[Chem. Pharm. Bull. 24(12)3226—3228(1976)]

UDC 547.456.02.04 : 541.63.02

Equilibrium States of 3-Ketoses and Sedoheptulose—The Factor Favoring α-Furanose Formation of Coriose[1)]

Furanose was found by the spectral methods to be preponderant in the equilibrated solutions of coriose and sedoheptulose, while pyranose was shown to be the main constituent in equilibrated DL-*gluco*-3-heptulose and D-*ido*-3-heptulose. These examples show stableness of five-membered ring having three hydroxyl groups *vic* and *cis* to each other, relative to six-membered ring having 1,3-diaxial hydroxyl groups.

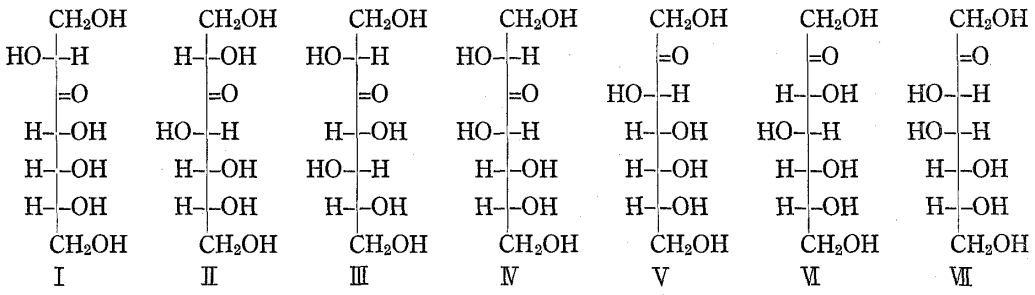
The analyses of equilibrium states of sugars, which offer essential data underlying the sugar analyses such as those by optical rotation and gas chromatography (GLC) of trimethylsilyl (TMS) ether *etc.*, have mostly been presented for pyranoses which are formed as the main components at equilibrium of majority of aldoses,[2)] and calculations of the stability of sugar tautomers have also been carried out for aldopyranoses.[3)] As for furanoses, there had been no established example of furanose-forming crystalline monosaccharide, before the structure determination of crystalline coriose (I) which was found to form α-furanose (Ia) in spite of substantial torsions due to *vic* hydroxyl groups *cis* to each other.[4)] Determination of the extents of existence of furanoses such as Ia in the equilibrium mixtures may give evidences of hitherto unknown stability correlations between furanoses and pyranoses. Although α-furanose has been found to be preponderant specimen at equilibrium of D-allulose,[5,6)] additional examples of furanose as the main component at equilibrium would be required for this purpose.

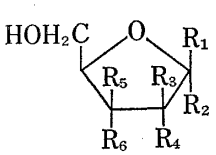
The equilibration of I was examined initially with proton magnetic resonance (PMR) spectra.[7)] The spectra obtained in DMSO-d_6 every several minutes after dissolution of crystalline I exhibited decrease of C_3–OH proton of Ia (δ 5.19, s), and increase of another singlet at δ 5.36, in 20 minutes during which the initial fast mutarotation[4)] was finished. Two other singlets at δ 5.57 and 5.89, and a doublet at δ 5.64 attributable to a hydroxyl proton hydrogen-bonded to the carbonyl oxygen in the open-chain form, then appeared and their growth was observed until the equilibrium state, in which the peak areas of these signals were *ca.* 43, 14, 14, 13 and 15%, respectively was attained 24 hours later. The equilibrium states of I in DMSO-d_6 (Table I) and in D_2O (Table II) were then measured from ^{13}C nuclear magnetic resonance (CMR) spectra,[8)] the assignments of signals being based on Roberts' method.[9)] and also on the data of 2-hexuloses.[5,6)] The ratios of tautomers were based on the C_3 signal heights. α-Furanose (Ia) was thus found to be preponderant species at equilibrium.[10)] The notable amount of the open-chain form as exhibited by the PMR data, which is another

1) Presented at the 8th International Symposium on Carbohydrate Chemistry, Kyoto, Aug. 18, 1976.
2) I.M. Campbell and R. Bentley, "Carbohydrates in Solution," American Chemical Society, Washington, D. C., 1973, pp. 1—19.
3) E.L. Eliel, N.L. Allinger, S.J. Angyal, and G.A. Morrison, "Conformational Analysis," Interscience Publishers, New York, 1965, pp. 351—432.
4) T. Okuda, K. Osaki, and T. Taga, *Chem. Comm.*, **1969**, 851; T. Taga, K. Osaki, and T. Okuda, *Acta Cryst.*, **B26**, 991 (1970).
5) L. Que, Jr. and G.R. Gray, *Biochemistry*, **13**, 146 (1974).
6) P.C.M. Herve du Penhoat and A.S. Perlin, *Carbohyd. Res.*, **36**, 111 (1974).
7) 90 MHz, tetramethylsilane as internal standard.
8) 22.6 MHz, tetramethylsilane as internal standard.
9) D.E. Dorman, S.J. Angyal, and J.D. Roberts, *J. Am. Chem. Soc.*, **92**, 1351 (1970); D.E. Dorman, J.D. Roberts, *ibid.*, **92**, 1355 (1970).
10) Personal communication from Prof. S.J. Angyal informed similar observation, to whom we wish to express our thanks. The main part of our result was presented at the 95th Annual Meeting of Pharmaceutical Society of Japan, Nishinomiya, April, 1975.

