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On the Molecular Form of D-Xylo-5-hexulosonate in Aqueous Solutions

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Molecular forms of D-xylo-5-hexulosonate (5-keto-D-gluconate) in aqueous solutions were investigated by ultraviolet (UV), infrared (IR) and nuclear magnetic resonance (NMR), respectively, to see a reactive form that would participate in its catalytic hydrogenation by metals. Inspection of UV and IR spectra led to the result that both ketal and ketone forms coexist and that the two forms are readily convertible with each other. NMR spectra of 5-keto-D-gluconates were presented and discussed complementarily.

The crystal structure of calcium D-xylo-5-hexylosonate (calcium 5-keto-D-gluconate) has been determined by Balchin and Carlisle[2] on the basis of X-ray analysis. They have shown that the ring closure occurred between α and δ carbon, resulting in a nonplanar furanoid ring with a new asymmetric center at δ as shown in Fig. 1a. In the previous paper,[3] we have investigated the catalytic hydrogenation of this compound dispersed in aqueous phase with special interest in the selective formation of calcium L-idonate. Since it is generally known that a ketal form is resistive against the hydrogenation by metal catalyst or sodium borohydride, our result that the hydrogenation of 5-keto-D-gluconic acid and its salts proceeds fairly well in its aqueous solution,[4] suggests the possibility of the presence of a carbonyl form (Fig. 1b, c) in its dissolved state in aqueous solution in contrast with the hemi-ketal ring structure of calcium 5-keto-D-gluconate (Fig. 1a) in its solid state. Undoubtedly, the molecular form of this compound in aqueous solution, especially either hemi-ketal (Fig. 1a), chain (b) or γ-lactone (c), should play an important role for the reaction. Thus, it was thought desirable for us to get information concerning to molecular forms of this compound in aqueous phase.

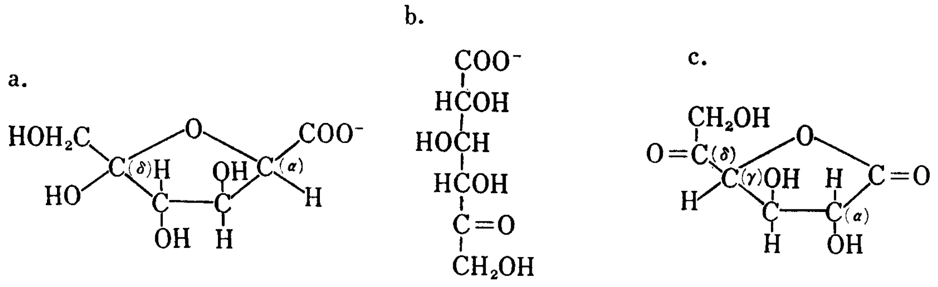

Fig. 1. Possible Molecular Form of 5-Keto-D-gluconic Acid

a. cyclic hemi-ketal form b. chain form c. γ-lactone form

In the present paper will be presented the result of investigation on the molecular form of sodium 5-keto-D-gluconate and its acid form in aqueous solutions by ultraviolet (UV), infrared (IR) and nuclear magnetic resonance (NMR) spectroscopic techniques, respectively.

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[1] Location: *7-3 Hongo, Bunkyo-ku, Tokyo.*

[2] A.A. Balchin and C.H. Carlisle, *Acta Cryst.*, **19**, 103 (1965).

[3] C.Y. Chen, H. Yamamoto and T. Kwan, *Chem. Pharm. Bull.* (Tokyo), **17**, 2349 (1969).

[4] C.Y. Chen, H. Yamamoto and T. Kwan, *Chem. Pharm. Bull.* (Tokyo), submitted for publication

Experimental

Samples of calcium 5-keto-D-gluconate, calcium D-gluconate and sodium L-idonate were supplied from Takeda Chemical Industries. 5-Keto-D-gluconic acid was prepared by passing a suspended aqueous solution of calcium 5-keto-D-gluconate through the column packed with Amberlite CG–120 H^+ type ion exchange resin, and its sodium salt was prepared by neutralizing the acid to pH 7—8 with sodium hydroxide solution followed by evaporation. The pH of sample solutions was 3 for acid form and 7—8 for salt form.

