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Acetalation Mechanism of 2-Formyl-3-methoxypropionitrile in Methanolic Hydrogen Chloride[1]

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2-Dimethoxymethyl-3-methoxypropionitrile (I), an important compound for thiamine production, was obtained in good yield by the hydrogen chloride-catalyzed acetalation of 2-formyl-3-methoxypropionitrile (II) in methanol. The reaction was proved not to proceed through direct acetalation of the formyl group but *via* the pathway of II→allyl hydroxy-(V) and allyl ether-(VI) cations→2-dimethoxymethylacrylonitrile (III)⇌2-methoxymethylene-3-methoxypropionitrile (IV)⇌I. The reaction gave 2-oxopiperidines (VII, VIII) and pyrans (IX, X) as minor products which should be formed by the attack of the allyl cations to II or IV. Kinetic studies on the reaction pathway of III⇌IV⇌I revealed that the *cis* isomer of IV was more reactive than the *trans* counterpart. The same acetalation of methyl 2-formyl-3-methoxypropionate (XVI) was similarly investigated.

Keywords——2-formyl-3-methoxypropionitrile; acetalation; allyl cation; tetrahydropyrans; 2-oxopiperidines; *cis-trans* isomerization; simulation of reaction profile; interconversion reaction; rate constants; methyl 2-formyl-3-methoxypropionate

2-Dimethoxymethyl-3-methoxypropionitrile (I) is a useful compound for the synthesis of heterocycles.[3] The condensation of I with acetamidine is one of the economically most profitable reactions to manufacture 2-methyl-4-amino-5-aminomethylpyrimidine, a key synthetic intermediate for thiamine production.[4] The studies of our laboratory have been aimed at clarifying the reaction behavior of I. The reaction mechanism in alkaline medium had been discussed.[5] The literature, however, contains a few scattered references to the reactions of I under acidic conditions.[6] Now we wish to report an interesting reaction mechanism involving an allyl cation intermediate for the acid-catalyzed acetalation of 2-formyl-3-methoxypropionitrile (II).

Hydrogen chloride was selected as the catalyst of the reaction since the previous authors had failed to obtain I in a good yield using sulfuric acid or hydrochloric acid.[6a] As a result, 70—75% conversion of the sodium salt of II into I was successfully achieved by refluxing the salt (0.1—1 M) for a few hours in 0.1—2 N methanolic hydrogen chloride. Thus-obtained crude I contained a small amount of 2-dimethoxymethylacrylonitrile (III) and the *cis*(IV_{cis}) and *trans*(IV_{trans}) isomers[7] of 2-methoxymethylene-3-methoxypropionitrile (IV). The residual oil was a mixture of unknown degradation products.

1) Presented at the 93rd Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April, 1973.
2) Location: *192, Imafuku, Amagasaki, Hyogo, 660, Japan.*
3) A. Takamizawa, K. Hirai, Y. Hamashima, and M. Hata, *Chem. Pharm. Bull.* (Tokyo), **12**, 558 (1964); A. Takamizawa, K. Hirai, Y. Sato, and K. Tori, *J. Org. Chem.*, **29**, 1740 (1964).
4) M. Tomita, S. Uyeo, A. Takamizawa, and R. Maeda, *Yakugaku Zasshi*, **74**, 742 (1954); A. Takamizawa and R. Maeda, *ibid.*, **74**, 746 (1954); A. Takamizawa, *ibid.*, **74**, 748 (1954); *idem, ibid.*, **74**, 759 (1954); A. Takamizawa, K. Ikawa, and M. Narisada, *ibid.*, **78**, 632 (1958).
5) T. Nishino, M. Kiyokawa, Y. Miichi, and K. Tokuyama, *Bull. Chem. Soc. Japan*, **45**, 1127 (1972); *idem, ibid.*, **45**, 2010 (1972); *idem, ibid.*, **46**, 253 (1973).
6) *a*) A. Takamizawa, K. Ikawa, and M. Narisada, *Yakugaku Zasshi*, **78**, 637 (1958); *b*) *Idem, ibid.*, **78**, 643 (1958).
7) "C_{is}" means that the nitrile group and the methoxy group of the 2-methoxymethylene moiety are located on the same side against double bond, while "*trans*" means that they are found on the opposite side.

Monitoring of the reaction by gas–liquid chromatography (GLC) revealed an unexpected reaction feature. Figure 1 shows the result obtained by the reaction of II (0.25 M) with methanol in the presence of hydrogen chloride (0.5 M) at the boiling temperature: the compound III appeared at the initial stage of the reaction and then both I and IV_{cis} emerged with the decrease of III. The compound I finally became the major product as with the decrease of IV_{cis}. During the course of the reaction, IV_{trans} was also detected but its content was very small (0.2% or less).

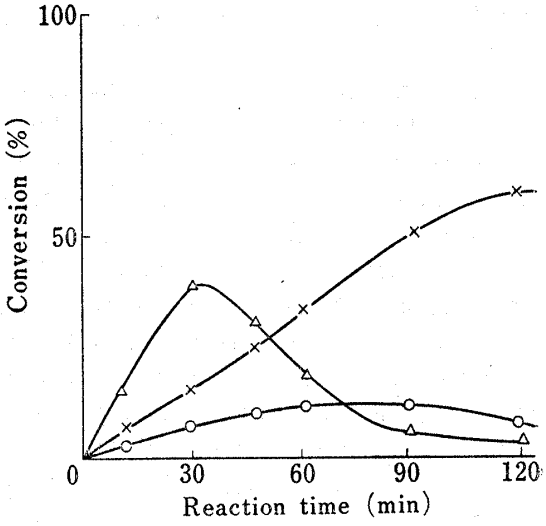

Fig. 1. Reaction Profile for Acetalation of II in Methanolic Hydrogen Chloride at 63°

Initial concentration of II=0.25 M, [HCl]=0.5 M, —×—: I; —△—: III; —○—: IV_{cis}.

