Effects and Role of the Substituents upon 2-Pyridone-catalyzed Mutarotation of 2,3,4,6-Tetra-*O*-methyl-D-glucose

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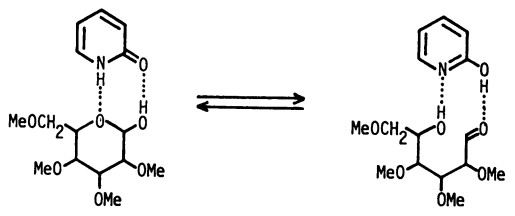
We have studied the catalytic activities of various substituted 2-pyridones on the mutarotation of 2,3,4,6-tetra-*O*-methyl-D-glucose (TMG). The results in an acetone solution at 37 °C showed that an introduction of the polar substituents into the 5- or 6-position, regardless of the nature of the substituents, retarded the relative rate of the mutarotation as compared to a parent compound, while that of alkyl substituents accelerated such rates. Further striking rate enhancements were observed in 5,6-dimethyl-substituted derivatives. Based on experimental results, we concluded that the 2-pyridones which can act as an effective catalyst are such that the 2-pyridone tautomeric form predominantly exists in solution due to its greater association ability and that the 2-pyridinol tautomeric form is energetically more stable for a lower activation energy of the double-proton transfer process in the 2-pyridone-TMG complex.

In a previous paper,[1] we described the influence on the tautomeric properties of 2-pyridones–2-pyridinols exerted by the introduction of substituents on the basis of the quantum mechanical quantities obtained from semiempirical molecular orbital calculations.

The importance of simultaneous two-proton transfers in a bifunctional catalysis is well known in relation to the enzymatic catalysis, and many related systems have been studied along these lines.[2] Among those is the classical 2-pyridone-catalyzed mutarotation of 2,3,4,6-tetra-*O*-methyl-D-glucose (TMG), which is of continued interest and is still under active investigations because of its high catalytic activity. Its very high catalytic efficiency can not be explained by the concerted general acid-base concept, since 2-pyridone is a relatively weak acid and base. Also, the reported rationalization of the catalytic functions are somewhat controversial. This indicates that a delicate balance of many blends of the effects can affect catalytic activities, and that the phenomenon can not be explained in a simple manner.

Tautomeric properties are considered to be of particular importance related to the efficiency of bifunctional catalytic activities, yet full details of the relationship to the tautomeric properties have not yet been understood. Part of our efforts in this area have involved an attempt to explore the substituent effects on the rate of the 2-pyridone-catalyzed mutarotation of TMG.

We report here on the interesting features of such effects and discuss the relations to the tautomeric properties. We also discuss the mechanism on the mutarotations with the aid of quantum mechanical quantities reported in a previous paper.[1]



Scheme 1.

Experimental

^{1}H-NMR spectra were obtained on a Hitachi R-20 spectrometer (60 MHz), in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard. All chemical shifts are in parts per million (δ) from TMS. IR spectra were taken on KBr disks with a JASCO A-102 spectrophotometer and were calibrated against polystyrene. UV spectra were measured in cyclohexane with a Hitachi 323 spectrophotometer. Mass spectra were obtained at 70 eV with a JEOL JMS-D300 spectrometer. Elemental analyses were carried out by the Microanalytical Laboratory, Gifu Pharmaceutical University. All melting points are uncorrected.

2-Pyridone (**1**) and 6-chloro-2-pyridinol (**17**) were commercially available. 3-Methyl- (**2**), 4-methy- (**3**), 5-methyl- (**4**), 6-methyl- (**5**), and 4,6-dimethyl-2-pyridone (**7**) were prepared by diazotization of the corresponding substituted 2-pyridinamine, respectively.[3] 3,5-Dimethyl-2-pyridone (**6**) was prepared from 3,5-lutidine *N*-oxide according to the method of Bain and Saxtone.[4] 4,5,6-Trimethyl-2-pyridone (**9**),[5] 5-bromo-3-methyl-2-pyridone (**13**),[6] 3-methyl-5-nitro-2-pyridone (**14**),[7] 2,3-dihydro-4-methylfuro[2,3-*b*]pyridin-6-ol (**15**),[8] and 6-methoxy-2-pyridinol (**16**)[9] were prepared according to reported procedures. 2,3,4,6-Tetra-*O*-methyl-D-glucose (TMG) was prepared according to a method found in the literature.[10] All compounds used for the present study gave satisfactory spectral properties and elemental analyses.