The UV spectra were recorded on a Cary 11 ultraviolet spectrophotometer. Temperature dependency of the UV absorption was investigated in nitrogen atmosphere by a Shimadzu QV–50 ultraviolet spectrophotometer attached with a temperature controlling device.

The IR spectra were recorded with a DS-402G infrared spectrophotometer (Japan Spectroscopic Co.). Samples were measured in deuterium oxide (D_2O) solution as a thin liquid film at room temperature.

The 60 MHz NMR spectra were recorded with a Japan Electron Optics JNM 60 type high-resolution spectrometer equipped with a variable temperature device. Chemical shifts were determined by using sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as an internal standard. The measurement was undertaken mostly at room temperature.

Results and Discussion

The UV spectra of 5-keto-D-gluconic acid and its sodium salt were investigated in aqueous solutions. Both forms of the compound gave essentially the same spectra exhibiting a maximum absorption around 280 mμ. The molar absorption coefficient was found to be 7 at 25°. On the other hand, no absorption was found around this wavelength for any of L-idonic acid, D-gluconic acid and their sodium salts which lack carbonyl group. So, this absorption for 5-keto-D-gluconic acid is assignable to the carbonyl group. The spectra of D-gluconic acid

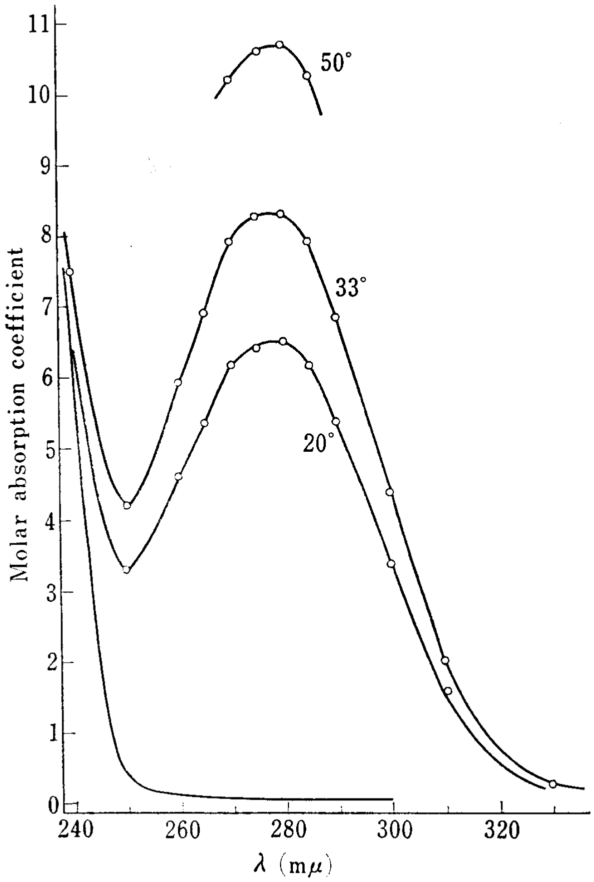

Fig. 2. The UV Spectra of D-Gluconic Acid (20°) and 5-Keto-D-gluconic Acid (20°, 33° and 50°)

