THE REACTIVITY OF MONOCYCLIC 1,2,3-TRIAZINE[#]

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Abstract - The reactivity of unsubstituted 1,2,3-triazine was investigated using various nucleophilic and electrophilic reagents, molecular orbital calculations, and low temperature nmr measurements.

In recent years we have been investigating the synthesis and the reactions of monocyclic 1,2,3-triazines.[1] We have reported the general synthetic method for 1,2,3-triazines *via* the oxidation of corresponding 1-aminopyrazoles. Monocyclic 1,2,3-triazines thus obtained were allowed to react with a number of reagents, and it was revealed that they are highly π-deficient compounds.[2] However, the substrates used were mainly 4,6-disubstituted triazines because of the availability and the stability of them under various reaction conditions. Hence the intrinsic nature of monocyclic 1,2,3-triazines is remained unclarified. In this paper, we describe the detailed results of the characterization of monocyclic 1,2,3-triazine.

X-ray crystallography and *ab initio* molecular orbital calculations

Parent 1,2,3-triazine (**1a**) was obtained as colorless plates[1b] and the structure was elucidated by X-ray crystallographic analysis(Figure 1 and Table 1).[3] The ring is almost planar, and its bond lengths (Table 2) also suggested the aromatic nature of **1a**. The values of N-N bond lengths are in good agreement with those found in 4,5,6-tris[*p*-methoxyphenyl]-1,2,3-triazine.[4] The C-C bond length is significantly shorter than the normal C-C bond length, and is inconsistent with the compound.[4] The facts indicate that the removal of the steric repulsion of the substituents shortened the C-C bond length.

[#] This paper is dedicated to Professor Emeritus Masatomo Hamana on the occasion of his 75th birthday.

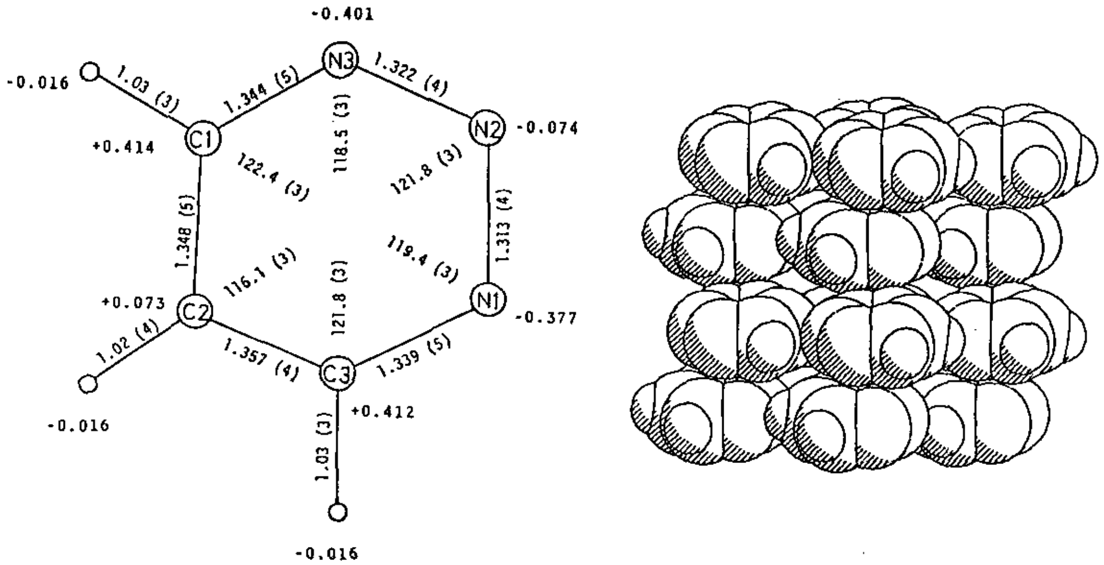
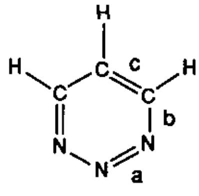


Figure 1. Bond lengths (Å), angles (°) and net atomic charges (a. u.) in 1,2,3-triazine (**1a**) (left). CPK model drawing of **1a** in the crystal (right). Van der Waals radii are assumed to be C=1.6, N=1.4 and H=1.0 (Å). Drawing by the PLUTO program.[5]