Preparation of 2-Pyridones (10, 11, and 12). General Procedure: To polyphosphoric acid (125 g) were added the β-ketonitrile (0.05 mol)[11,12] and the ketone (0.05—1.10 mol). The mixture was stirred at 70 °C for 1.5 h, then at 100—120 °C for 1.5 h. The dark mixture was then added to crushed ice (*ca.* 1 Kg) while stirring. Then, ether (500 ml) was added. The resulting mixture was stirred for 30 min. The aqueous layer was neutralized with solid sodium hydrogencarbonate. The precipitated solid was collected and recrystallized from ethanol to give the 2-pyridones.

3,4,5,6-Tetramethyl-2-pyridone (10): Colorless plates, mp 255—256 °C. Found: C, 71.27; H, 8.80; N, 9.04%. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26%. ^{1}H-NMR: δ=1.98 (s, 3H, 3-Me), 2.11 (s, 6H, 4-Me and 5-Me), 2.32 (s, 3H, 6-Me), 13.0 (br, s, 1H, NH); IR: 3200—2200 (br, NH), 1630 cm^{-1} (C=O); UV: 237 (ε 6600), 304 nm (ε 6500); EIMS: *m/z* (% of base) 151 (M^+, 100), 123 (20), 122 (75), 108 (35).

3,5,6-Trimethyl-4-phenyl-2-pyridone (11): Colorless plates, mp

216—217°C. Found: C,78.98; H, 7.21; N, 6.64%. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.08; N, 6.56%. ^{1}H-NMR: δ= 1.67 (s, 3H, 3-Me), 1.85 (s, 3H, 5-Me), 2.35 (s, 3H, 6-Me), 13.2 (s, 1H, NH); IR 3200—2400 (br, NH), 1640cm^{-1} (C=O); EIMS: *m/z* (% of base) 213 (M^+, 62), 212 (100), 194 (17), 184 (11), and 167 (13).

*3-Methyl-4-phenyl-2*H*-cyclopenta[*b*]pyridin-2-one (12)*: Colorless needles, mp 213—215°C. Found: C, 79.94; H, 7.76; N, 6.13%. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22%. ^{1}H-NMR: δ=1.98 (s, 3H, 3-Me), 2.02 (br, m, 2H, CH_2), 2.46 (br, t, J=6Hz, 2H, CH_2), 2.97 (br, t, J=9Hz, 2H, CH_2), 7.05—7.63 (m, 5H, Ar), 13.35 (br s, 1H, NH); IR: 3200—2200 (br, NH), 1630cm^{-1} (C=O); UV: 228 (ε 14800), 319nm (ε 5600); EIMS: *m/z* (% of base) 225 (M^+, 57), 224 (100), 216 (15), 196 (7).

Rate Measurements. The solvents of acetone and benzene (Extra-pure grade, Wako-pure Chemicals, Ltd.) were purified by distillation before use. The rate of mutarotation was followed using a JASCO DIP-4 digital polarimeter. The rate measurements were carried out according to the method of Smith and Hearn.[13] The pseudo first-order rate constants for the mutarotation were calculated by a least-squares method.

Infrared Spectral Measurements for Intensities of the Monomeric NH Stretching Bands (log I_o/I). The solvent of carbon tetrachloride (spectroscopic grade) was dried over molecular sieves. Measurements were made with a JASCO DS-403G Infrared Grating spectrophotometer using a 20mm NaCl cell. The infrared spectra (3600—3200cm^{-1}) were recorded with solvent compensation using a five-fold-scale expansion in transmittance at room temperature.

Results and Discussion

For the substituent effects of 2-pyridones on the mutarotation of TMG, only the study of each of its four monomethyl-substituted 2-pyridones in the 3-, 4-, 5- or 6-position and electron-withdrawing groups in the 5-position has been reported as far as we are aware.[13] It has been shown that the electron-withdrawing groups in the 5-position retarded the rate of mutarotation and that the active catalyst was in the 2-pyridone form. The tautomeric properties are considered to be an important factor in determining the reaction rate. All the 2-pyridones examined, however, were those known to exist largely in the 2-pyridone form in a polar solvent.