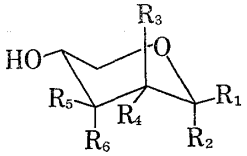
marked aspect of equilibrated I, is also shown by the ultraviolet (UV) absorption of isolated ketone (Table III).

The equilibrium states of DL-gluco-3-heptulose (II)[11] and D-*ido*-3-heptulose (III)[12] in D_2O were also determined by CMR spectra, the signals being assigned by comparison with

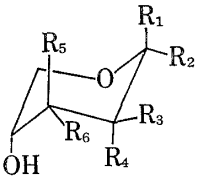




Ia,b, IIa,b, IIIa,b

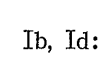


Ic, IIc, IIIc

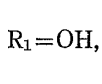


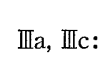
Id, IId, IIId

Ia, Ic: R_1=  , R_2=OH
R_3=H, R_4=OH
R_5=H, R_6=OH

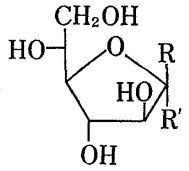
Ib, Id: R_1=OH, R_2= 
R_3=H, R_4=OH
R_5=H, R_6=OH

IIa, IIc: R_1=  , R_2=OH
R_3=OH, R_4=H
R_5=H, R_6=OH

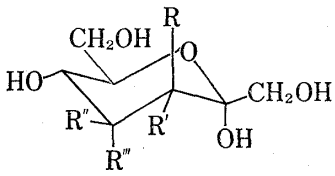
IIb, IId: R_1=OH, R_2= 
R_3=OH, R_4=H
R_5=H, R_6=OH

IIIa, IIIc: R_1=  , R_2=OH
R_3=H, R_4=OH
R_5=OH, R_6=H

IIIb, IIId: R_1=OH, R_2= 
R_3=H, R_4=OH
R_5=OH, R_6=H



Va : R=CH_2OH, R′=OH
Vb : R=OH, R′=CH_2OH



Vc : R=OH, R′=H
R″=H, R‴=OH
VIc : R=H, R′=OH
R″=OH, R‴=H
VIIc : R=OH, R′=H
R″=OH, R‴=H

Chart 1[13]

TABLE I. Equilibrium Composition of Coriose in DMSO-d_6

Method	α-Furanose	β-Furanose	α-Pyranose	β-Pyranose	Open-chain form
PMR	44.2				15.1
CMR[a]	43.3(103.7)[b]	14.0(105.8)	14.0(98.6)	13.3(99.3)	15.1[a]

a) Amounts (%) of the cyclic forms were calculated after substracting that of the open-chain form measured by PMR.
b) chemical shifts, δ in ppm

11) T. Okuda, S. Saito, and Y. Shiobara, *Carbohyd. Res.*, 39, 237 (1975).
12) T. Okuda, S. Saito, and K. Watanabe, The 94th Annual Meeting of Pharmaceutical Society of Japan, Sendai, April, 1974.
13) Pyranoses are represented by either C1 or 1C conformation, which is regarded as more favored than the other.

Table II. Equilibrium Compositions of 3-Ketoses and Sedoheptulose in D_2O Based on the Hemi-ketal Signals in CMR spectra[a]

Ketose	α-Furanose	β-Furanose	α-Pyranose	β-Pyranose
Coriose	55.5(104.6)[b]	17.4(107.0)	11.3(99.4)	15.8(100.2)
DL-*gluco*-3-Heptulose	16.7(106.3)	34.8(102.4)	—	48.5 (99.6)
D-*ido*-3-Heptulose	13.6(103.0)	—	86.4(99.5)	—
D-*arabino*-3-Hexulose	81.6(104.0)	18.4(107.2)	—	—
L-*xylo*-3-Hexulose	16.2(107.4)	83.8(104.1)	—	—
Sedoheptulose	17.9(105.4)	66.3(102.4)	15.8(98.1)	—

a) Open-chain forms which are hardly analyzed guantatively by CMR are excluded.
b) chemical shifts, δ in ppm

Table III. UV Absorptions of Ketoses

	Solvent	λ_{max}(nm)	ε
D-Fructose	H_2O	277	0.9
	DMSO	283	1.8
Coriose	H_2O	275	3.8
	DMSO	283	5.6
DL-*gluco*-3-Heptulose	H_2O	277	4.9
D-*arabino*-3-Hexulose	H_2O	287	35.8
L-*xylo*-3-Hexulose	H_2O	287	49.6

those of D-fructose and L-sorbose, respectively. Furanoses of these two 3-heptuloses are exhibited in smaller amounts than main pyranose, although their furanoses (IIa, IIb, IIIa and IIIb) do not have *cis* arrangement of hydroxyl groups except those at C_3 and C_4 in β-furanose and therefore are regarded as stabler than Ia. The equilibrium states of I, II and III are generally analogous to those of 2-hexuloses[5,6] having identical configurations on the ring carbons.