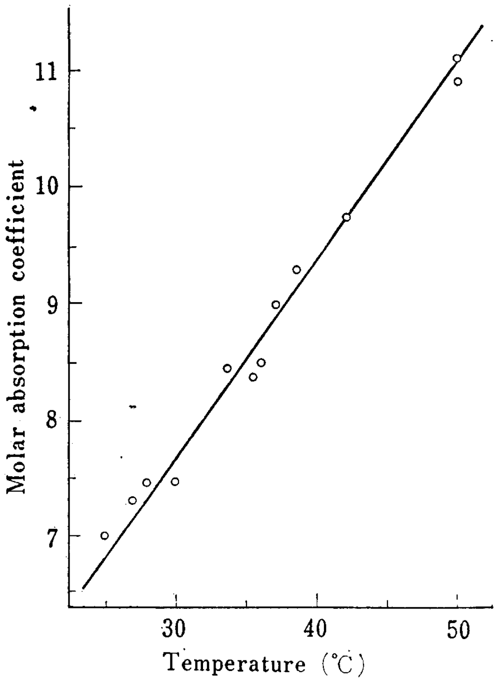

Fig. 3. The Change of the Molar Absorption Coefficient of 5-Keto-D-gluconic Acid and Sodium 5-Keto-D-gluconate with Temperature Variations

and 5-keto-D-gluconic acid are compared in Fig. 2, where temperature dependecny of the maximum absorption is also illustrated for 5-keto-D-gluconic acid. It should be noted that the intensity of the absorption around 280 mμ increases with increasing temperature.

The changes in the absorption intensity were reversible with respect to temperature variations and so quick enough as apparently controlled by the temperature of the cell. In Fig. 3 is shown the change of the molecular absorption coefficient of 5-keto-D-gluconic acid against temperatures. From the data of Fig. 3 the temperature coefficient was calculated to be 4—5 kcal/mole. Similar temperature dependency of the molar absorption coefficient was recognized also with sodium 5-keto-D-gluconate.

It is generally accepted that carbonyl group of organic compounds in aqueous solution exhibits a maximum absorption around 270—285 mμ with molar absorption coefficient from 20 to 30.5) It is also known that the absorption intensity of the carbonyl group of aldoses tends to decrease due to the formation of a cyclic hemi–ketal ring.6) In this connection, reference may be made to the work by Hurd and Saunders,7) who studied the position of equilibrium of acyclic⇌cyclic transformation of ω-hydroxy aldehydes on the basis of the molar absorption coefficient near 290 mμ and that of the corresponding ω-methoxy aldehydes. The work indicated that the molar absorption coefficient of a carbonyl group is about 20.

In the light of the work mentioned above, our observation on the UV spectra of 5-keto-D-gluconic acid and its sodium salt seems to indicate, at least qualitatively, the presence of carbonyl group; 5-keto-D-gluconic acid and its sodium salts exist primarily as the cyclic hemiketal form (Fig. 1a) in aqueous solutions, while a part of them (20—30%) is believed to exist as the ketonic form (Fig. 1b or c) at room temperature. The two forms are in equilibrium and the transformation between them is very fast. The amount of the ketonic form increases with increasing temperature. Thus, above 60°, where the catalytic hydrogenation of 5-keto-D-gluconic acid has been investigated,4) the ketonic form may well be the main species.

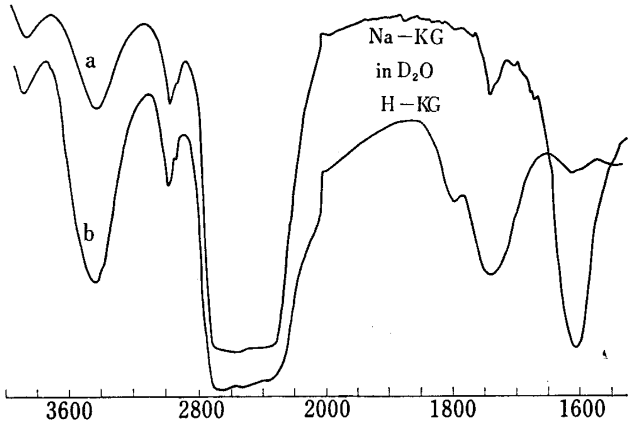

Fig. 4. The IR Spectra of a. Sodium 5-Keto-D-gluconate in D$_2$O, b. 5-Keto-D-gluconic Acid in D$_2$O

The IR spectra of 5-keto-D-gluconic acid and its sodium salt were investigated in deuterium oxide to obtain further informations on their molecular forms. These spectra are shown in Fig. 4. As shown in Fig. 4a, sodium 5-keto-D-gluconate gave rise to absorptions at 1600 cm^{-1} and 1730 cm^{-1} assignable to –COO$^-$ and $>$C=O, respectively. Judging from the relative intensity of the 1730 cm^{-1} absorption and of the 2950 cm^{-1} band due to the C–H absorption as compared with those of the corresponding absorptions of such compounds as acetone, cyclohexanone or α-hydroxycyclohexanone8), it seems very probable that a minor part of sodium 5-keto-D-gluconate exists as the chain form (Fig. 1b) consistently with the result of the UV spectra.

