The Formation Pathway of 3,5-Bis(methoxymethyl)perhydro-1,3,5-oxadiazin-4-one

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The investigation of the reactions of urea and its methyl derivatives with formaldehyde elucidated the formation pathway of 3,5-bis(methoxymethyl)perhydro-1,3,5-oxadiazin-4-one. 1) The addition of formaldehyde to urea became increasingly difficult according to the increase of the number of added formaldehyde molecules, probably because of the steric hindrance of the hydroxymethyl groups. 2) 3,5-Bis(methoxymethyl)perhydro-1,3,5-oxadiazin-4-one was concluded to be derived from urea via tris(hydroxymethyl)urea and 3-(hydroxymethyl)perhydro-1,3,5-oxadiazin-4-one but not via tetrakis(hydroxymethyl)urea or perhydro-1,3,5-oxadiazin-4-one.

Urea-formaldehyde resins have been commercially available as important adhesives in the wood industry because of their low cost. However, previous works on their chemical structure and reaction mechanisms are not necessarily adequate. The maximal number of formaldehyde molecules added to urea has been considered to be 4, because the formation of 3,5-bis(methoxymethyl)perhydro-1,3,5-oxadiazin-4-one (U-2Mcyc2F) has been reported.[1] Although there are several reports[1-4] on the preparations of tris- and tetrakis- substituted products from urea and formaldehyde, the basic problem of the formation pathway of U-2Mcyc2F remained uncertain. Until now, two different pathways for the formation of U-2Mcyc2F have been proposed. Kadowaki[1] proposed that U-2Mcyc2F was produced from urea and formaldehyde via tetrakis(hydroxymethyl)urea (U-4F). Alternatively, Takahashi[4] proposed the formation pathway via perhydro-1,3,5-oxadiazin-4-one (Ucyc2F). These proposals have remained hypothetical partly because of the uncertain confirmation of U-4F.

Ito[2] analyzed the reaction products from urea and a large excess of formaldehyde in the presence of a strong base at 50 °C by two-dimensional paper chromatography. He considered one of the spots to be U-4F. However, Tomita and Hirose[3] assigned it to U-2Mcyc2F by its ^{1}H NMR spectrum and published a negative report on the production of U-4F.

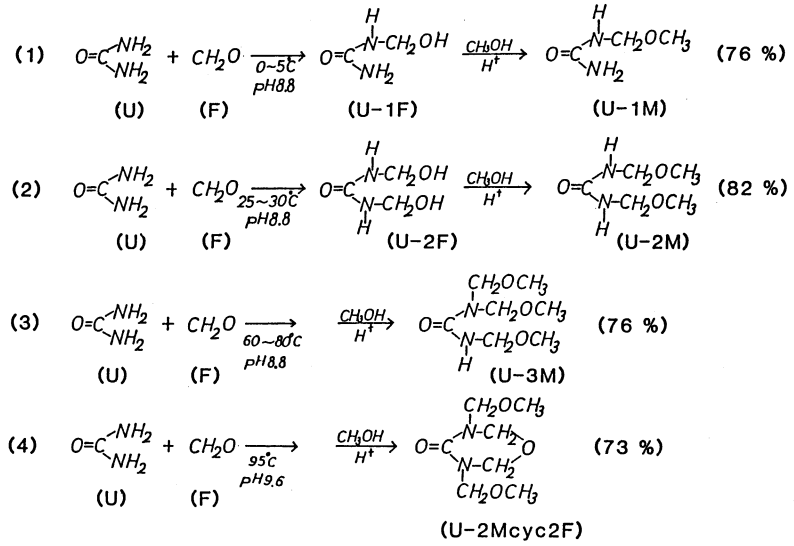
In order to obtain a clue for the elucidation of the formation pathway of U-2Mcyc2F, urea or its methyl derivatives were allowed to react with formaldehyde under various conditions. In our present report, we wish to propose a new formation pathway for U-2Mcyc2F.