These observations of furanose-pyranose equilibrium would be rationalized as follows. The strong interaction between 1,3-diaxial hydroxyl groups on the pyranose ring in Ic and Id can be regarded as the force making the amount of furanoses larger than pyranoses in I, and the absence of such interaction in IIc and IId and also in IIIc and IIId would make the amount of pyranoses larger than furanoses. The high ratio of Ia to β-furanose (Ib) in equilibrated I is attributable to the stronger interaction between C–C and C–O bond than that between two C–O bonds[6] at C_3 and C_4.

Although GLC of perTMS ethers of 3-ketoses show the open-chain form to be preponderant,[12] the present data indicate that the equilibrium states are quite different between free 3-ketoses and their perTMS ethers, and that the large amounts of the open-chain forms in perTMS ethers of 3-ketoses, *i.e.*, II, III and D-*manno*-3-heptulose (IV),[12] and 3-hexuloses,[14] are mainly products of the ring-opening tautomerization occurred in analogous way as that of I.[15]

The equilibrium state of syrupy sedoheptulose (V) has been unknown, although the mass spectrum of its TMS ether shows abundance of furanose.[16] The CMR spectrum of V whose purity was proved by combined gas chromatography–mass spectrometry of TMS derivative on several stationary phases, upon which the main peak and the minor peak are shown to be due to furanose and pyranose, respectively, now indicates that β-furanose (Vb)

14) T. Okuda, S. Saito, K. Watanabe, and C. Hieda, *Chem. Pharm. Bull.* (Tokyo), **22**, 2202 (1974).
15) T. Okuda and K. Konishi, *Chem. Comm.*, **1969**, 1117; T. Okuda, K. Konishi, and S. Saito, *Chem. Pharm. Bull.* (Tokyo), **22**, 1624 (1974).
16) T. Okuda and K. Konishi, *Chem. Comm.*, **1969**, 796.

is preponderant component accompanied by smaller amounts of α-furanose (Va) and α-pyranose (Vc) (Table II). The CMR spectra of D-*gluco*-heptulose (VI) and D-*manno*-heptulose (VII), whose GC–MS data of TMS ether exhibit pyranose only, and whose stabler conformation (α-pyranose, Cl) has no *cis* correlation of axial substituents, indicate that both of them form almost solely α-pyranose (VIc and VIIc), in accord with the observation by Perlin, *et al.*[16] The preponderance of furanose in V would then be attributable to the interaction between 1,3-diaxial hydroxyl groups in pyranose, and the high ratio of β-furanose (Vb) to α-furanose (Va) is consistent in the structural features with the Ia formation as the main component in equilibrated I. Analogous correlations of the equilibrium data of anomers with structures of 3-hexuloses are also observed (Table II).

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Received September 24, 1976

17) A.S. Perlin, P.Herve du Penhoat, and H.S. Isbell, "Carbohydrates in Solution," American Chemical Society, Washington, D. C., 1973, pp. 39—50.

[Chem. Pharm. Bull. 24(12)3229—3231(1976)]

UDC 547.773.04.08 : 543.544.45.061

Formation of 4-Formylaminoantipyrine as a New Metabolite of Aminopyrine. II.[1] Enzymatic Demethylation and Oxidation of Aminopyrine and 4-Monomethylaminoantipyrine

4-Formylaminoantipyrine, a new metabolite of aminopyrine, was formed on the incubation with rat or rabbit liver slices, or with the microsomal fraction of rabbit liver.

In the previous papers,[2–4] we reported the detection of 4-formylaminoantipyrine (FAA) as a new metabolite of aminopyrine (AM) in the urine after the oral administration to man, rabbit, guinea pig or rat. Moreover, the formation route of FAA was clarified with ^{13}C-labeled AM by gas chromatography–mass spectrometry (GC–MS) and ^{13}C-nuclear magnetic resonance (^{13}C-NMR) as shown in Chart 1. The observation mentioned above is very valuable, since neither report concerning the metabolite FAA itself nor such type of oxidative metabolite with formylamino group has been published.

The present communication describes further studies on the formation of FAA from AM or 4-monomethylaminoantipyrine (MAA) in liver system. The liver removed from 24 hr fasted animal immediately after stunning and slaughtering by exsanguination was used to obtain liver slices and microsomal fraction.

1) Part I: A. Noda, T. Goromaru, N. Tsubone, K. Matsuyama, and S. Iguchi, *Chem. Pharm. Bull.* (Tokyo), **24**, 1502 (1976).
2) S. Iguchi, T. Goromaru, and A. Noda, *Chem. Pharm. Bull.* (Tokyo), **23**, 932 (1975).
3) S. Iguchi, T. Goromaru, A. Noda, and N. Tsubone, *Chem. Pharm. Bull.* (Tokyo), **23**, 1889 (1975).
4) T. Goromaru, A. Noda, K. Matsuyama, and S. Iguchi, *Chem. Pharm. Bull.* (Tokyo), **24**, 1376 (1976).