This kinetic profile clearly indicates that the acetalation does not proceed *via* a simple pathway such as II→I involving a direct acetalation of the formyl group, as reported previously.[6a] An alternative pathway, II→ III ⇗ IV_{cis} ⇘ ⇗ IV_{trans} ⇘ I, should be responsible for the above observation. The conversion of III into IV must proceed *via* an intermediate allyl cation which should be formed by the elimination of methanol from the protonated species

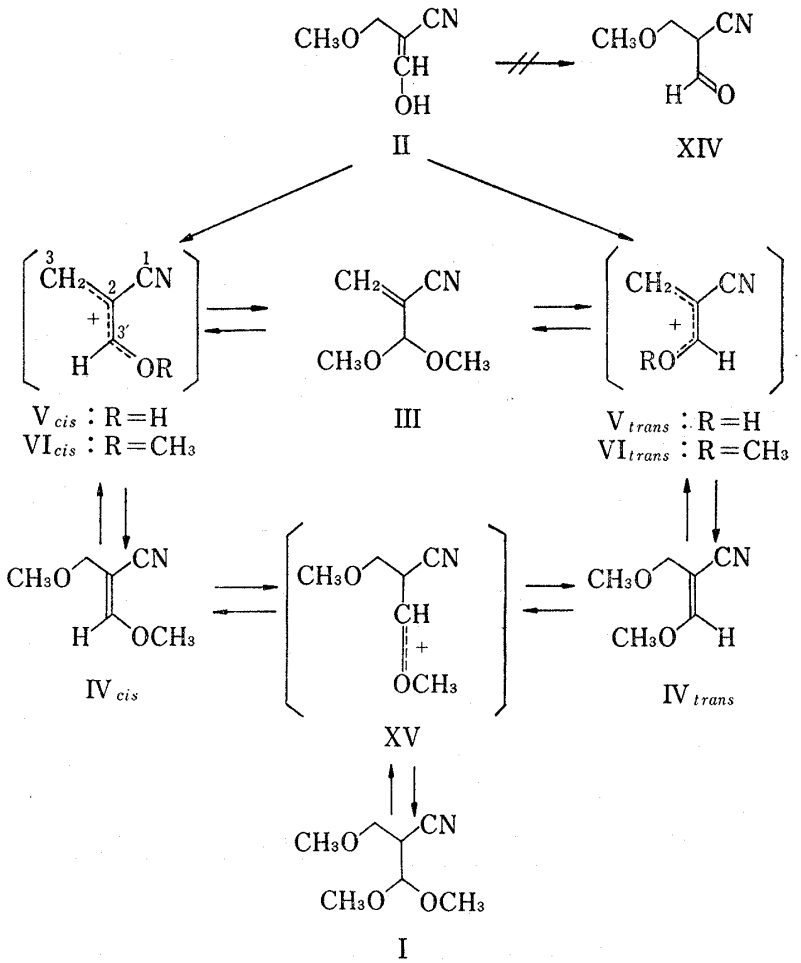

Chart 1. Acetalation Pathway from II to I

of III. Thus we propose the reaction mechanism as shown in Chart 1 for the acetalation of II.

The existence of such allyl cation intermediates (V and VI) was ascertained by the isolation of the following dimeric products. Chromatographic separation of the degradation products of the residual oil afforded four compounds, VII (mp 177—179°), VIII (mp 176—177°), IX (mp 164—165°), and X (mp 156—158°) whose molecular formula are $C_{11}H_{16}N_2O_4$, corresponding to dimeric substances of the allyl cations.

The infrared (IR) spectrum of VII showed the bands characteristic to a non-conjugated nitrile group at 2240 cm^{-1} and to an amide group at 3200 cm^{-1} (NH), 1680 cm^{-1} and 1622 cm^{-1} (C=O). The ultraviolet (UV) absorption band at 245 nm in methanol indicated the presence of an α,β-unsaturated carbonyl system. The NMR spectrum in $CDCl_3$ (Table I) exhibited the signal due to NH proton (He) at the lowest field (7.72 ppm) as a broad multiplet. Decoupling through a H–D exchange by D_2O addition showed that this proton coupled with the methine proton H_d at 4.63 ppm (J=5 Hz). An olefinic proton H_a at 7.48 ppm coupled with AB-type methylene protons H_b and $H_{b'}$ centered at 2.40 ppm and 2.84 ppm in the highest field ($J_{bb'}$=18 Hz, J_{ab}=2.5 Hz, and $J_{ab'}$=1 Hz). The signal due to the proton $H_{b'}$ revealed the weak coupling with H_d proton. The above spectral data are consistent with the partial structure $>CH_d$-NH_eCO-C(=CH_a-)-$CH_bH_{b'}$-. Considering the additional presence of the three methoxy groups, an isolated methylene group (H_c and $H_{c'}$, AB-type quartet centered at 3.58 ppm), and the nitrile group, the structure of VII was established to be 6-methoxy-5-cyano-5-methoxymethyl-3-methoxymethylenepiperidin-2-one. According to the "W-letter" rule,[8] the observed long-range coupling between $H_{b'}$ and H_d exhibits a diequatorial configuration of these protons. This leads to the axial configuration of the methoxy group attached to the carbon bearing H_d proton.