Table 1 Fractional Atomic Coordinates and Equivalent Isotropic Temperature Parameters (X 10^4 for nonhydrogen atoms, and X 10^3 for hydrogen atoms) with Estimated Standard Deviations in Parentheses

	X	Y	Z	B_{eq} ($Å^2$)
N(1)	2176 (4)	4667 (4)	3790 (5)	5.95 (0.06)
N(2)	2547 (4)	3922 (5)	1532 (5)	6.05 (0.06)
N(3)	2893 (4)	1633 (5)	377 (5)	6.25 (0.07)
C(1)	2853 (5)	40 (5)	1565 (6)	5.70 (0.07)
C(2)	2464 (5)	687 (5)	3873 (6)	5.19 (0.07)
C(3)	2134 (5)	3067 (5)	4958 (6)	5.56 (0.07)
H(1)	312 (5)	-170 (5)	47 (6)	7.7 (0.8)
H(2)	267 (5)	-28 (6)	506 (6)	9.2 (0.9)
H(3)	187 (4)	382 (5)	675 (6)	7.6 (0.8)

Next, full-optimized geometry of **1a** was calculated using STO 4-31G basis set.[6] Table 2 exhibits the comparison of the crystallographic bond lengths with the calculated ones. Those data show that this level of MO calculation is adequate for 1,2,3-triazine.[7]



1a

Table 2

Bond Length (Å)	a	b	c
X-ray analysis	1.318	1.342	1.353
STO 4-31G(OPT)	1.311	1.330	1.376

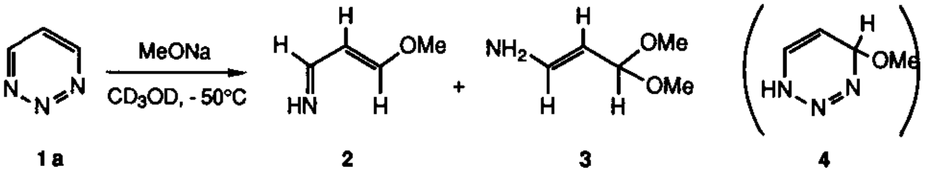
The calculated charge distributions and LUMO coefficients of **1a** were summarized in Table 3. The results suggested that charge-controlled nucleophilic reaction might occur at C-4(6) position, whereas frontier-controlled reaction at C-5.[8]

Table 3 The Calculated Parameters of 1,2,3-Triazine (**1a**)

	N1	N2	C4	C5
charge distribution	-0.330	-0.005	+0.073	-0.222
LUMO coefficient	0.0948	0.3659	0.0941	0.4059

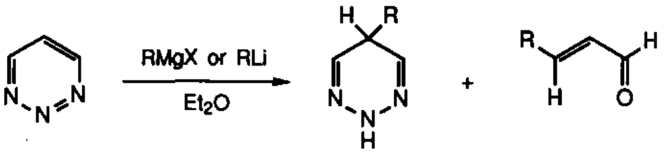
Reaction of 1a with nucleophiles

The compound (**1a**) was extremely unstable under nucleophilic conditions. For example, only dissolving in methanol caused **1a** to decompose promptly. In order to investigate the reaction, nmr measurements were performed at -50°C. Dihydro-adduct (**4**) was not observed despite careful search, and ring-opening products (**2**) and (**3**) were assigned instead (Scheme 1). Moreover, the succeeding addition of the oxidizing reagent such as DDQ or chloranil did not afford corresponding 4-methoxy-1,2,3-triazine.



Scheme 1

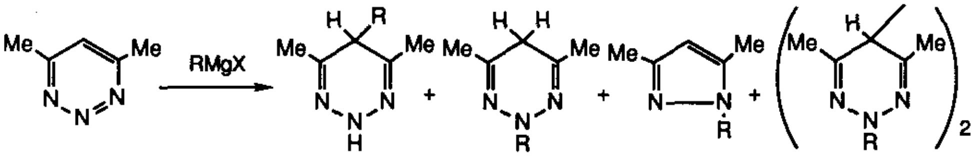
Methoxide ion is considered to be a hard nucleophile, thus the above results showed that the attack by a hard nucleophile occurred at C-4 position as predicted by MO calculations, and that the succeeding nitrogen elimination was too fast to rearomatize. Next, organometallic reagents were allowed to react with **1a**.[9] Scheme 2 depicts the results of the reactions. Methylmagnesium iodide, which is classified as a soft nucleophile, underwent the attack at C-5 position of **1a**, while the hard phenyllithium reacted at C-4. These experimental data also agreed with the results of the MO calculations.



