-5-methylperhydro-1,3,5-oxadiazin-4-one (**3**) was produced from methylurea (**2**) and formaldehyde. These results could be explained by the importance of a steric hindrance; a decrease in the steric hindrance enabled a further addition of formaldehyde molecule to the fourth hydrogen atom in the amino groups.

The reactivity of CG can be understood in terms of a steric hindrance of the cyanoimino group and of a difference in the electron-attracting nature between =O (in urea) and =N–C≡N (in CG). The latter reason may explain why **11** could not react with formaldehyde. However, it may also be explicable in terms of the former reason, since the cyanoimino group in **11** may restrict the movement of the methyl group in the proximal methylamino group; thus, this methyl group may interfere with the addition of a formaldehyde molecule to the other methylamino group. Figure 1 shows the molecular structures of urea, CG and **8**. Four atoms (one oxygen, one carbon, and two nitrogen atoms) in urea lie on the same plane. Each of the six atoms (two carbon and four nitrogen atoms) in CG and **8** lie nearly on the same plane, respectively. The cyanoimino group is located unequivalently in the two amino groups in CG in the crystalline state while the two amino groups in urea are equivalent. The double-bond character of C(1)–N(2), N(2)–C(2), C(2)–N(3), and C(2)–N(4) in CG and **8** can be calculated by using the theoretical single- and double-bond lengths reported by Schomaker and Stevenson[10]: 85, 50, 45, and 59% in CG, and 73, 67, 56, and 60% in **8**, respectively. Therefore, the planary structure of CG can be expected to remain while in solution. Thus, the two amino groups in CG are not equivalent to the addition of a formaldehyde molecule, because of a steric hindrance of the cyanoimino group. This steric

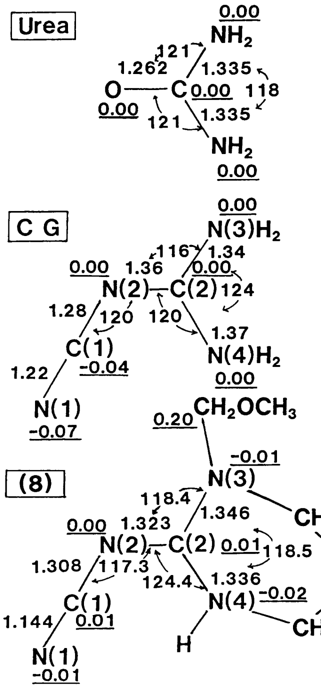
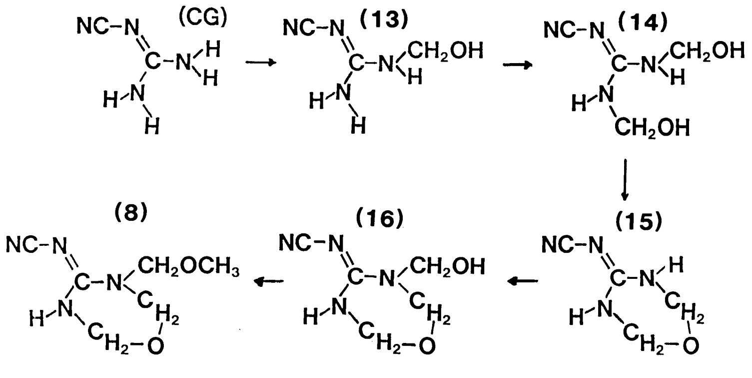


Fig. 1. The molecular structures of urea, *N*″-cyanoguanidine (CG), and 4-cyanoimino-3-(methoxymethyl)perhydro-1,3,5-oxadiazine (**8**) with the selected numbering scheme. Underscored numbers are the heights of Å of the atoms above or below the planes which are composed of four atoms in urea, four atoms (guanidine moiety) in CG and six atoms (*N*″-cyanoguanidine moiety) in **8**, respectively. The signs of ← → represent bond angles and other small numbers represent bond lengths in Å. These data were cited from Vaughan and Donohue's (urea),[8] Hughes' (CG),[6] and our report (**8**).[9]



Scheme 2. Proposed formation pathway of 4-cyanoimino-3-(methoxymethyl)perhydro-1,3,5-oxadiazine (**8**).

hindrance is supported by the assembly of the CPK model for CG.

We wish to propose a formation pathway of **8**, shown in Scheme 2. The first addition of a formaldehyde molecule occurs on the most remote hydrogen atom from the cyanoimino group, producing *N*-hydroxymethyl-*N*″-cyanoguanidine (**13**); the second addition of a formaldehyde molecule on the hydrogen atom in a different amino group produces *N*,*N*′-bis(hydroxymethyl)-*N*″-cyanoguanidine (**14**). The two hydroxymethyl groups condense into an oxadiazine ring by eliminating water to produce 4-(cyanoimino)-perhydro-1,3,5-oxadiazine (**15**); a decrease in the steric hindrance of the hydroxymethyl groups enables a third addition of a formaldehyde molecule on the remote hydrogen atom from the cyanoimino group to produce 4-cyanoimino-3-(methoxymethyl)perhydro-1,3,5-oxadiazine (**16**). Thus, **8** is derived from **16** and MeOH.

Experimental

The Reaction of CG and Its Methyl Derivatives with Formaldehyde. According to the published procedure,[4] **8** was prepared from CG and a large excess of formaldehyde. *N*-Methyl-*N*″-cyanoguanidine (**9**) and *N*,*N*′- and *N*,*N*-dimethyl-*N*″-cyanoguanidine (**11** and **12**) were prepared from a mixture of ammonia or methylamine with *N*-cyano-*N*′-methyl-*O*-ethylisourea or *N*-cyano-*N*′,*N*′-dimethyl-*O*-ethylisourea,[11] which was prepared from cyanamide according to a virtually identical procedure described by Suyama and Odo.[12] The methyl derivatives of CG and a large excess of formaldehyde (the feed mole ratio of **9**, **11**, or **12**/formaldehyde=1/5) were mixed and the pH of the solution was adjusted to 9.0. The solution was stirred for 30 min at 95 °C. 4-Cyanoimino-3-methylperhydro-1,3,5-oxadiazine (**10**) was derived from **9** and formaldehyde. However, no products were obtained and the starting materials were recovered unchanged in the reaction of **11** or **12** with formaldehyde.

4-Cyanoimino-3-methylperhydro-1,3,5-oxadiazine (10): Yield: 42%: Mp 121—122 °C (decomp): Found: C, 42.57; H, 5.86; N, 39.82%: Calcd for $C_8H_8N_4O$: C, 42.85; H, 5.75; N, 39.98%: ^{1}H NMR (DMSO-d_6): δ=8.20 (s, 1H, -NH-), 4.79, 4.74 (s, 2H, $-CH_2-$), 2.81 (s, 3H, $-CH_3$).

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