Table I. NMR Spectral Data[a] for VII, VIII, IX, and X ($CDCl_3$, 60 MHz)

VII	VIII	IX	X	No. of protons	Assignment
2.40 (q, $J_{bb'}$=18)	2.66 (q, $J_{bb'}$=17)	2.30 (q, $J_{bb'}$=13)	2.11 (q, $J_{bb'}$=15)	1	C–C$\underline{H}_b$$H_{b'}$–C
2.84 (q, $J_{ab'}$=1)	2.99 (q, $J_{ab'}$=2)	2.60 (q, J_{bf}=11)	2.57 (q, J_{bf}=5.5)	1	C–$CH_b\underline{H}_{b'}$–C
3.58 (q, $J_{cc'}$=10)	3.46[b]	3.65 (s)	3.58 (s)	2	C–C$\underline{H}_c\underline{H}_{c'}$–$OCH_3$
4.63 (q, J_{de}=5)	4.64 (q, J_{de}=5)	4.96 (s)	4.52 (s)	1	O–C$\underline{H}_d$–N (or O)
7.72 (b.m.)	7.55 (b.m.)	—	—	1	C–N$\underline{H}_e$–C
7.48 (q, J_{ab}=2.5)	7.40 (q, J_{ab}=1.5)	—	—	1	C=C$\underline{H}_a$–OCH_3
—	—	4.95 (d, J_{fg}=3)	4.65 (d, J_{fg}=3)	1	O–C$\underline{H}_g$–O
—	—	2.8—3.2 (m, $J_{b'f}$=5)	3.0—3.2 (m, $J_{b'f}$=5.5)	1	$CH_bH_{b'}$–C$\underline{H}_f$–C
3.38 (s)	3.40 (s)	3.43 (s)	3.41 (s)	3	C–CH_2–O$\underline{CH}_3$
3.45 (s)	3.46 (s)	3.50 (s)	3.41 (s)	3	N(or O)–CH_d–O$\underline{CH}_3$
3.87 (s)	3.87 (s)	3.55 (s)	3.60 (s)	3	C=CH_a–O$\underline{CH}_3$

a) Chemical shifts (δ) and coupling constants (J) are given in ppm and Hz, respectively. Abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; b.m., broad multiplet.
b) Overlapping with methoxy group at 3.46 ppm.

8) L.M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed., Pergamon Press, Oxford, 1969, p. 334.

As the IR and NMR spectra of VIII were quite similar to those of VII (see Table I), VIII should be a stereoisomer of VII. Especially the absence of long-range coupling between $H_{b'}$ and H_d in the NMR spectrum suggests that VIII is the stereoisomer at the carbon bearing H_d proton.

The IR spectrum of IX showed the presence of non-conjugated nitrile group at 2240 cm^{-1}, but the absorption bands due to carbonyl and NH groups were absent. The NMR spectrum in $CDCl_3$ (Table I) closely related with those of VII and VIII, except for the absence of the signals due to the $-NHCO-C(=CHOCH_3)-CH_2-$ moiety. Alternatively, the moiety of $-CH_bH_{b'}-CH_f-CH_g(-O-)-O-$ was exhibited as an ABXY-pattern; H_b and $H_{b'}$ appeared as a pair of quartet at 2.30 and 2.60 ppms ($J_{bb'}$=13 Hz, J_{bf}=11 Hz, and $J_{b'f}$=5 Hz), and H_f appearing as a multiplet at 2.8—3.2 ppm further coupled with the proton H_g at 4.95 ppm (J=3 Hz). Therefore the structure of IX was elucidated to be 3,5-dicyano-2,6-dimethoxy-3-methoxymethyltetrahydropyran.

The closely similar spectral data of X (see Table I) showed that X was a stereoisomer of IX.

The formation of these four compounds can be reasonably explained by assuming the attack of the allyl cation V (or VI) to the C_2-position of IV (or II) to give an intermediate XI, as shown in Chart 2. The intramolecular acetalation of XI should form the pyrans IX and X. Further addition of methanol to the nitrile group of XI should give rise to the formation of another intermediate XII. The nucleophilic attack of the nitrogen atom to the cationic carbon should generate an piperidine imido ether XIII, which should be easily hydrolyzed during the work-up to give 2-oxopiperidines VII and VIII.

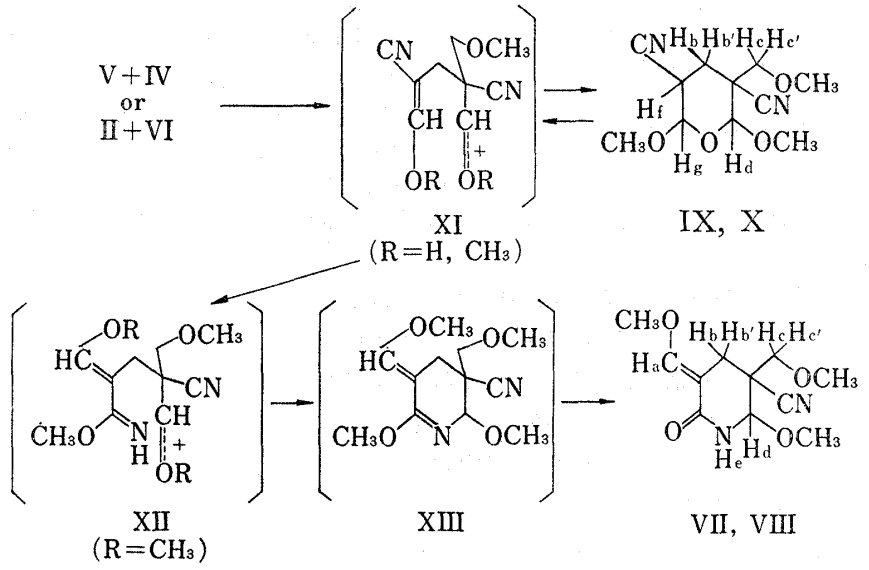

Chart 2. Formation Pathway of VII, VIII, IX, and X

The GLC analysis also showed that there should be a great difference in reactivity between the *cis* isomer IV_{cis} and the *trans* isomer IV_{trans}. Thus the reaction was investigated kinetically to obtain further detailed informations on the relative reactivity of the two isomers.

The reaction profile shown in Fig. 2a was obtained from the reaction of III (0.5 M) with methanol in the presence of hydrogen chloride (2.25 M) at 50°. As with the decrease of III, IV_{cis} appeared and then decreased. Finally I increased accompanying with a small content of IV_{trans}.