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5) R.M. Silverstein and G.C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley & Sons, Inc., 1963, p. 104; "Jikken Kagaku Koza" Vol. 1, ed. by Japan Chemical Society, 1956, p. 50.

6) E.L. Eliel, N.L. Allinger, S.J. Angyal, and G.A. Morrison, "Conformational Analysis," John Wiley & Sons, Inc., 1963, p. 380; B. Capon and W.G. Overend, *Advance in Carbohydrate Chemistry*, **15**, 27 (1960).

7) C.D. Hurd and W.H. Saunders, Jr., *J. Am. Chem. Soc.*, **74**, 5324 (1952).

8) Sheehan, O'Neill and White have shown9) that α-hydroxycyclohexanone exists as a dimer hemi-ketal form in solid state. On the other hand, our investigation10) indicated that the molecule exists mainly as a dimer in DMSO solution similar to the case of solid state, while it exists literally as a monomer in aqueous solutions.

In the spectra of 5-keto-D-gluconic acid no absorption was observable at 1600 cm^{-1} while a strong absorption at 1730 cm^{-1} due to –COOH and $\rangle$C=O was detectable. Also a weak absorption around 1790 cm^{-1} due to γ-lactone[11] is noticeable in the spectra. As both the γ-lactone and the hemi-ketal ring can not intramolecularly coexist, the existence of γ-lactone (Fig. 1c) would mean the presence of carbonyl group. Lactones of D-gluconic acid are known to be more stable than chain form in an acidified aqueous solution.[12] So, the above result on UV and IR spectra seems to indicate that a major part of 5-keto-D-gluconic acid exists as the hemi-ketal form (Fig. 1a) accompanied with the γ-lactone form (Fig. 1c) as a minor one.

The NMR spectra of calcium D-gluconate, 5-keto-D-gluconic acid and its sodium salt were investigated in deuterium oxide. These spectra, measured mostly at room temperature, are shown in Fig. 5.