Results snd Discussion

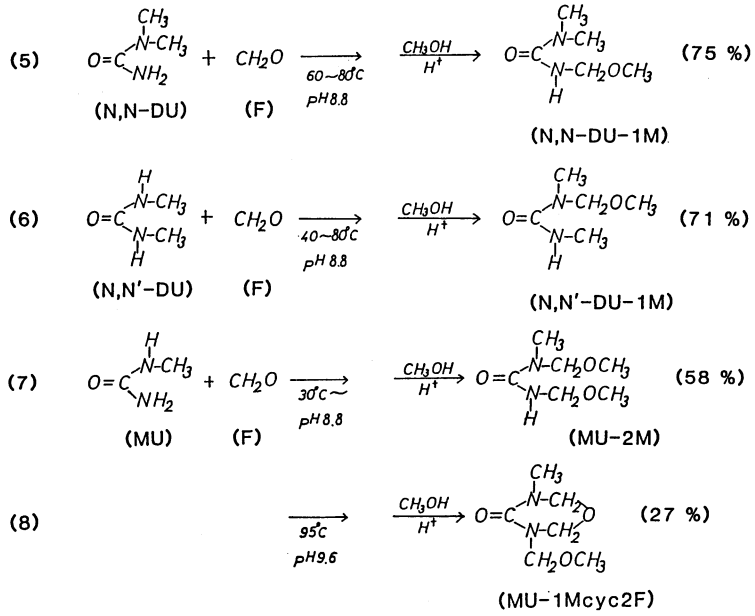
Several reports[5-8] on the selective preparation of mono- and bis(hydroxymethyl)urea (U-1F and U-2F) have been published. They suggested that the number of added formaldehyde molecules could be controlled by the feed ratio of urea/formaldehyde and the reaction temperature. U-1F and U-2F have been reported to be easily isolated from the reaction solution. However, tris(hydroxymethyl)urea (U-3F) and U-4F were difficult to isolate, probably because of their lability to heat, acids or bases. In order to isolate these products, all the hydroxymethylated products were converted to their methyl ethers under the optimal conditions described in the Experimental section. The methylation conditions used were such that the amount of HCl was 50—100 times greater than in the conventional method and the reaction temperature was lowered from 64—65 °C of the conventional method to 0—5 °C. Under these conditions, the condensation and acid hydrolysis of the hydroxymethylated products did not occur and the hydroxymethylated products were stoichiometrically converted to their methyl ethers.

The optimal preparation conditions of mono-, bis-, tris-, and tetrakis-substituted products from urea and formaldehyde are shown in Scheme 1 together with their reaction equations and their highest yields. Although Zigeuner[9] reported the production of the asym-type of U-2F as well as that of the sym-type, the amount of U-2F obtained was speculated not to contain the former from its ^{1}H NMR spectrum. The optimal temperatures were raised from 0—5 °C to 25—30, 60—80, and 95 °C with the increase of the number of added formaldehyde molecules, respectively. Furthermore, the preparation of tris(methoxymethyl)-urea (U-3M) or U-2Mcyc2F necessitated the large excess of formaldehyde in addition to high temperatures. In order to examine the production of tetrakis-(methoxymethyl)urea (U-4M), the products from urea and formaldehyde under appropriate reaction conditions between the optimal conditions for U-3M and U-2Mcyc2F were analyzed by gas-liquid chromatography, but no other products than U-3M and U-2Mcyc2F were detected.

These results suggest that the addition of formaldehyde to urea becomes increasingly difficult according to the increase of the number of added formaldehyde molecules. This is probably due to steric hindrance



Scheme 1.



Scheme 2.

by the hydroxymethyl groups. This speculation is supported by the fact that sym-U-2F is prepared more easily than asym-U-2F by a factor of about ten.[3] U-2Mcyc2F is speculated to be produced via another pathway than those proposed by Kadowaki[1] and Takahashi[4] because neither U-4M nor Ucyc2F was detected. From these facts, the formation pathway of U-2Mcyc2F is proposed as follows:

$$\text{Urea} \rightarrow \text{U-3F} \rightarrow \text{U-1Fcyc2F} \rightarrow \text{U-2Mcyc2F}$$

Under such strong alkaline conditions that the binding of the dimethylene ether may be formed.[10-11] The oxadiazine ring may feasibly be formed from the two hydroxymethyl groups in sym-position of U-3F and this ring formation may be a rate-limiting step in the formation of U-2Mcyc2F. This speculation is supported by the results of the reaction of methyl derivatives of urea with formaldehyde.

The optimal preparation conditions for methoxymethylated products from methylurea (MU), 1,1-dimethylurea (*N,N*-DU), and 1,3-dimethylurea (*N,N'*-DU) with formaldehyde are shown in Scheme 2 together with their reaction equations and their highest yields. By comparison of the optimal temperatures for the highest yields of MU → MU-2M, *N,N*-DU → *N,N*-DU-1M, and *N,N'*-DU → *N,N'*-DU-1M with those for urea → U-3M, it is seen that the nitrogen atoms in methyl derivatives of urea are equally or more easily attacked by $CH_2(OH)_2$ than those in urea itself because of the electron-donating nature of the

methyl group. Its electron-donating nature is partly compensated by its bulkiness. Although the optimal conditions of MU → MU-1Mcyc2F were closely identical with those of urea → U-2Mcyc2F, the yield of MU-1Mcyc2F was lower than that of U-2Mcyc2F. This may be explained by the probability of the formation of an oxadiazine ring.

