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The Reaction of Cyanoguanidine with Formaldehyde. I. Hydroxymethylation and Methoxymethylation of Cyanoguanidine

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In order to examine the reactivity of cyanoguanidine (CG) with formaldehyde, CG was first hydroxymethylated, then methoxylated, and finally exhaustively hydroxymethylated with a large excess of formaldehyde. 4-Cyanoimino-3-methoxymethylperhydro-1,3,5-oxadiazine was isolated as a major reaction product of 1,3-bis(methoxymethyl)-2-cyanoguanidine with formaldehyde. This product is an adduct of 3 mol of formaldehyde per mole of CG and a six-membered cyclic ether. Minor products were further methoxylated and 3,5-bis(methoxymethyl)-4-methoxymethyl(carbamoylimino)perhydro-1,3,5-oxadiazine was isolated. This is an adduct of 2 mol of formaldehyde to the amidinated product derived from the major product by the hydration of the cyano group. The ring structure of perhydro-1,3,5-oxadiazine was so stable that it could not be decomposed under acidic conditions if the methoxymethyl groups were fully acid-hydrolyzed.

The resinous products of cyanoguanidine (CG) with formaldehyde are useful as sticking agents for dyes,$^{1)}$ modifiers for urea- and melamine–formaldehyde resins$^{2)}$ and commercial flocculants.$^{3)}$ CG is first hydroxymethylated with formaldehyde; this procedure is followed by the condensation and polymerization into CG–formaldehyde resin. The reaction mechanism and properties of CG have seldom been reported, in contrast to the abundant reports on urea- and melamine–formaldehyde resins.$^{4-7)}$

Hamada,$^{8)}$ Yamada,$^{9)}$ and Miyaoka and Matsui$^{10)}$ observed that the pH value of the reaction solution of CG with formaldehyde approached 8.5—9.0 from the initial value under acidic or alkaline conditions as the reaction proceeded. Under acidic conditions, a partial conversion of CG to amidinourea (AU), a basic compound, was confirmed by IR spectrometry. Under alkaline conditions, possible conversions of CG to cyanourea or urea and of formaldehyde to MeOH and formic acid have been speculated about, but the details of the reaction remained to be elucidated. Only two hydroxymethylated products, mono- and 1,3-bis-(hydroxymethyl)-2-cyanoguanidine (CG-1F and CG-2F), were isolated$^{8)}$ and other hydroxymethylated products were not obtained in the reaction of CG with formaldehyde. Therefore, the reactivity of CG with formaldehyde (the maximal number of the introduced hydroxymethyl groups to CG) has been estimated to be 2 or 3 at the most. However, it can be anticipated to be 4 by analogy with urea which has the analogous structure to CG and reacts with formaldehyde into tetrakis(hydroxymethyl)urea derivatives.

Furthermore, the maximal wavelength of the strong absorption band in the UV region ($\lambda_{\max}$) of hydroxymethylated products depends on the number of the introduced hydroxymethyl groups; their band positions shift to the longer wavelength side against the number of the hydroxymethyl groups in the reaction of melamine, melam, melem, ammelide or ammeline with formaldehyde.$^{11-12)}$ If a similar relationship occurs for hydroxymethylated CG, our observation on $\lambda_{\max}$ of CG, CG-1F, CF-2F, and products of CG with a large excess of formaldehyde suggests that the reactivity of CG is about 4. In order to examine this suggestion, CG was exhaustively hydroxymethylated.

Results and Discussion

1,3-Bis(methoxymethyl)-2-cyanoguanidine (CG-2M) was used as a starting material for the exhaustive hydroxymethylation of CG with formaldehyde, because the usual hydroxymethylation is always attended by the reverse reactions and fails to prepare tris- and tetrakis(hydroxymethyl)-2-cyanoguanidine and because hydroxymethylated CG polymerizes and CG converts to AU together with other unknown compounds under severe reaction conditions. CG-2M could be prepared from CG-2F and MeOH in good yield by the addition of a large excess of an acid catalyst at low temperatures while, at the boiling point of MeOH in the presence of a small amount of an acid, intermolecular condensates were largely produced and CG-2M was poorly prepared. CG-2M was assigned by the elemental analysis and the appearance of ^{1}H-NMR signal of the methyl proton (δ=3.20) and the disappearance of the signal of the hydroxyl proton (δ=5.72 in CG-2F).