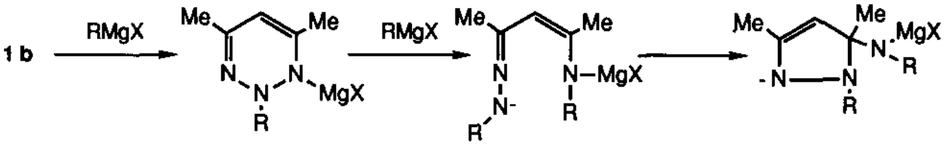
	5a	**6a**
MeMgI	42%	trace
PhMgBr	13%	52%
PhLi	0	49%

Scheme 2

There were interesting results that the Grignard reagents attacked at N-2 position when 4,6-dimethyl-1,2,3-triazine (**1b**) was adopted as a substrate (Scheme 3). These phenomenon suggested that 1,2,3-triazine ring was so electron deficient that the nucleophile could attack at nitrogen against the repulsion by unshared pair of electrons. The formation mechanism of **8** was speculated as shown in Scheme 3.



1b	**5**	**7**	**8**	**9**
R=Me, X=I	15%	17%	10%	6%
R=Ph, X=Br	6%	37%	10%	6%



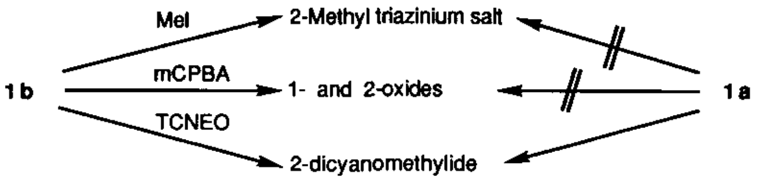
$\longrightarrow$ **8** + RNHMgX $\longrightarrow$ RNH_2

Scheme 3

4,6-Disubstituted 1,2,3-triazines were reduced by $NaBH_4$ to afford corresponding 2,5-dihydrotriazines.[10] However, even under -20°C in methanol, parent **1a** was not reduced, and the solvolysis proceeded in a similar manner as Scheme 1. Thus, it was revealed that **1a** was attacked more easily by a hard nucleophile at its 4-position in spite of the presence of BH_4^- anion.

Reaction of **1a** with electrophiles

Reactions of **1a** with electrophiles at carbon atoms did not occur because of the π-electron deficiency of triazine ring.[11] Electrophilic attack at nitrogens was also expected hardly to occur because of the results shown in Scheme 3. However, when 4,6-disubstituted triazines such as **1b** were methylated or oxygenated at their N-2 (or N-1) positions although the reaction rates were much slower than those of pyridines or pyridazines.[12,13] The reactivity of **1a** to electrophiles was further lower, and tetracyanoethylene oxide (TCNEO) was an only reagent to react with **1a** to form corresponding dicyanomethylide.



Scheme 4

The formation of dicyanomethylide from **1a** was probably due to energetically favorable character of the product, and the normal reactivity of 1,2,3-triazine toward electrophiles was considered to be very low unless the electron-donating group existed on the ring.

In this paper, we reported the properties of monocyclic 1,2,3-triazine. Its aromatic nature is obvious from the X-ray crystallographic analysis and nmr spectra,[1c] but the ring is fairly unstable and apts to eliminate nitrogen when 4-position is attacked by nucleophile. Therefore the general method for the substitution of six-membered azaaromatics (nucleophilic attack followed by oxidation)[14] is not available for the compound. The molecular orbital calculation indicated that C-4 position is hard site whereas C-5 is soft one. The reactions with organometallic reagents gave the results which were consistent with the MO presumption.[15]

ACKNOWLEDGMENT

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EXPERIMENTAL

All melting points were taken on a Yanaco micro melting point apparatus and are uncorrected. The ^{1}H-nmr and ^{13}C-nmr spectra were measured with JEOL JNM-FX100 and GX400 spectrometers using tetramethylsilane as an internal standard.