Even in the reaction of *N,N*-DU or *N,N'*-DU with a large excess of formaldehyde at high temperatures under strong alkaline conditions, no 1,1-dimethyl-3,3-bis(methoxymethyl)urea or 1,3-dimethyl-1,3-bis(methoxymethyl)urea could be obtained. These results can be understood if two methyl groups and one hydroxymethyl group of 1,1-dimethyl-1-hydroxymethylurea or 1,3-dimethyl-1-hydroxymethylurea interfere with the further addition of formaldehyde and if they cannot form an oxadiazine ring. As an oxadiazine ring can be formed from two hydroxymethyl groups of 1-methyl-1,3-bis(hydroxymethyl)urea (MU-2F), MU-1Mcyc2F can be derived from MU-2F via 3-methyl-perhydro-1,3,5-oxadiazin-4-one.

Experimental

Preparation of Tris(methoxymethyl)urea (U-3M). Twelve grams of urea and 88.7 g of formalin were mixed and the pH of the mixture was maintained at 8.8 by the successive addition of a 0.1 M (1 M=1 mol dm^{-3}) NaOH solution. While the solution was stirred for 30 min, its temperature was kept at 65 °C. The reaction mixture was then evaporated to dryness under reduced pressure below 40 °C. The desiccated products were dissolved in 400 ml of MeOH. Keeping the temperature of the solution below −15 °C in a Dry Ice-MeOH bath, 5 ml of concd HCl was added dropwise to the solution. The solution was stirred for 10 min at 0—5 °C. After neutralization with 6 M NaOH solution and evaporation of MeOH, the methoxymethylated products were extracted with EtOH, then with dichloromethane, finally with diethyl ether. The solvent was distilled off. The resulting viscous solution was distilled at 1 Torr (1 Torr=133.322 Pa), and a distillate of 128—131 °C containing U-3M was collected (yield :76%). Found; C, 43.66; H, 8.45; N, 14.49%: Calcd for $C_7H_{16}N_2O_4$; C, 43.75; H, 8.33; N, 14.58%: ^{1}H NMR(DMSO-d_6): δ=7.34 (1H, t, J=6 Hz, -NH-), 4.69 (4H, s,-CH_2-), 4.49 (2H, d, J=6 Hz, -CH_2-), 3.21 (6H,s,-CH_3), and 3.17 (3H, s, -CH_3): ^{13}C NMR (DMSO-d_6): δ=162.43 (O=C<), 82.25, 77.70 (-CH_2-), and 59.98, 59.85 (-CH_3): MS(FD): m/z =192(M^+).

The by-products were U-2M and condensation polymers. With rise in the hydroxymethylation temperature above 65 °C, a decrease of U-2M and an increase of condensation polymers resulted and a trace amount of U-2Mcyc2F was produced.

Preparation of U-2Mcyc2F. U-2Mcyc2F was prepared by the virtually identical procedure described in the preparation of U-3M except for a reaction temperature of 95 °C with the pH of the reaction solution of 9.6. The resulting viscous solution was placed on an alumina column. U-2Mcyc2F was eluted with a hexane-dichloromethane (7:3) mixture (yield: 73%). Found; C, 44.14; H, 7.45; N, 14.60%: Calcd for $C_7H_{14}N_2O_4$; C, 44.21; H, 7.37; N, 14.74%: ^{1}H NMR($CDCl_3$): δ=4.93 (4H, s, -CH_2-), 4.79 (4H, s, -CH_2-) and 3.34 (6H, s, -CH_3): ^{13}C NMR($CDCl_3$): δ=152.25 (O=C<), 76.67, 74.34 (-CH_2-) and 54.24 (-CH_3): MS (FD): m/z= 190(M^+).

All of the remainder other than U-2Mcyc2F in the distillate was elucidated to be U-3M by gas-liquid chromatography on a column of PEG-20M (ϕ 3 mm×2 m) at 190 °C. However, its content was as low as 10%.

Without the successive addition of a 0.1 M NaOH solution, the pH of the reaction solution fell from 9.6 to 7.0—7.2 and the yield of U-2Mcyc2F decreased into 16% and those of U-3M and condensation polymers increased.