A quite similar profile was obtained for the reaction starting with IV_{cis} (Fig. 2b).

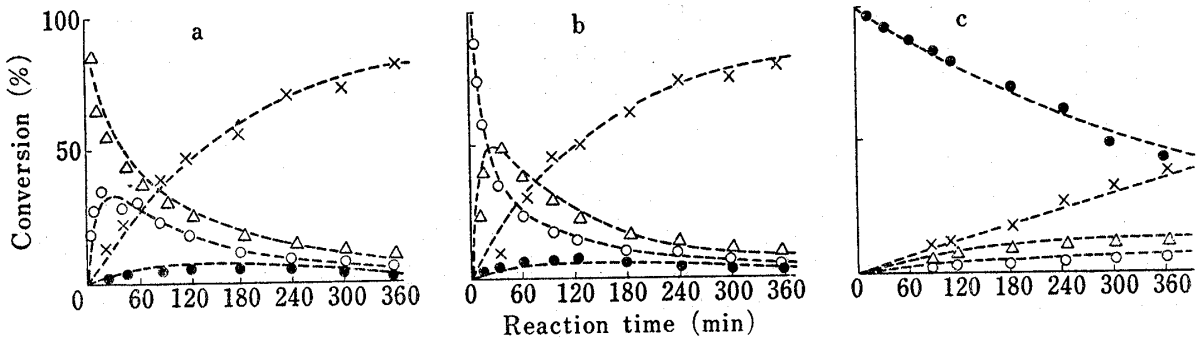

Fig. 2. Kinetic Profiles of Interconversion among I, III, IV_{cis}, and IV_{trans} at 50° and Simulation Curves

a: initial concentration of III=0.5 M, [HCl]=2.25 M.
b: initial concentration of IV_{cis}=0.5 M, [HCl]=2.64 M.
c: initial concentration of IV_{trans}=0.5 M, [HCl]=2.55 M.
------: simulation curves,
×: I; △: III; ○: IV_{cis}; ●: IV_{trans}.

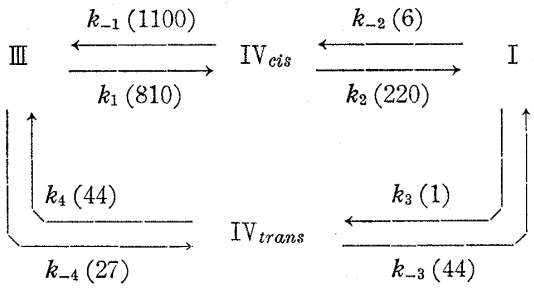

Chart 3. Interconversion among I, III, IV_{cis}, and IV_{trans}

The values in parentheses represent the relative rate constants.

On the contrary to the above-observed rapid interconversion among IV_{cis}, III, and I, a quite slow interconversion was observed for IV_{trans} (Fig. 2c). These results clearly indicate that the *cis* isomer IV_{cis} is much more reactive than the *trans* isomer IV_{trans}.

A kinetic scheme shown in Chart 3 can be depicted for the above-observed interconversion among I, III, IV_{cis}, and IV_{trans}. The symbols k_{1-4} and k_{-1--4} represent the specific rate constants of each forward and reverse reaction, respectively.

The following rate equations can be set up by assuming that the reactions obey to the pseudo-first order kinetics.

$$-d[\mathrm{III}]/dt = (k_1+k_{-4})[\mathrm{III}] - k_{-1}[\mathrm{IV}_{cis}] - k_4[\mathrm{IV}_{trans}]$$
$$-d[\mathrm{IV}_{cis}]/dt = (k_2+k_{-1})[\mathrm{IV}_{cis}] - k_{-2}[\mathrm{I}] - k_1[\mathrm{III}]$$
$$-d[\mathrm{IV}_{trans}]/dt = (k_4+k_{-3})[\mathrm{IV}_{trans}] - k_3[\mathrm{I}] - k_{-4}[\mathrm{III}]$$
$$-d[\mathrm{I}]/dt = (k_3+k_{-2})[\mathrm{I}] - k_{-3}[\mathrm{IV}_{trans}] - k_2[\mathrm{IV}_{cis}]$$

The principle of microscopic reversibility[9] leads to the following relations:

$$k_1[\mathrm{III}]_e = k_{-1}[\mathrm{IV}_{cis}]_e$$
$$k_2[\mathrm{IV}_{cis}]_e = k_{-2}[\mathrm{I}]_e$$
$$k_3[\mathrm{I}]_e = k_{-3}[\mathrm{IV}_{trans}]_e$$
$$k_4[\mathrm{IV}_{trans}]_e = k_{-4}[\mathrm{III}]_e$$

where the subscript e denotes the equilibrium concentration.

The values of k_1/k_{-1}=2.4/3.3, k_2/k_{-2}=92.3/2.4, k_3/k_{-3}=2.0/92.3, and k_4/k_{-4}=3.3/2.0 were obtained from the equilibrium concentrations at 50° which were determined by GLC measurement; $[\mathrm{I}]_e$=92.3%, $[\mathrm{III}]_e$=3.3%. $[\mathrm{IV}_{cis}]_e$=2.4%, and $[\mathrm{IV}_{trans}]_e$=2.0%.