Substituent Effect of 2-Pyridone on the Catalytic Activity. We have studied the substituent effects on the rate of the mutarotation of TMG in acetone using various substituted 2-pyridones including compounds (**15**—**17**) whose tautomeric equilibria are experimentally known to favor the 2-pyridinol form in solution.[14] Acetone was chosen as a solvent because of the high solubility of the substituted 2-pyridones.

The rate-constants obtained at 37°C are listed in Table 1.

Table 1 shows that the catalytic activities of 2-pyridones are not amenable to a simple rationalization and discloses several interesting features. The derivatives (**13**—**17**) which possess a polar substituent at the 5- or 6-position regardless of the electron-withdrawing or -donating substituents showed much less catalytic activity compared to that of the parent compound; the compounds bearing a rather strong electron-withdrawing group at the 5-position (**13**, **14**), which favor the 2-pyridone form over the 2-pyridinol form,[14] and the ones bearing a polar substituent (-OMe and -Cl) at the 6-position (**15**—**17**), which exist very largely in the 2-pyridinol form,[14] are both poor catalysts.

Hence, it appears that the catalytic activity of 2-pyridones on the mutarotation of TMG is not simply related to the apparent abundance of either of the tautomeric forms.

In contrast, the alkylated derivatives (**2**—**12**) were shown to display higher catalytic activities than the parent compound (**1**). Among them, the 6-methyl substituent seems to exert the strongest influence on the rate acceleration.[15] Further striking rate enhancements were observed in derivatives bearing methyl substituents at both the 5- and 6-positions (**8**—**10**).

It is known that each of 2-pyridones and TMG undergoes self-association by hydrogen bonding in nonpolar solvents[16] and that the tautomerisms occur *via* a dynamic process involving double proton transfers in self-association forms.[17] However, the initial stage of the 2-pyridone-catalyzed mutarotations of TMG must involve the formation of a hydrogen-bonded complex between 2-pyridone and TMG. Therefore, the association ability should closely be related to the catalytic activity of the 2-pyridones.

The self-association abilities can be regarded as an experimental criteria for the 2-pyridone-TMG association ability. Such abilities of several methyl derivatives were measured by IR spectra based upon the intensity of the NH stretching band (around 3400cm^{-1}) of the monomeric species as log (I_o/I).

The relative catalytic activities (k_r) in Table 1 were plotted against log (I_o/I), and are shown in Fig 1.

It can be seen from Fig. 1 that the abundance of the monomeric form in a series of 6-methy derivatives (**5** and **7**—**10**) is obviously small. This fact is also consistent with the greater self-association ability of these derivatives deduced from the CNDO/2 calculations previously reported.[1] Although the data, thus measured, are not of high accuracy due to experimental limitations, the relative catalytic activities (k_r) of **1**—**7** were shown to be considerably well correlated with log (I_o/I), as indicated in Fig. 1. Thus, it seems reasonable, to a first approximation, to consider that the catalytic activity of the 2-pyridone is proportional to its association ability.

However, the large deviation of 5,6-dimethyl derivatives (**8**—**10**) from the line strongly indicated that other factors could contribute to the higher catalytic activities of this series.

Concerning a Pronounced Effect of 5,6-Dimethyl Substitutions. In view of the observations that the association abilities of the 6-methyl (**5**) and (**7**), and

Table 1. Pseudo first- order rate constants for mutarotation of TMG catalyzed by substituted 2-pyridones at 37 °C[a)]

2-Pyridones catalyst	Substituent				$k_{obsd}/10^{-3}\,min^{-1}$	r[b)]	k_r[c)]
	R_3	R_4	R_5	R_6			
1	H	H	H	H	4.16	0.9896	1.000
2	Me	H	H	H	4.25	0.9984	1.022
3	H	Me	H	H	7.45	0.9981	1.791
4	H	H	Me	H	6.56	0.9976	1.577
5	H	H	H	Me	8.55	0.9965	2.055
6	Me	H	Me	H	6.35	0.9982	1.526
7	H	Me	H	Me	9.67	0.9805	2.325
8	H	H	Me	Me	14.12	0.9973	3.394
9	H	Me	Me	Me	21.24	0.9861	5.106
10	Me	Me	Me	Me	20.45	0.9991	4.916
11	Me	Ph	Me	Me	24.25	0.9977	5.829
12	Me	Ph	$-(CH_2)_3-$		10.01	0.9968	2.406
13	Me	H	Br	H	2.32	0.9921	0.558
14	Me	H	NO_2	H	0.93	0.9903	0.224
15	H	Me	$-CH_2CH_2O-$		3.74	0.9978	0.899
16	H	H	H	OMe	0.92	0.9733	0.221
17	H	H	H	Cl	1.41	0.9879	0.339

a) [TMG]=0.09 M and [2-pyridones]=0.005 M. (1 M=1 mol dm^{-3}) b) Correlation coefficient. c) $k_{obsd}/k_{obsd(parent)}$