The X-Ray Crystallographic Analysis of 1a

The analysis was performed using a crystal of dimensions 0.45 X 0.32 X 0.25 mm, which was grown from dioxane-ether solution as a colorless flake. The lattice constants and intensity data were obtained on a Philips PW1100 diffractometer with graphite-monochromated CuKα radiation using the θ-2θ scan method. The space group of the crystal is triclinic P1 with two molecules per cell. The cell dimensions are a=6.941(3), b=5.785(3), c=5.751(3)Å, α=112.71(2), β=104.02(2), γ=97.58(2)°. A total of 678 reflections were measured within the 2θ range of 6° through 156°. The decay in intensities of three different standard reflections measured every two hours was less than 1% during data collection. The crystal structure was determined by direct methods using MULTAN and refined by the block-diagonal least-squares method. The final R was 0.059 including hydrogen atoms. The atomic coordinates are listed in Table 1.

The Reaction of 1a with Sodium Methoxide at -50°C

Attempts to separate the products of the reaction were unsuccessful. Thus the nmr measurement at low temperature was adopted for the investigation. Sodium methoxide and **1a** were dissolved in CD_3OD at -50°C, and ^{1}H-nmr was measured at the same temperature immediately after the mixing. No signals originated from **1a** were observed, and the existence of two compounds was suggested by the coupling constants of the nmr spectra of the mixture. Compound A: δ 5.64 (1H, dd, J=12.5 Hz, 9.2 Hz), 7.21 (1H, d, J=12.5 Hz), 8.06 (1H, d, J=9.2 Hz). Compound B: δ 4.56 (1H, dd, J=13.6 Hz,7.0 Hz), 4.63 (1H, d, J=7.0 Hz), 6.30 (1H, d, J=13.6 Hz). We supposed the structure of A and B as 3-imino-1-methoxy-1-propene (**2**) and 1-amino-3,3-dimethoxy-1-propene (**3**), respectively.

The Reaction of 1a with Methylmagnesium Iodide

Methylmagnesium iodide, which was prepared from 7.0 mmol of magnesium and 6.48 mmol of methyl iodide in ether under nitrogen atmosphere, was allowed to react with **1a** (6.17 mmol) at 0°C for 30 min. Then saturated aq. NH_4Cl (5 ml) was added to quench excess amount of the reagent, and the organic layer was dried over $MgSO_4$, and evaporated off. The residue was chromatographed on alumina to give 5-methyl-2,5-dihydro-1,2,3-triazine (42%). The existence of crotonaldehyde was confirmed by the gcms of the reaction mixture in comparison with standard sample. The starting material (**1a**) was recovered in 10% yield.

5-Methyl-2,5-dihydro-1,2,3-triazine

Colorless flakes; mp 53-55°C (hexane-ether). ^{1}H-Nmr ($CDCl_3$)δ: 1.32 (3H, d, J=6.7Hz), 2.16 (1H, q, J=6.7Hz), 6.50 (2H, s), 8.80 (1H, br s). Anal. Calcd for $C_4H_7N_3$: C, 49.46; H, 7.27; N, 43.27. Found: C, 48.22; H, 7.00; N, 42.50.

The reaction of 1a with Phenylmagnesium Bromide

Phenylmagnesium bromide was obtained from Mg, bromobenzene, and trace amount of iodine in ether under nitrogen. Then the solution of **1a** was added at 0°C, and the mixture was stirred at 0°C for 30 min. Thereafter, residual reagent was quenched by aq. NH_4Cl, and the organic layer was dried over $MgSO_4$ and evaporated off. The residue was chromatographed on alumina to give the compounds shown below.

5-Phenyl-2,5-dihydro-1,2,3-triazine

Yield 8%. Colorless needles; mp 94-97°C (hexane-ether). ^{1}H-Nmr ($CDCl_3$)δ: 3.18 (1H, br s, J=1.5 Hz), 6.61 (2H, d, J=1.5 Hz), 7.10-7.50 (5H, m), 8.82 (1H, br s). Ms (*m/z*) 159 (M^+). The compound was oxidized in air to 5-phenyl-1,2,3-triazine.

5-Phenyl-1,2,3-triazine

Yield 5%. Colorless needles from ether-$CHCl_3$; mp 139-141°C. ^{1}H-Nmr ($CDCl_3$)δ: 7.55-7.80 (5H, m), 9.31 (2H, s). Anal. Calcd for $C_9H_7N_3$: C, 68.77; H, 4.49; N, 26.74. Found: C, 68.64; H, 4.50; N, 26.78.

Cinnamaldehyde was identified by the comparison of the spectral data with those of an authentic sample.