The low reactivity of IV_{trans} and the small value of k_{-2}/k_2 can approximate the above reaction system to the kinetic system

9) *a*) L.P. Hammett, "Physical Organic Chemistry," 2nd ed., McGraw-Hill, New York, N.Y., 1970, pp. 142—144; *b*) K.J. Laidler, "Chemical Kinetics," 2nd ed., McGraw-Hill, New York, N.Y., 1965, pp. 110—111.

$$\text{III} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \text{IV}_{cis} \xrightarrow{k_2} \text{I}$$

Since the reaction profiles illustrate that the rate of $IV_{cis} \rightarrow I$ is by far slower than that of $III \rightleftarrows IV_{cis}$ ($k_1+k_{-1} \gg k_2$), the following equation can be derived,[10] where the subscript o denotes the initial concentration.

$$[I]/[III]_0 = 1 - \exp\{-k_1/(k_1+k_{-1}) \times k_2 t\}$$

The k_2 values at 50° were roughly estimated from the slope (k_1k_2/k_1+k_{-1}) of the straight line obtained by a plot of ln $(1-[I]/[III]_0)$ against the reaction time t; $k_2=1.1\times10^2$, 1.4×10^{-2}, and 2.1×10^{-2} min^{-1} for the acid concentrations of 2.1, 2.3, and 2.5 M, respectively.

The computer simulations were performed by the Runge–Kutta integration[11] using the above values. The theoretical curves shown in dotted lines of the Figures are well fitted with the observed data. Thus-obtained parameters are listed in Table II. The mean values of the relative rate constants are presented in parentheses of Chart 3. The equilibrium constants (K) and the corresponding free-energy differences ($\Delta\Delta G°$) at 50° are listed in Table

Table II. Kinetic Parameters[a] at 50° for the Interconversion among I, III, IV_{cis}, and IV_{trans}

[HCl] (M)	Rate constants[b] (min^{-1}).							
	k_1 ($\times10^2$)	k_{-1} ($\times10^2$)	k_2 ($\times10^2$)	k_{-2} ($\times10^4$)	k_3 ($\times10^5$)	k_{-3} ($\times10^3$)	k_4 ($\times10^3$)	k_{-4} ($\times10^3$)
2.1	4.8	6.6	1.3	3.4	6.5	2.6	2.6	1.6
2.3	5.3	7.3	1.5	3.8	6.0	2.9	2.9	1.8
2.5	8.1	11.0	2.2	5.8	10.0	4.5	4.5	2.7

a) Determined by computer simulation for the reaction profiles starting with III.
b) The values were identical with those obtained from the reaction starting with IV_{cis} and IV_{trans}.

Table III. The Equilibrium Constants (K) and the Free-Energy Differences ($\Delta\Delta G°$) at 50° among I, III, IV_{cis}, and IV_{trans}

Ratio	K_{323}	$\Delta\Delta G°$ (kcal/mol)
$IV_{cis}/III=2.4/3.3$	7.3×10^{-1}	0.2
$IV_{trans}/III=2.0/3.3$	6.1×10^{-1}	0.3
$IV_{cis}/I=2.4/92.3$	2.6×10^{-2}	2.3
$IV_{trans}/I=2.0/92.3$	2.2×10^{-2}	2.4

Table IV. The Estimated Values of the Free Energy Differences of Activation ($\Delta\Delta G^{\ddagger}$) at 50°

Ratio of the relative rate constants	$\Delta\Delta G^{\ddagger}$(kcal/mol)
$k_{-2}/k_3=6$	$\Delta G^{\ddagger}(I \longleftrightarrow IV_{trans})$[a] $-\Delta G^{\ddagger}(I \longleftrightarrow IV_{cis})=1.2$
$k_{-1}/k_2=5$	$\Delta G^{\ddagger}(IV_{cis} \longleftrightarrow I)-\Delta G^{\ddagger}(IV_{cis} \longleftrightarrow III)=1.0$
$k_4/k_{-3}=1$	$\Delta G^{\ddagger}(IV_{trans} \longleftrightarrow I)-\Delta G^{\ddagger}(IV_{trans} \longleftrightarrow III)=0$
$k_1/k_{-4}=30$	$\Delta G^{\ddagger}(III \longleftrightarrow IV_{trans})-\Delta G^{\ddagger}(III \longleftrightarrow IV_{cis})=2.2$

a) Represents the free energy of activation for the process.

10) See 9*a*), pp. 73—89.
11) *cf.* R.W. Southwork and S.L. Deleeuw, "Digital Computation and Numerical Method," McGraw-Hill, New York, N.Y., 1965, p. 420.

III. The ratio of the rate constants determines the free energy difference between the transition states ($\Delta\Delta G^{\neq}$)[12] as evaluated in Table IV.

These thermodynamic data present an energy diagram as illustrated in Fig. 3 for the interconversion among the four components.

The energy diagram reflects the following two features of the reaction: (i) the greater reactivity of IV_{cis} than IV_{trans} is due to the transition-state stability rather than the ground-state stability, and (ii) the *cis-trans* isomerization between IV_{cis} and IV_{trans} proceeds *via* stable intermediates I and/or III.

The former fact is consistent with the result reported by Okuyama, *et al.*[13] for the acid-catalyzed hydrolysis of vinyl ethers. They explained the greater reactivity of each *cis* isomer in terms of the favorable Coulombic interaction in the transition state. This interaction energy should influence the reactivity of IV similarly.

Here we can realize the entire reaction scheme from II to I indicated in Chart 1. The equilibrium between enolic-(II) and aldehyde-(XIV) forms should completely shift to the former in the acidic solution. The elimination of methanol from the protonated species of II should give rise to the formation of the allyl hydroxy cation V, which should be subsequently converted into the allyl ether cation VI by the replacement of the hydroxy group with methoxy group.

