

The Preparation and the Crystal Structure of 1,3,5,7-Tetramethyltetrahydro-1,3,5,7-tetrazocine-2,6(1*H*,3*H*)-dione

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Synopsis. 1,3,5,7-Tetramethyltetrahydro-1,3,5,7-tetrazocine-2,6-(1*H*,3*H*)-dione was prepared in a good yield, and its crystal structure was determined by means of X-ray analysis. The molecule is centrometric. It has practically a planar structure except for four methyl groups and two methylene linkages and a hole of 0.5–1.6 Å in the interior of the ring structure.

Many investigators^{1–5)} have reported on the condensation products of urea and urea derivatives with formaldehyde since Tollens.⁶⁾ Although most of these products are soluble crystalline compounds, however, no report on their crystal structures has been published.

1,3,5,7-Tetramethyltetrahydro-1,3,5,7-tetrazocine-2,6-(1*H*,3*H*)-dione (tetramethyldimethylenediurea: TMDMU) was prepared as needle crystals by Kadowaki in 1936.⁷⁾ *N,N'*-Dimethylurea was hydroxymethylated with formalin in the presence of barium hydroxide. Without the isolation of the hydroxymethylated products, they were methylenized in MeOH and concd HCl using the procedure of Kadowaki.⁷⁾ The yield of TMDMU from *N,N'*-dimethylurea was found to be 13%. It was supposed to have an eight-membered ring structure.

In order to confirm the cyclic nature of this compound and to elucidate its structural characteristics, TMDMU was prepared in a good yield and its crystal structure was determined by means of X-ray analysis.

Experimental

Preparation of TMDMU. Ten grams of *N,N'*-dimethylurea and 23.5 g of formalin were mixed, and the pH of the reaction solution was adjusted to 8.8 by the successive addition of a 0.1M NaOH solution (1 M=1 mol dm⁻³). While its temperature was kept at 50 °C, the solution was stirred for 30 min. These hydroxymethylation conditions were milder than those adopted by Kadowaki.⁷⁾ The reaction mixture was then evaporated to dryness under reduced pressure at a low temperature. A large excess of MeOH was added to the desiccated products. Keeping the temperature of the solution at 0–5 °C by using an ice bath, the hydroxymethylated products were methoxymethylated in the presence of concd HCl. After 30 min, the reaction solution was neutralized with a 20% NaOH solution below –15 °C and then concentrated under reduced pressure. The resulting viscous solution was distilled at 1–2 Torr (1 Torr=133.322 Pa), and a distillate of 95–99 °C containing *N*-methoxymethyl-*N,N'*-dimethylurea was collected (71% yield). As an acid catalyst, 100 mg of *p*-toluenesulfonic acid was added to 5 g of *N*-methoxymethyl-*N,N'*-dimethylurea. The reaction mixture was heated in an oil bath at 110 °C for 30 min. On cooling, white crystals were deposited; they were subsequently recrystallized from EtOH. The yield of TMDMU from *N*-methoxymethyl-*N,N'*-dimethylurea was 86%. The overall yield of TMDMU from *N,N'*-dimethylurea was ca. 60%.

Possibly this good yield is due to the mild hydroxymethylation and the use of isolated *N*-methoxymethyl-*N,N'*-dimethylurea and *p*-toluenesulfonic acid. The use of concd HCl or sulfonic acid slightly decreased the yield of TMDMU and increased the amount of bis(*N,N'*-dimethylureido)-methane. TMDMU was identified by means of elemental analysis, FD-MS, and ¹H NMR spectrometry. Mp 258 °C: Found: C, 47.98; H, 8.14; N, 27.99%; ¹H NMR (DMSO-*d*₆): δ=2.99 (12H, s, –CH₃), 4.33 (4H, q, *J*_{ab}=15 Hz, –CH₂–): MS (FD): *m/z*=200 (*M*⁺).

X-Ray Analysis. A white crystal with dimensions of ca. 0.2×0.2×0.3 mm³ was used. The intensity data were measured on a Rigaku AFC-6S automated four-circle X-ray diffractometer, with graphite-monochromated Mo Kα radiation (λ=0.7107 Å), by means of the ω–2θ scan technique up to 2θ of 60° (scan speed=4° min⁻¹). The absence of systematic (0*k*0) reflections for *k*=2*n*+1 and (*h*0*l*) for *l*=2*n*+1 indicates that the space group is *P*2₁/*c*.

Crystal Data: C₈H₁₆N₄O₂, M.W.=200.24, monoclinic, space group *P*2₁/*c*: *a*=4.095(2), *b*=11.262(2), *c*=11.134(2) Å, β=103.68(4)°, *V*=498.9(5) Å³, *Z*=2, *D*_c=1.33 g·cm⁻³, μ(Mo Kα)=0.9 cm⁻¹. Among the 1462 reflections measured, 1119 reflections with |*F*_o|>3σ(|*F*_o|) were used for the structure determinations. The measured intensities were corrected for the Lorentz-polarization factors, but no absorption correction was applied. All the calculations were carried out on a HITAC M-680H computer at the Computer Center of The University of Tokyo, using the local version of UNICS.⁸⁾ All the scattering factors were taken from the International Tables for X-Ray Crystallography.⁹⁾ The structure of TMDMU was solved by the direct method and refined by the block-diagonal least-squares procedure to a final *R* value of 0.047. The final atomic parameters are listed in Table 1. The complete table of observed and calculated structure factors is kept as Document No. 8800 at the Editor of the Bulletin of the Chemical Society of Japan.