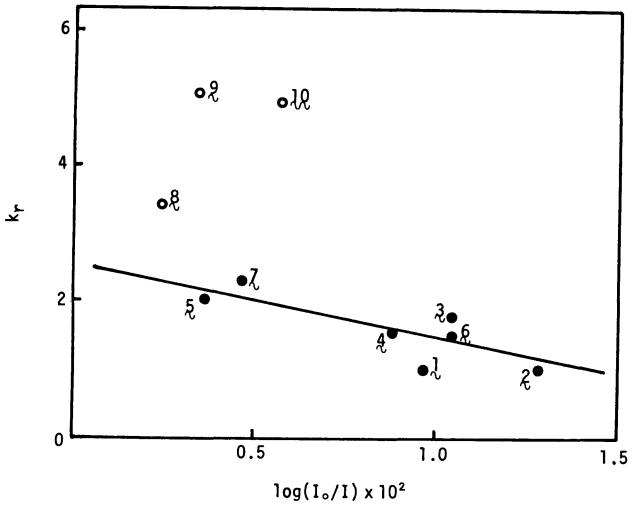


Fig. 1. Plot of the relative catalytic activities (k_r) *vs.* the intensities of the monomeric NH stretching band ($\log(I_0/I)$).
The straight line obtained by a least squares method of **1**—**7** may be expressed as $Y(k_r)=-1.2131\,X(\log(I_0/I))+2.6677$ and the correlation coefficient (r) was obtained as $r=-0.8126$.

5,6-dimethyl derivatives (**8**—**10**) are more or less the same (Fig. 1), such abilities do not account for the striking rate enhancement of a series of 5,6-dimethyl derivatives (**8**—**12**).

The 6-methyl substituent has been shown to render the effect in nature similar to the polar substituents on the relative energetic between the two tautomers (*i.e.* the greater stabilization of 2-pyridinol form), but to a much lesser extent and, to make the tautomeric equilibria labile to the molecular environment. It has also been shown that this propensity was further strengthened by 5,6-dimethyl substitutions.[1)] The origin of these particular substituent effects can be interpreted as due to bond lengthenings at the C_5–C_6 bond, which apparently weaken the diene character to lead to the more 2-pyridinol-like ring structure.

The ring structural difference between the two tautomeric forms should also be related to the kinetics of the tautomerization. Such may be inversely proportional to each other based on the principle of least nuclear motion,[18)] and the derivatives, which require less structural variations during the tautomerization, may be of small activation energies.

Thus, the further acceleration of the rate of the mutarotation catalyzed by 2-pyridones is ascribed to the tautomeric properties, since such reactions proceed with the tautomerization of 2-pyridones.

Inversely, the extremely large predominance to either of the two tautomeric forms induced by an introduction of polar substituents would lead to a retardation of the dynamic process involving the double proton transfers. This rationalization is consistent with the fact that 2-pyridones bearing 6-polar substituents were poor catalysts (*vide supra*), and no further rate enhancement of the mutarotation was observed in the cyclopenta-derivative (**12**) as compared to that of the other derivatives bearing two methyl groups at both 5- and 6-positions, since the C_5–C_6 bond in **12** is no longer lengthened due to the absence of the buttressing effects of the methyl group on each other.

Reactions in Benzene. We have measured the rate of the TMG-mutarotations on several methyl derivatives (**1**, **5**, and **8**) in benzene at various temperatures (10 °C—38 °C) because of the greater tendency for the enhancement of the association in a nonpolar solvent. The pseudo first-order kinetics (k_{obsd}) are summarized in Table 2 along with the correlation coefficient (r) of the least-squares treatment at each temperature.