As the rotation about each partial double bond of allyl cations should be restricted,[14] the allyl cations (V and VI) must exist in two isomeric forms such as V_{cis} and VI_{cis} and V_{trans} and VI_{trans}. The relative stability of these isomeric allyl cations should be essentially similar to that of the parent 1-hydroxy allyl cations[14b] whose *cis* conformation predominates. Therefore it appears obvious that V_{cis} and VI_{cis} should be the more stable intermediates than the corresponding geometrical isomers. The fact is also consistent with the well-known thermodynamic preference of *cis* geometry for allyl cations.[15]

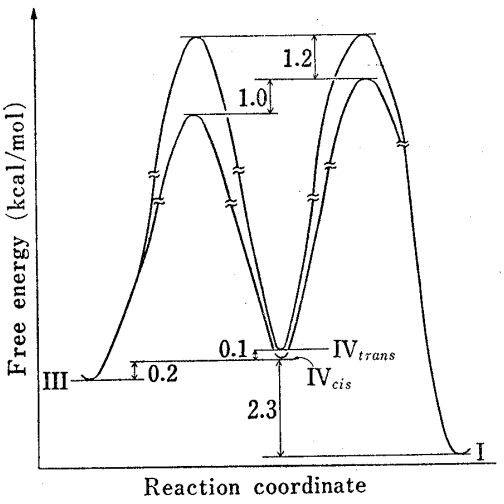

Fig. 3. Energy Diagram for the Interconversion among I, III, IV_{cis}, and IV_{trans} in Methanol Hydrogen Chloride at 50°

[I+III+IV_{cis}+IV_{trans}]=0.5 M, [HCl]=2.2—2.6 M.

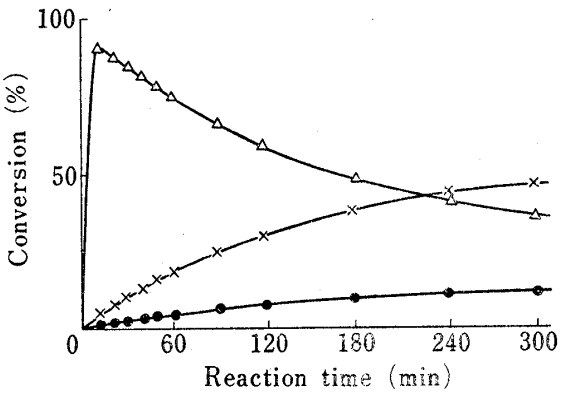

Fig. 4. Reaction Profile for Acetalation of XVI in Methanolic Hydrogen Chloride at 50°

Initial concentration of XVI =0.5 M, [HCl]=0.06 M, —●—: $XVII_{trans}$; —△—: XVIII;: —×—: XIX.

12) M. Friedman and J.S. Wall, *J. Am. Chem. Soc.*, **86**, 3735 (1964); Ref. R. Taft, Jr., in "Steric Effects in Organic Chemistry," M.S. Newman, Ed., John Wiley and Sons, Inc., New York, N.Y., 1956, Chapter 13.
13) T. Okuyama and T. Fueno, *J. Org. Chem.*, **39**, 3156 (1974).
14) *a*) W.G. Young, H. E. Green, and A.F. Diaz, *J. Am. Chem. Soc.*, **93**, 4782 (1971); *b*) R.F. Childs, E.F. Lund, A.G. Marshall, W.J. Morrisey, and C.V. Rogerson, *J. Am. Chem. Soc.*, **98**, 5924 (1976).
15) See 14 *b*), references cited therein.

The preferential appearance of the compound III at the kinetical phase (Fig. 1) indicates that the nucleophilic attack of methanol to VI occurs favorably at the C_3'-position to give III at first. In the course of the conversion of III into IV, the *cis* isomer IV_{cis} predominates because of the relatively lower activation energy. The protonation to the double bonds of IV_{cis} and IV_{trans} should result in the formation of the same cationic intermediate XV with free rotation of the C_2-C_3' single bond. The methanol addition to XV should lead to the thermodynamically most stable product I.

A similar reaction profile shown in Fig. 4 was obtained from the acetalation of methyl 2-formyl-3-methoxypropionate (XVI)[16] which was prepared as sodium salt from methyl acrylate by the usual method.

However, only one isomer was detected for methyl 2-methoxymethylene-3-methoxypropionate (XVII) in the reaction pathway of methyl 2-dimethoxymethylacrylate (XVIII)⇄XVII⇄methyl 2-dimethoxymethyl-3-methoxypropionate (XIX) (see Chart 4). Thus-formed XVII was identified as the *trans* isomer ($XVII_{trans}$) by the comparison of its NMR spectrum with that of the *cis* isomer ($XVII_{cis}$) which was obtained as a minor component from the methylation of the sodium salt of XVI with methyl iodide in an aprotic dipolar solvent such as dimethyl sulfoxide or dimethylformamide. The olefinic proton of the *cis* isomer $XVII_{cis}$ appeared at the higher field (6.50 ppm) than that of the *trans* isomer $XVII_{trans}$ (7.33 ppm).[17] No finding of the *cis* isomer $XVII_{cis}$ in the acidic acetalation should be attributed to the unfavorable steric interaction between the methoxycarbonyl group and the methoxy group of the 2-methoxymethylene moiety.

The rate constants shown in Chart 4 were analogously determined by the computer simulation, using the values of $k_5/k_{-5}=1.4$ and $k_6/k_{-6}=21.0$ which were given by the equilibrium amounts at 50°; $[XVII_{trans}]_e=4,4\%$, $[XVIII]_e=3.2\%$, and $[XIX]_e=92.4\%$. The

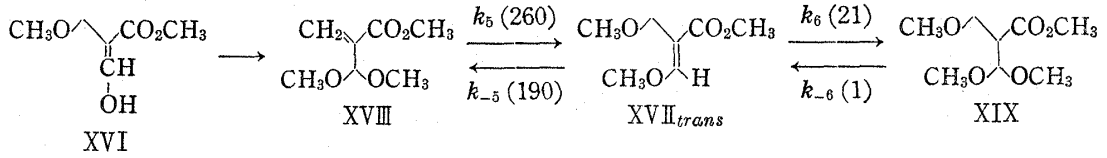

Chart 4. Acetalation of XVI

The values in parentheses represent the relative rate constants.