1-Methoxymethyl-2-cyanoguanidine (CG-1M) was obtained from CG-1F and MeOH and assigned in a similar way.

CG-2M was further hydroxymethylated in the presence of excess formaldehyde. The major product was assigned as 4-cyanoimino-3-methoxymethylperhydro-1,3,5-oxadiazine (CG-1Mcyc2F), a six-membered cyclic ether, by the elemental analysis, FD-MS and ^{1}H-NMR spectrometry. The X-ray diffraction data which will be reported elsewhere also confirmed this assignment. The $\lambda_{\max}$ of this product was plotted on the extrapolation of the linear $\lambda_{\max}$ *versus* the number of hydroxymethyl and/or methoxymethyl groups of CG, CG-1F, CG-1M, CG-2F, and CG-2M. Figure 1 shows that this contains three hydroxymethyl and/or methoxymethyl groups. This was probably derived by the intramolecular elimination of MeOH between the hydroxymethyl group which was introduced to one of two imino groups in CG-2M and the methoxymethyl group in the other imino group because the newly introduced hydroxymethyl group was labile and stabilized by the cyclization. This was an adduct of 3 mol of formaldehyde per mole of CG and showed that the reactivity of CG is 3 at least.

Then, in order to prepare 1,3-bis(hydroxymethyl)-1,3-bis(methoxymethyl)-2-cyanoguanidine (CG-2F2M) or 4-cyanoimino-3,5-bis(methoxymethyl)perhydro-1,3,5-oxadiazine (CG-2Mcyc2F), CG-2M was treated with formaldehyde under various conditions. Under mild conditions, no hydroxymethyl group was introduced into CG-2M. Under severe conditions, condensated polymers were mainly produced. The value of λ_{max} (232 nm) of the solution containing these products as shown in Fig. 1 suggested the possible production of CG-2F2M and/or CG-2Mcyc2F but none of them could be isolated.

CG-1Mcyc2F was also prepared from CG-1M and formaldehyde in a comparable yield with that from CG-2M and formaldehyde (scheme 1). In this preparation, two molecules of formaldehyde were added, one by one, to the free amino group and then to the imino group which had a methoxymethyl group. The dehydration from two of the hydroxymethyl groups selectively occurred and the MeOH elimination from one hydroxymethyl and one methoxymethyl group did not, because 4-cyanoimino-3-hydroxymethylperhydro-1,3,5-oxadiazine (CG-1Fcyc2F) could not be obtained.

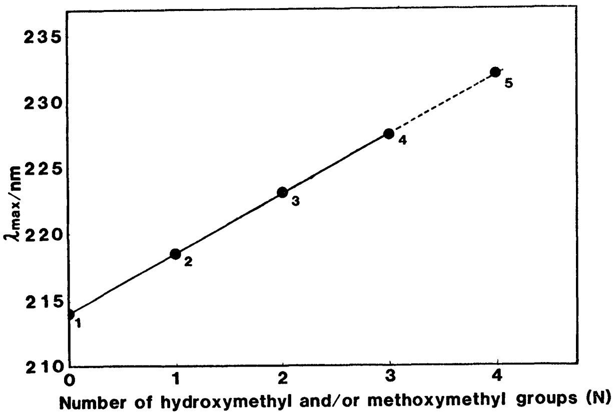
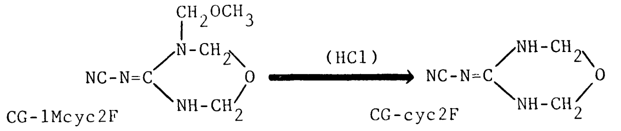