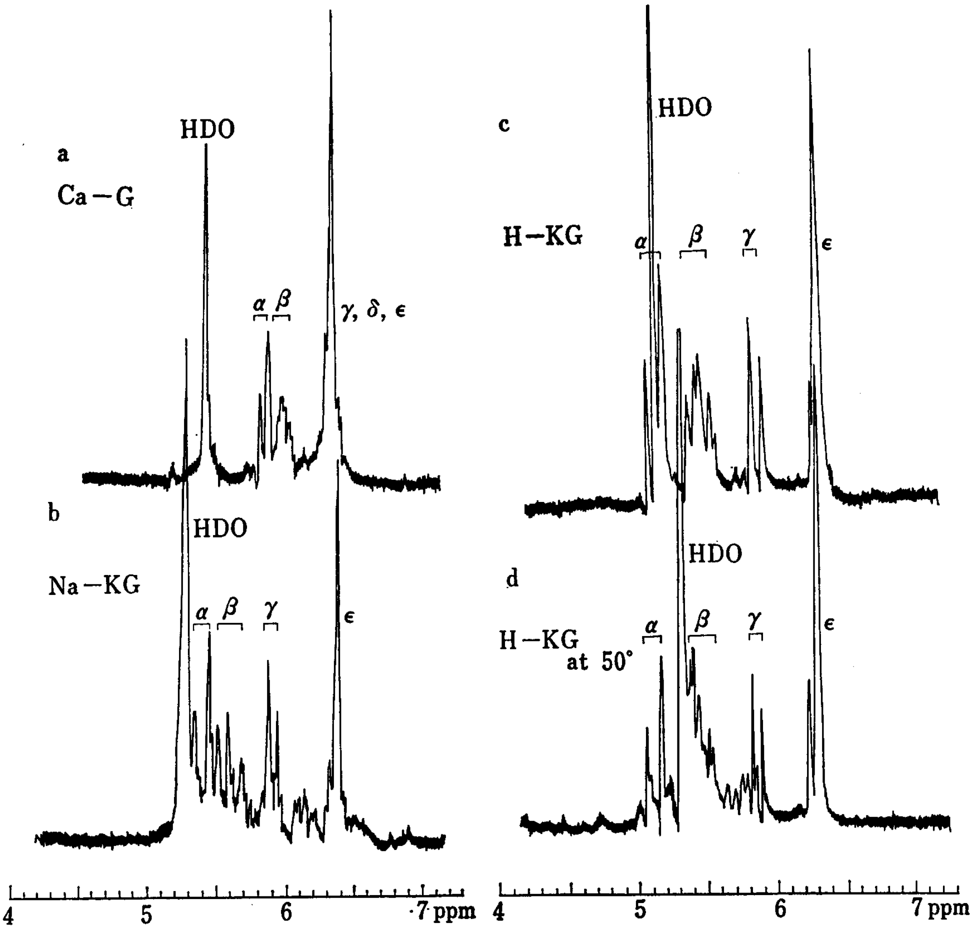

Fig. 5. The NMR Spectra of a. Calcium D-Gluconate, b. Sodium 5-Keto-D-gluconate, c. 5-Keto-D-gluconic Acid, d. 5-Keto-D-gluconic Acid(50°)

The NMR spectra of D-gluconate ion were essentially the same with those reported by Sawyer and Brannan.[13] According to their interpretation, the NMR spectrum for calcium D-gluconate, was analyzed (Fig. 5a). The spectra of 5-keto-D-gluconic acid were observed in both basic and acidic media respectively (Fig. 5b and c). They consisted of doublet, quartet,

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9) J.C. Sheehan, R.C. O'Neill, and M.A. White, *J. Am. Chem. Soc.*, 72, 3376 (1950).

10) H. Yamamoto, T. Oka, C.Y. Chen, and T. Kwan, unpublished data.

11) A.D. Cross, "An Introduction to Practical Infrared Spectroscopy," Butterworths Scientific Publications, 1960, p. 64.

12) H.S. Isbell and H.L. Frush, "Methods in Carbohydrate Chemistry," Vol. 2, Academic Press, New York, 1963, p. 16.

13) D.T. Sawyer and J.R. Brannan, *Anal. Chem.*, **38**, 192 (1966).

doublet and singlet signal from the lower field to the higher, the intensity ratios being given approximately as 1:1:1:2. The signals were assigned, as shown in the figure, on the basis of the splittings, intensity ratios and the shift of the lowest doublet signal which appeared to depend on the pH of the medium.

In the spectra for 5-keto-D-gluconic acid and its salt, the signals of the α, β, and γ protons appeared at rather lower field compared with those of calcium D-gluconate. The phenomenon may probably be due to the formation of a hemi–ketal ring. The interpretation is not inconsistent with the observed result of UV or IR as mentioned before. The minor component of the signals observable in the spectra b and c was somewhat obscure due to their ill-resolution. However, the spectrum of 5-keto-D-gluconic acid, measured at 50°, showed the decrease of α and γ protons accompanied by some side signals around the original ones as shown in Fig. 5d. It would be possible to interpret this phenomenon with regard to the formation of γ-lactone in correlation with the UV and IR spectra described above. However, further studies are required to draw an unambiguous remark on the interpretation of the NMR spectra.

Summing up the discussions, it is suggested that sodium 5-keto-D-gluconate consists of a mixture of hemi-ketal and ketone forms in aqueous solutions and that its catalytic hydrogenation by metals is associated with the ketone form.

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