Preparation of 1,1-Dimethyl-3-methoxymethylurea (*N,N*-DU-1M). The pH of the reaction mixture of 17.6 g of 1,1-dimethylurea (*N,N*-DU) and 40.3 g of formalin was adjusted to 8.8. The solution was stirred for 30 min at 70 °C. The procedures of methoxymethylation and extraction were the same as described above. The resulting viscous solution was permitted to stand for at least 2—3 days. The deposited crystals were recrystallized from EtOH as white rod-like crystals (yield: 75%). Mp 54.0—55.0 °C: Found; C, 45.32; H, 9.14; N, 21.15%; Calcd for $C_5H_{12}N_2O_2$; C, 45.45; H, 9.09: N, 21.21%: ^{1}H NMR (DMSO-d_6): δ=7.26 (1H,t, J=6Hz, -NH-), 4.49 (2H, d, J=6Hz, -CH_2-), 3.15 (3H, s, -OCH_3), and 2.81 (6H, s, -CH_3): ^{13}C NMR (DMSO-d_6): δ=157.41 (O=C<), 72.49 (-CH_2-), 54.10 (-OCH_3), and 35.54 (-CH_3): MS (FD): m/z=132(M^+).

Preparation of 1,3-Dimethyl-1-methoxymethylurea (*N,N'*-DU-1M). A mixture of 17.6 g of 1,3-dimethylurea (*N,N'*-DU) and 40.3 g of formalin was stirred at 50 °C for 30 min while the pH of the solution was kept at 8.8. The methoxymethylation and extraction procedures were the same as descrived above. A distillate of 95—99 °C at 1 Torr was collected (yield: 71%). Found; C, 45.31; H, 9.14; N, 21.14%: Calcd for $C_5H_{12}N_2O_2$; C, 45.45; H, 9.09; N, 21.21%: ^{1}H NMR (DMSO-d_6): δ=6.43 (1H, m, -NH-), 4.60 (2H, s, -CH_2-), 3.14 (3H, s, -OCH_3), 2.82 (3H, s, -CH_3), and 2.58 (3H, d, J=4Hz, -CH_3), ^{13}C NMR (DMSO-d_6): δ=158.18 (O=C<), 79.15 (-CH_2-), 54.15 (-OCH_3), 33.10 (-CH_3), and 26.84 (-CH_3): MS (FD): m/z=132 (M^+).

Preparation of 1-Methyl-1,3-bis(methoxymethyl)urea (MU-2M). The mixture of 14.8 g of methylurea (MU) and 40.3 g of formalin (F/MU=5) was stirred at 50 °C for 30 min while the pH of the mixture was kept at 8.8. The methoxymethylation and extraction procedures were the same as described above. A distillate of 137—142 °C at 1 Torr was collected (yield: 58%). Found; C, 44.34; H, 8.75; N, 17.14%: Calcd for $C_6H_{14}N_2O_3$; C, 44.44; H, 8.64; N, 17.28%: ^{1}H NMR (DMSO-d_6): δ=6.36 (1H, m, -NH-), 4.63 (4H, s, -CH_2-), 3.20 (6H, s, -OCH_3), and 2.63 (3H, d, J=4Hz, -CH_3): ^{13}C NMR (DMSO -d_6): δ=157.45 (O=C<), 77.94 (-CH_2-), 54.37 (-OCH_3), and 26.85 (-CH_3): MS(FD): m/z=162 (M^+).

The optimal temperature in the preparation of MU-2M was above 30 °C, and over a broad range of temperature the major product from MU and formaldehyde was MU-2M.

Preparation of 3-Methyl-5-methoxymethyl-perhydro-1,3,5-oxadiazin-4-one (MU-1Mcyc2F) The mixture of 7.4 g of MU and 80.6 g of formalin (F/MU =10) was stirred at 95 °C for 30 min while the pH of the solution was kept at 9.6. The methoxymethylation and extraction procedures were the same as described above. The resulting viscous solution was placed on an alumina column and MU-1Mcyc2F was eluted with a hexane-dichloromethane (7 : 3) mixture

(yield: 27%). Found; C, 44.87; H, 7.61; N, 17.41%: Calcd for $C_6H_{12}N_2O_3$; C, 45.00; H 7.50; N, 17.50%: ^{1}H NMR (DMSO-d_6): δ=4.87, 4.78, 4.63 (2H, s, -CH_2-), 3.17 (3H, s, -OCH_3) and 2.74 (3H, s, -CH_3): ^{13}C NMR (DMSO-d_6): δ=153.09 (O=C$\lesssim$), 79.18, 77.56, 75.31 (-CH_2-), 54.62(-OCH_3), and 30.07 (-CH_3): MS(FD): m/z=160(M^+).

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