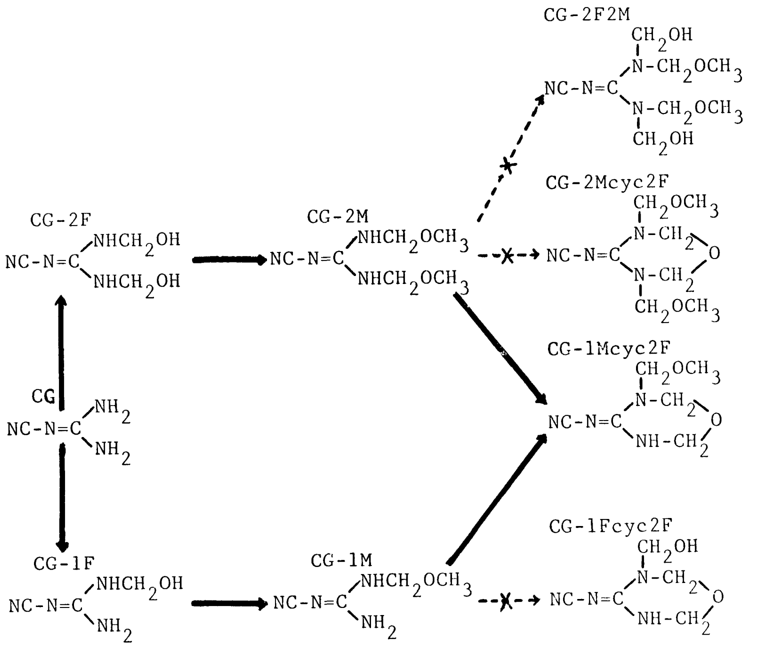
Fig. 1. Relationship of the maximal wavelength of absorption bands in UV region (λ_{max}) of CG, hydroxymethylated CG and methoxymethylated CG with the number (N) of hydroxymethyl and/or methoxymethyl groups.
1; CG, 2; CG-1F or CG-1M, 3; CG-2F or CG-2M, 4; CG-1Mcyc2F, 5; pasty products of CG-2M with a large excess of formaldehyde at 85—90 °C for 20 min.

4-Cyanoimino-3-ethoxymethylperhydro-1,3,5-oxadiazine (CG-1Ecyc2F) was prepared from 1-ethoxymethyl-2-cyanoguanidine (CG-1E) and formaldehyde in a 76% yield and condensated polymers and by-products were minimized. In the reaction of 1-alkoxymethyl-2-cyanoguanidine (CG-1M or CG-1E) with formaldehyde, the ring formation by the dehydration was a major reaction and preceded the intermolecular condensation, while in the reaction of hydroxymethylated CG which was not alkoxylated, this condensation preceded the ring formation.



As 4-(cyanoimino)perhydro-1,3,5-oxadiazine (CG-cyc2F) could be obtained from CG-1Mcyc2F by acid-hydrolysis, the six-membered cyclic structure was so stable that it remained undecomposed but the methoxymethyl group was fully acid-hydrolyzed into formaldehyde, whose quantity was determined colorimetrically to be in agreement with the calculated amount.

After removal of the major reaction product of CG-2M with formaldehyde, the minor products were further treated with MeOH under acidic conditions. The isolated product lost the absorption band at 2140—2180 cm^{-1} in IR spectrum which is characteristic of

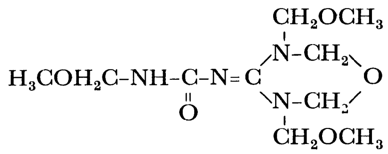


Scheme 1.