Table 1. Final Atomic Parameters (Positional ×10⁴, for H×10³) and Thermal Parameters (*B*_{eq} for non H×10, *B*_{iso} for H×10), with Their Estimated Standard Deviations in Parentheses

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> _{eq} (<i>B</i> _{iso})/Å ²
O	–1513(4)	2981(1)	2924(1)	37(1)
N ₁	814(4)	3533(1)	4910(1)	25(1)
N ₂	–1997(4)	4907(1)	3483(1)	25(1)
C ₁	–940(5)	3750(2)	3713(2)	24(1)
C ₂	201(5)	5871(2)	4073(2)	23(1)
C ₃	2332(6)	2358(2)	5153(2)	34(1)
C ₄	–4199(6)	5139(2)	2270(2)	32(1)
H ₂₁	256(6)	557(2)	436(2)	6(5)
H ₂₂	19(6)	646(2)	339(2)	17(6)
H ₃₁	362(7)	215(2)	456(2)	25(6)
H ₃₂	70(7)	179(2)	516(3)	25(6)
H ₃₃	394(4)	234(2)	595(2)	22(6)
H ₄₁	–513(7)	594(2)	223(2)	21(6)
H ₄₂	–618(6)	461(2)	215(2)	18(6)
H ₄₃	–308(6)	506(2)	165(2)	16(5)

Results and Discussion

A perspective drawing of the molecular structure of TMDMU is shown in Fig. 1. This figure is a view perpendicular to the plane which is composed of O, C₁, N₁, and N₂. The four atoms of O', C₁', N₁', and N₂' are placed on practically the same plane. The structure agrees with that deduced from the spectroscopic data. The selected interatomic distances and angles are given in Table 2. The observed interatomic distance for the carbonyl group in TMDMU (1.216 Å(C₁-O)) is in fair agreement with 1.207 Å (C=O),¹⁰ but differs from that of 1.262 Å in urea.¹¹ The C-N bonds of the

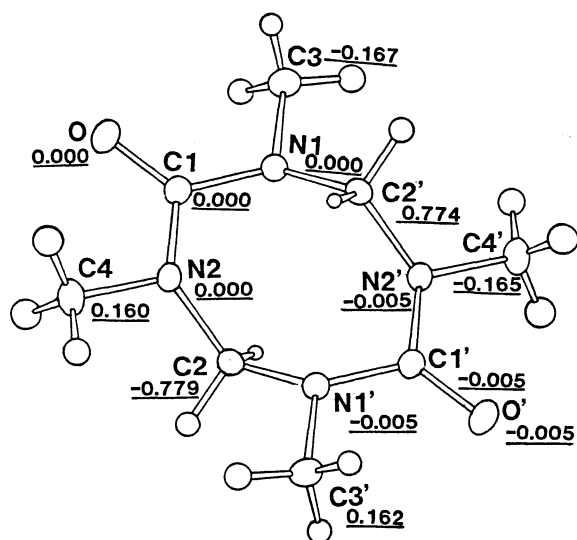


Fig. 1. The structure of 1,3,5,7-tetramethyltetrahydro-1,3,5,7-tetrazocine-2,6(1H,3H)-dione projected on the plane composed of O, C₁, N₁, and N₂. Underscored numbers are heights in Å of the atoms above or below the plane.

Table 2. Selected Interatomic Distances and Bond Angles for 1,3,5,7-Tetramethyltetrahydro-1,3,5,7-tetrazocine-2,6(1H,3H)-dione
N₁' is the nitrogen atom opposite to N₁.

Bond distance	<i>l</i> /Å	Bond angle	ϕ /°
O-C ₁	1.216(7)	C ₁ -N ₁ -C ₃	116.2(7)
N ₁ -C ₁	1.377(3)	C ₁ -N ₂ -C ₂	119.0(11)
N ₁ -C ₃	1.461(5)	C ₁ -N ₂ -C ₄	116.1(4)
N ₂ -C ₁	1.378(4)	C ₂ -N ₂ -C ₄	117.5(12)
N ₂ -C ₂	1.464(7)	O-C ₁ -N ₁	122.7(6)
N ₂ -C ₄	1.459(9)	O-C ₁ -N ₂	122.7(10)
C ₁ -N ₁ '	1.458(9)	N ₁ -C ₁ -N ₂	114.6(5)
		N ₁ -C ₂ -N ₂	115.6(8)
		N ₂ -C ₂ -N ₁	115.6(8)

ureido moiety in TMDMU (C₁-N₁: 1.377 and C₁-N₂: 1.378 Å) are longer than that of 1.335 Å in urea. These differences are correlated to the extent to which resonance occurs in TMDMU and urea. Furthermore, the difference in the C-O bond is probably due to the absence and presence of hydrogen bonds in TMDMU and urea respectively. All the hydrogen atoms of the two amino groups have been substituted in TMDMU, while four hydrogen atoms in urea form hydrogen bonds with oxygen atoms in the adjacent three molecules.¹¹

In TMDMU, the interatomic distances between C₁-C₁', C₂-C₂', N₁-N₁', and N₂-N₂' are 4.09, 2.88, 3.38, and 3.76 Å respectively. The molecule has a hole which is surrounded by four electronegative nitrogen atoms, four hydrophobic methyl groups, and two methylene linkages. The size of the hole is estimated to be 0.5–1.6 Å by considering the radius of van der Waals. When the addition of TMDMU to the solution of phenol alkaline metal salts, the characteristic shoulder at 225 nm disappears and the absorption spectrum in UV region changes to that of phenol. This spectral change is observed in the solution of Li or Na salt, but not in that of K salt. The addition of *N,N'*-dimethylurea or *N*-methoxymethyl-*N,N'*-dimethylurea causes no spectral change in the solution of phenol alkaline metal salts. Although the details remain to be elucidated, these may be a specific interaction between TMDMU and Li⁺ or Na⁺.

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