Table 2 clearly indicated that a considerable rate

TABLE 2. TEMPERATURE- DEPENDENT RATE CONSTANT FOR MUTAROTATION OF TMG CATALYZED BY SUBSTITUTED 2-PYRIDONES IN BENZENE[a)]

2-Pyridones catalyst	Temp/°C	k_{obsd}/ 10^{-3} min^{-1}	r[b)]
1	10.0	3.947	0.9966
	18.0	9.857	0.9940
	26.0	21.588	0.9984
	38.0	57.995	0.9966
5	10.0	4.817	0.9970
	18.0	13.054	0.9978
	27.0	27.141	0.9958
	36.5	56.956	0.9971
8	10.5	9.339	0.9979
	18.0	17.876	0.9989
	28.5	52.438	0.9975
	37.0	96.927	0.9987

a) [TMG]=0.09 M and [2-pyridones]=0.002 M. b) Correlation coefficient.

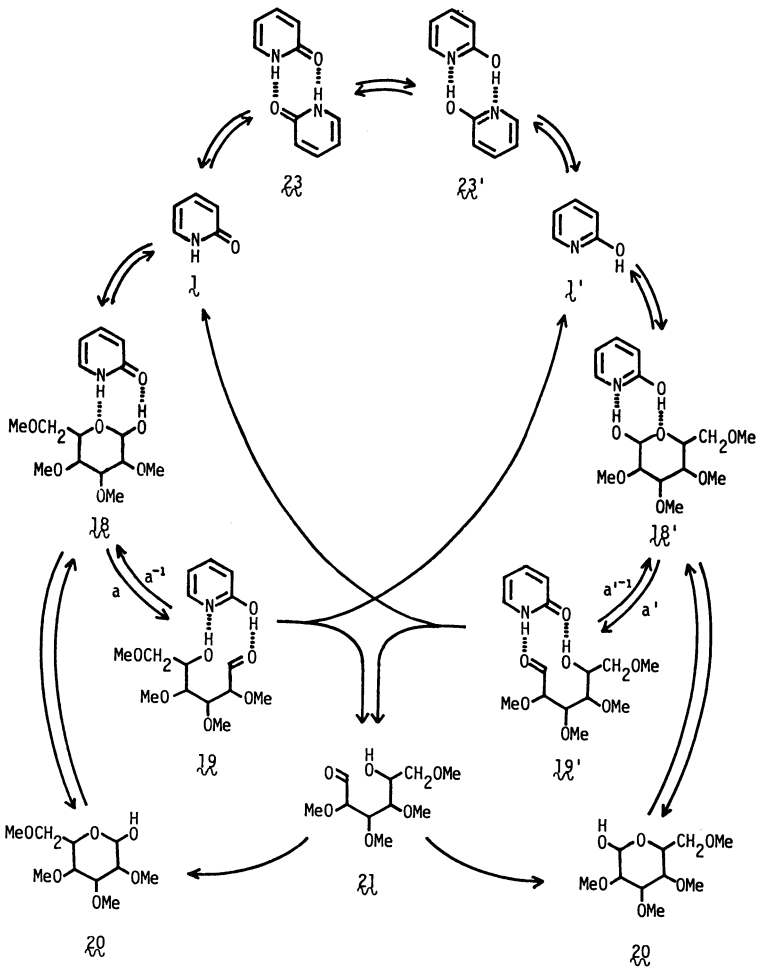
enhancement was observed in a benzene solution as compared to those in acetone at the same temperature. The solvent effect of acetone upon the lower rate can be rationalized in terms of the lower concentration of the 2-pyridone–TMG complex and a higher activation energy of the double proton-transfer process by the greater solvation in such a complex.

Conclusions

On the basis of the results and discussion described above, we deduced the sequences for the mutarotation of TMG catalyzed by 2-pyridones as shown in Scheme 2 for a parent compound (**1**) as an example.

In Scheme 2, the ring-opening processes, ***a*** and ***a'***, include the breaking of the σ-bond in TMG and are considered to require the largest activation energy, and to be important in determining the rate of mutarotation. Of these, process ***a*** is apparently important due to the greater association ability of the pyridone form and the activation energy is considered to be dependent on the relative energetics of **18** and **19**.

It can be concluded, therefore, that for the 2-pyridones to be effective catalysts, the 2-pyridone form predominantly exists in solution due to a greater self-association ability (for higher concentration of the complex (**18**)), and the 2-pyridinol tautomeric form is intrinsically more stable (for a lower activation energy of process ***a***). The tautomeric properties of 6-methyl derivatives, especially 5,6-dimethyl and 4,5,6-trimethyl derivatives, meet the above mentioned requirements[1)]



Scheme 2.

and, indeed, these derivatives were all effective catalysts.

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