Table 1. ^{13}C-NMR spectra of CG and related compounds

	$-\underline{C}N$	$=N-\underline{C}O-N=$	$-N=\underline{C}\langle^{N=}_{N=}$
CG	118.3	—	163.1
Urea	—	159.7	—
AU	—	160.3	164.7
CG-1Mcyc2F	116.7	—	156.5
Hydrated product	—	155.3	163.6

the stretching vibration of –CN. The results in the ^{13}C-NMR spectrum shown in Table 1 suggest that this product has the structure of =N–CO–N= derived by the hydration of the cyano group of CG-1Mcyc2F and that the hydrated CG-1Mcyc2F is one of the minor products of CG-2M with formaldehyde. The λ_{max} of this product was 238 nm, which deviated to the wavelengths longer than the extrapolated value in Fig. 1 probably because of the structural conversion of CG itself to AU. This product had three easily acid-hydrolyzed methoxymethyl groups, whose presence was ascertained by the colorimetric determination of formaldehyde released. The following two structures were considered for this hydrated product. The structure of **1**, 3,5-bis(methoxymethyl)-4-methoxymethyl(carbamoylimino)perhydro-1,3,5-oxadiazine (AU-3Mcyc2F) is thought more feasible than **2** from the ^{13}C-NMR and ^{1}H-NMR spectra using a shift reagent.



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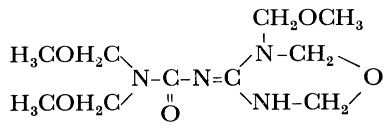

2

Two molecules of formaldehyde were added to the newly formed amino group and to the imino group in the ring, one by one, to form AU-3Mcyc2F. However, it remained obscure how the hydrogen of the imino group in the ring could be substituted for by the hydroxymethyl group in the presence of the cyano group which had not been hydrated.

The reaction mechanisms and characteristics of CG-1Mcyc2F and AU-3Mcyc2F are under investigation and will be reported elsewhere.

Experimental

NMR spectra of reaction products in DMSO-d_6 were obtained at 90 MHz on a JOEL FX-90Q instrument using TMS as an internal standard.

1,3-Bis(methoxymethyl)-2-cyanoguanidine (CG-2M). Keeping the temperature of the solution at 14—15 °C by using an ice bath, 5 ml of concentrated HCl was added dropwise with stirring to 2 g of CG-2F which was prepared according to the procedure of Hamada[8)] in 50 ml of MeOH. After 15 min, the reaction solution was neutralized with 20% NaOH solution to the endpoint of phenolphthalein and evaporated to dryness under reduced pressure at low temperatures. A product, CG-2M, was recrystallized from EtOH as columnar crystals. (yield in crude; *ca.* 70%): mp 121.5—122.2 °C: Found: C, 41.75; H, 7.05; N, 32.15%: Calcd for $C_6H_{12}N_4O_2$, C, 41.86; H, 6.98; N, 32.56%: ^{1}H-NMR(DMSO-d_6): δ=3.20 (6H, s, $-C\underline{H}_3$), 4.53 (4H, d, J=6 Hz, $-C\underline{H}_2OCH_3$), 8.04 (2H, t, J=6 Hz, $-N\underline{H}-$).

CG-1M was prepared from CG-1F and MeOH in a similar way as CG-2M (yield in crude; *ca.* 70%): mp 121.5—122.2 °C: Found: C, 37.38; H, 6.41; N, 43.54%: Calcd for $C_4H_8N_4O$, C, 37.49; H, 6.29; N, 43.73%: ^{1}H-NMR (DMSO-d_6): δ=3.09 (3H, s, $-C\underline{H}_3$), 4.47 (2H, d, J=6 Hz, $-C\underline{H}_2OCH_3$), 6.99 (2H, s, $-N\underline{H}_2$), 7.62 (1H, t, J=7 Hz, $-N\underline{H}-$).