TABLE V. Kinetic Parameters[a] at 50° for the Interconversion among $XVII_{trans}$, XVIII, and XIX

Starting material	[HCl] (M)	Rate constants (min^{-1})			
		k_5 ($\times 10^2$)	k_{-5} ($\times 10^2$)	k_6 ($\times 10^2$)	k_{-6} ($\times 10^3$)
XVIII (0.5M)	0.23	11.8	8.6	0.9	0.4
	0.10	5.3	3.8	0.4	0.2
$XVII_{trans}$ (0.5M)	0.24	11.0	8.0	0.8	0.4
	0.10	5.2	3.8	0.4	0.2

a) Determined by computer simulation.

16) a) A. Takamizawa, K. Tokuyama, and H. Satoh, *Yakugaku Zasshi*, **79**, 664 (1959); b) T. Nishino, Y. Miichi, and K. Tokuyama, *Bull. Chem. Soc. Jpn*, **46**, 580 (1973).

17) For example, H COOCH3 / H OCH3 (6.35 ppm) H COOCH3 / H3CO H (7.47 ppm) see S.J. Rhoads, J.K. Chattopadhay, and E.E. Waali, *J. Org. Chem.*, **35**, 3352 (1970).

values obtained are presented in Table V and the relative rate constants are shown in parentheses of Chart 4.

An energy diagram for the interconversion among XVIII, XVII$_{trans}$, and XIX was quite similar to that among III, IV$_{cis}$, and I, but the former interconversion was found to proceed 10 times or more faster than the latter. The rate enhancement should stem from the weaker inductive effect of the methoxycarbonyl group than that of the nitrile group since the electron-withdrawing effect should make the cationic transition states less stable and more difficult.

In conclusion, we unambiguously established the reaction mechanism of II to I in the acidic medium involving the allyl cation intermediates V and VI. The cations were found to react with some electrophile. Therefore, these cations seem to promise a usefulness as electrophilic reagent.

Experimental

All melting points were recorded on a Kofler block and have not been corrected. NMR spectra were taken with a Varian A-60-A spectrometer and chemical shifts are given in δ-values referred to the internal tetramethylsilane (s; singlet, d; doublet, t; triplet, q; quartet, m; multiplet). IR spectra were measured with a JASCO IRA-2 spectrometer and the UV spectra a Perkin Elmer 202 spectrometer. Silica gel (Wako gel Q-23) was used for column chromatography. Silica gel (Wako gel B-5F) was used for thin-layer chromatography (TLC) and separated materials were detected with iodine vapor or UV light. The solvents used were removed under reduced pressure.

Preparation of 2-Dimethoxymethyl-3-methoxypropionitrile (I)——A mixture of acrylonitrile (2.63 g) and methyl formate (8.93 g) was added dropwise to sodium methoxide (5.34 g) on ice-cooling with stirring for 2.5 hr. The stirring was continued for 2 hr below 10° to give a yellow syrup containing the sodium salt of 2-formyl-3-methoxypropionitrile (II). This syrup was dissolved in 0.5 N methanolic hydrogen chloride (200 ml). The acid concentration of the solution was determined by titration to be 1.6 M. The reaction mixture was refluxed with stirring for 2 hr and then neutralized with 48% aq. NaOH below 10°. After the removal of precipitates by filtration, the filtrate was concentrated to dryness. The residual oil was extracted with benzene. After washing with water, the benzene was removed. The residue was distilled and a fraction in the range of bp 40—150° (3—4 mmHg) was collected to give a yellow oil (6.3 g) containing III (0.38 g), IV$_{cis}$ (0.38 g), IV$_{trans}$ (0.35 g), and I (4.45 g) (74% as the combined yield).

Reaction Profile of II——The sodium salt of II was prepared by the above procedure. This was dissolved in 1.03 N methanolic hydrogen chloride (200 ml). The acid concentration of the solution was 0.5 M. The reaction mixture was kept at 63° with stirring. Samples (20 ml) were taken up at appropriate time intervals and quenched by neutralization with 48% aq. NaOH (*ca.* 0.6 ml). The solution was diluted to 25 ml with methanol and then precipitates were removed by filtration. The contents of four components I, III, IV$_{cis}$, and IV$_{trans}$ were determined by GLC (conditions: column, 0.3 cm × 2.25 m long stainless steel packed with 15% PEG 20 M on Chromosorb W-AW; column temperature, 180°; a flow rate, He 40 ml/min; retention times (min), III (2.6), IV$_{cis}$ (15.1), IV$_{trans}$ (13.3), I (7.4), acetophenone[18] (4.4), and α-methylnaphthalene[18] (10.4)). Results are shown in Fig. 1.

Isolation of VII, VIII, IX, and X——The oily distillation residues (22.5 g) resulting in the above reactions were collected and submitted to column chromatography on silica gel (488 g) which was eluted with chloroform (500 ml) as fraction 1 and then chloroform–acetone (5: 1) as fractions 2 (320 ml), 3 (160 ml), 4 (400 ml), 5 (160 ml), 6 (540 ml), and 7 (400 ml). Each fraction was evaporated to dryness to give an oily residue. Fractions 1, 2, 4, and 6 gave complex mixtures. The addition of a small amount of chloroform to the fraction 3 (6.92 g) gave crystals. Recrystallization from methanol gave 2,6-dimethoxy-3,5-dicyano-3-methoxymethyltetrahydropyran (IX) as colorless needles (100 mg), mp 164—165°. *Anal.* Calcd. for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 54.96; H, 6.67; N, 11.75. IR ν_{max}^{Nujol} cm^{-1}: 2240 (C≡N). Fraction 5 (2.82 g) was subjected to preparative TLC (AcOEt–benzene=1: 1) to give a syrup which crystallized in MeOH–ether (1: 1). Recrystallization from methanol gave colorless needles of X (90 mg), mp 156—158°. *Anal.* Found: C, 55.07; H, 6.67; N, 11.47. IR ν_{max}^{Nujol} cm^{-1}: 2240 (C≡N). Fraction 7 (6 g) was subjected to preparative TLC (ether–petr. ether–MeOH=2: 2: 1) to give a crystalline product in the fast-moving zone. Recrystallization from MeOH–ether (1:1) gave 6-methoxy-5-cyano-5-methoxymethyl-3-methoxymethyl-enepiperidin-2-one (VII) as colorless plates (80 mg), mp 177—179°. *Anal.* Found: C, 55.12; H, 6.76; N, 11.57. UV $\lambda_{max}^{methanol}$ nm (ε): 245 (14000). IR ν_{max}^{Nujol} cm^{-1}: 2240 (C≡N), 3200, 1680, 1632 (-CONH). A syrup was obtained from the slow-moving zone and crystallized by the repeated preparative TLC. Recrystallization from methanol gave VIII as colorless plates (30 mg), mp 176—177°. *Anal.* Found: C, 54.83; H, 6.69; N, 11.52. IR ν_{max}^{Nujol} cm^{-1}: 2240 (C≡N), 3200, 1680, 1620 (-CONH).