The Reaction of 1a with Phenyllithium

The compound (**1a**) was allowed to react with phenyllithium in ether at -50°C for 30 min under nitrogen atmosphere. Then water was added and the mixture was allowed to warm up to room temperature. The organic layer was seperated, dried over $MgSO_4$, and evaporated off. The residue was submitted to alumina chromatography to afford cinnamaldehyde. 10% of **1a** was recovered.

The Reaction of 1b with Methylmagnesium Iodide.

The ether solution of **1b** was added to the ether solution of methylmagnesium iodide at 0°C under nitrogen and stirred for 30 min. The same workup procedure as in the case of **1a** was applied and the residue was chromatographed on alumina.

4,5,6-Trimethyl-2,5-dihydro-1,2,3-triazine (yield 15%) and 2,4,6-trimethyl-2,5-dihydro-1,2,3-triazine (yield 17%) were characterized with compared to the standard samples reported elsewhere.[10] The existence of 1,3,5-trimethylpyrazole was confirmed by gcms using an authentic sample, and the yield was estimated with the nmr of the reaction mixture.

5,5'-Bis(2,4,6-trimethyl-2,5-dihydro-1,2,3-triazinyl)

Yield 6%. Colorless needles; mp 143-145°C (hexane-ether). ^{1}H-Nmr ($CDCl_3$) δ: 1.99 (3H, s), 3.20 (2H, s), 3.46 (6H, s). Ms (m/z) 124 (M^+/2). Anal. Calcd for $C_{12}H_{20}N_6$: C, 58.04; H, 8.12; N, 33.85. Found: C, 58.23; H, 8.20; N, 33.53.

The Reaction of 1b with Phenylmagnesium Bromide

The reaction procedure was same as mentioned above. The residue was applied to alumina column chromatography to afford the following compounds.

4,6-Dimethyl-5-phenyl-2,5-dihydro-1,2,3-triazine

Yield 6%. Colorless; mp 109-111°C (ether). ^{1}H-Nmr ($CDCl_3$) δ: 1.95 (6H, s), 3.75 (1H, s), 6.95-7.22 (5H, m), 8.08 (1H, br s). Anal. Calcd for $C_{11}H_{13}N_3$: C, 70.56; H, 7.00; N, 22.44. Found: C, 70.60; H, 6.99; N, 22.22.

4,6-Dimethyl-2-phenyl-2,5-dihydro-1,2,3-triazine

Yield 37%. Pale yellow prisms; mp 51-52°C (ether). ^{1}H-Nmr ($CDCl_3$) δ: 2.09 (6H, s), 2.59 (2H, s), 6.78-7.60 (5H, m). Exact ms (m/z)(M^+) Calcd for $C_{11}H_{13}N_3$: 186.103. Found: 186.101. Anal. Calcd for $C_{11}H_{13}N_3$: C, 70.56; H, 7.00; N, 22.44. Found: C, 70.25; H, 7.00; N, 22.43.

5,5'-Bis(4,6-dimethyl-2-phenyl-2,5-dihydro-1,2,3-triazinyl)

Yield 6%. Colorless needles; mp 185°C (ether). ^{1}H-Nmr ($CDCl_3$) δ: 2.11 (12H, s), 3.22 (2H, s), 6.90-7.68 (10H, m). Ms (m/z) 186 ($M^+/2$). Anal. Calcd for $C_{22}H_{24}N_6$: C, 70.94; H, 6.50; N, 22.57. Found: C, 70.59; H, 6.46; N, 22.32.

The spectral data of 3,5-dimethyl-1-phenylpyrazole were identical with those of previousely reported.[16]

The Reaction of 1a with Electrophiles

Triazine (**1a**) did not react with mCPBA or Me_2SO_4 even after 3 days' reaction. To the solution of **1a** in THF, the THF solution of TCNEO[17] (1.5 eq.) was added dropwise at 0°C, and allowed to react for 12 h at room temperature. Then the solvent was evaporated off and the residue was chromatographed on alumina to afford 1,2,3-triazinium 2-dicyanomethylide in 73% yield.

1,2,3-Triazinium 2-Dicyanomethylide

Colorless needles; mp 167°C (decomp.)(benzene). ^{1}H-Nmr (DMSO-d_6) δ: 7.48 (1H, t, J=5.0 Hz), 8.39 (2H, d, J=5.0 Hz). Anal. Calcd for $C_6H_3N_5$: C, 49.65; H, 2.08; N, 48.26. Found: C, 49.57; H, 1.78; N, 48.09.

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