4-Cyanoimino-3-methoxymethylperhydro-1,3,5-oxadiazine (CG-1Mcyc2F). Twenty-five ml of 37% formalin solution was added to 5 g of CG-2M (mole ratio of formaldehyde/CG-2M=10) and the pH of the solution was adjusted with 0.1 M NaOH solution to 8.8. After stirring for 10 min at 80 °C, the reaction mixture was cooled in an ice bath to stop the reaction and evaporated to dryness under reduced pressure at low temperatures. A large excess of acetone was added to the desiccated products. After the acetone-insoluble products were filtrated off, the acetone solution was concentrated to a viscous solution under reduced pressure; then a small amount of EtOH was added. On cooling, white powder was deposited (yield in crude; 51%). This was separated by filtration and recrystallized from 2-propanol to give plate crystals. Mp 113.8—114.0 °C: Found: C, 42.35; H, 5.88; N, 32.71%: Calcd for $C_6H_{10}N_4O_2$, C, 42.35; H, 5.88; N, 32.94%: ^{1}H-NMR(DMSO-d_6): δ=3.23 (3H, s, $-C\underline{H}_3$), 4.73, 4.81 (4H, s, $-C\underline{H}_2OC\underline{H}_2-$), 4.90 (2H, s, $-C\underline{H}_2OCH_3$), 8.47 (1H, t, J=4 Hz, –NH–): MS(FD): *m/e* 170 (M$^+$).

After removal of the major product, CG-1Mcyc2F, by filtration, the filtrate was concentrated to a viscous solution. A thin layer chromatogram of this viscous solution on silica gel (Merck F254) developed in 2-propanol showed three major spots under UV light. The isolation of these products by various solvents was, however, unsuccessful.

CG-1Mcyc2F was also prepared (yield in crude; 40%) from 5 g of CG-1M and 33 ml of 37% formalin solution (mole ratio of formaldehyde/CG-1M=10) in a way similar to the above.

The preparation conditions of 4-cyanoimino-3-ethoxymethylperhydro-1,3,5-oxadiazine (CG-1Ecyc2F) was virtually identical to that of CG-1Mcyc2F, but CG-1M was replaced with CG-1E. The yield of CG-1Ecyc2F was 76% in crude.

4-(Cyanoimino)perhydro-1,3,5-oxadiazine (CG-cyc2F). One g of CG-1Mcyc2F was dissolved in 50 ml of 0.1 M HCl and hydrolyzed at 80 °C for 20 min. The reaction mixture was neutralized and concentrated under reduced pressure. The resulting viscous solution was treated with EtOH and the deposited white crystals were recrystallized from dioxane. (yield in crude; 72%) mp 137.0—137.3 °C: Found: C, 38.12; H, 4.79; N, 44.31%: Calcd for $C_4H_6N_4O$, C, 38.09; H, 4.80; N, 44.42%: ^{1}H-NMR (DMSO-d_6): δ=4.73 (4H, s, $-C\underline{H}_2OC\underline{H}_2-$), 8.21 (2H, t, J=4 Hz, $-N\underline{H}-$): MS (70 eV): *m/e*(rel intensity) 126 (M$^+$, 67), 96 (100), 68 (88).

3,5-Bis(methoxymethyl)-4-methoxymethyl(carbamoylimino)perhydro-1,3,5-oxadiazine (AU-3Mcyc2F). To 5 g of the viscous solution described in the preparation of CG-1Mcyc2F, 100 ml of MeOH was added. The solution was chilled to below −10 °C by the use of Dry Ice and MeOH, then 5 ml of concentrated HCl was added and gradually allowed to warm to 10—12 °C. The reaction was carried out at 10—12 °C for 15 min. Keeping the temperature of the solution below −10 °C, the solution was neutralized with 20% NaOH solution. The solution was concentrated under reduced pressure at low temperatures. The resulting viscous solution was extracted with dioxane. Then, the dioxane soluble fraction was extracted with hexane three times. White crystals were obtained from hexane extracts (yield in crude; 12%). mp 58.0—58.6 °C: Found: C, 43.40; H, 7.27; N, 20.21%: Calcd for $C_{10}H_{20}N_4O_5$, C, 43.48; H, 7.25; N, 20.29%: ^{1}H-NMR(DMSO-d_6): δ=3.18 (6H, s, $-C\underline{H}_3$), 3.24 (3H, s, $-C\underline{H}_3$), 4.87 (4H, s, $-C\underline{H}_2OC\underline{H}_2-$), 4.93 (2H, s, $-C\underline{H}_2OCH_3$), 9.86 (1H, t, J=4 Hz, $-N\underline{H}-$): MS(FD): *m/e* 277 (MH^+).

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