18) Used as internal standard.

Reaction Profile of XVI——To an ice-cooled stirred powder of sodium methoxide (8.65 g) was added dropwise during 20 min a mixture of methyl acrylate (5.16 g) and methyl formate (10.8 g) below 5°. The stirring was continued for 1 hr at room temperature to give a pale yellow syrup containing the sodium salt of XVI. This syrup was dissolved in 3 N methanolic hydrogen chloride (200 ml). The acid concentration of the solution was 0.06 M. The reaction mixture was kept at 50° with stirring. Samples (20 ml) were taken up at appropriate time intervals and then analyzed by the procedure similar to that for I. Conditions of GLC: column, 0.3 cm × 3 m long stainless steel packed with 15% PEG 20 M on Chromosorb-W (60—80 mesh)–5% OV-17 on Gaschrom Q (80—100 mesh) (1: 1); column temperature, 154°; a flow rate, He 60 ml/min; retention times (min), XVIII (3.0), XVII*trans* (13.3), XIX (7.2), phenylacetate[18] (5.0), naphthalene[18] (9.0), and anethole[18] (12.0). Results are shown in Fig. 4.

Isolation of XVII*cis*——To a stirred solution of methyl 3-methoxypropionate (133 g) and methyl formate (276 g) in dry benzene (3 l) was added dropwise sodium hydride (50 g) washed with petr. ether. The reaction mixture was allowed to stand for 24 hr at room temperature. Precipitates were collected by filtration under dry nitrogen atmosphere, washed with dry benzene and then with dry ether. After dryness at 50° under reduced pressure, the sodium salt (50 g) of methyl 2-formyl-3-methoxypropionate (XVI) was obtained as a white powder and dissolved in a mixture of dimethyl sulfoxide (1.2 l) and dioxane (1.5 l). After the addition of methyl iodide (353 g) to the solution, the reaction mixture was stirred for 4 hr at 10—20°. After the removal of precipitates by filtration, the filtrate was poured into water (1 l) and extracted with benzene (2 l). The benzene extract was washed with water and dried over anhydrous Na_2SO_4. After the evaporation of the benzene, the residue was submitted to column chromatography on silica gel (ether–petr. ether=1: 1). The first eluate gave XVII*trans* as an oil (5 g) which was identified with an authentic sample reported in the previous paper.[19] XVII*trans*, $n_D^{26.5}$: 1.4644. UV $\lambda_{max}^{methanol}$ nm (ε): 237 (15200). IR ν_{max}^{film} cm^{-1}: 1712 (C=O), 1642 (C=C). NMR (CCl_4) δ: 3.18 (3H, s, $CH_2O\underline{CH_3}$), 3.65 (3H, s, $CO_2\underline{CH_3}$), 3.85 (3H, s, C=$CHO\underline{CH_3}$), 3.98 (2H, s, $\underline{CH_2}OCH_3$), 7.33 (1H, s, C=$C\underline{H}OCH_3$). The second eluate gave XVII*cis* as an oil (1.2 g), $n_D^{25.0}$: 1.4705. *Anal.* Calcd. for $C_7H_{12}O_6$: C, 52.49; H, 7.55. Found: C, 52.31; H, 7.56. UV $\lambda_{max}^{methanol}$ nm (ε): 240 (16000). IR ν_{max}^{film} cm^{-1}: 1710 (C=O), 1640 (C=C). NMR (CCl_4) δ: 3.25 (3H, s, $CH_2O\underline{CH_3}$), 3.67 (3H, s, $CO_2\underline{CH_3}$), 3.79 (3H, s, C=$CHO\underline{CH_3}$), 3.86 (2H, d, J=1Hz, $\underline{CH_2}OCH_3$), 6.50 (1H, t, J=1 Hz, C=$C\underline{H}OCH_3$).

Reaction Profiles of III, IV*cis*, IV*trans*, XVII*trans* and XVIII——The reaction was carried out in a 20 ml mess-flask equipped with a stopper. To the flask were transferred a starting material and a methanol solution of hydrogen chloride. The solution was diluted to 20 ml with methanol to be brought to required concentrations and then kept at 50±1°. The acid concentration of the solution was determined by titration with NaOH. Samples (1 ml) were withdrawn at appropriate time intervals, neutralized with a methanol solution of NH_3, diluted to 10 ml with methanol, and then analyzed quantitatively by GLC. The equilibrium concentration was determined by the relative peak height of the sample against 1 and 2% standard solutions. Conditions of GLC: column, 0.3 cm × 3.2 m long glass packed with 15% PEG 20 M on Chromosorb-W (80—100 mesh) A-W; column temperature, 197°; a flow rate, He 60 ml/min; retention times (min), III (2.6), IV*trans* (12.4), IV*cis* (13.6), I (7.5), acetophenone[18] (4.3), phenylacetonitrile[18] (10.4) and nitrobenzene[18] (5.8). The same GLC conditions as mentioned above were used for XVII*trans*, XVIII, and XIX.

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19) The previous authors[16b] have not established the configuration.