CHIROPTICAL AND CONFORMATIONAL PROPERTIES OF KETOHEXOSES

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Circular dichroism of acyclic forms of D-fructose, L-sorbose, D-tagatose, and four deoxy derivatives of D-fructose has been interpreted from the point of view of the equilibrium of rotamers around the bond of the chromophore and chiral residue of the molecule. The conformational equilibrium manifested by the double-sign dichroic curve changes with constitutional, solvation, and temperature conditions. It can be characterized as a *syn* $\rightleftharpoons$ *anti* equilibrium according to mutual orientation of the carbonyl and vicinal hydroxyl groups.

The chiroptical and conformational properties of ketohexoses in acyclic form, which coexists with the well investigated cyclic form[1], are not well understood yet. The attempts at generalization of the chiroptical properties of acyclic saccharides was expressed in the symmetry rule which correlates the sign of the Cotton effect with the absolute configuration[2]. Recently we have shown[3] that this rule is of limited validity. This fact was documented by spectra of circular dichroism (CD) of ketopentoses which, in alcoholic solution, show the dominant Cotton effect of the sign opposite to that predicted by this rule. The chiroptical phenomenon was explained on the basis of conformational equilibrium of the rotamers of carbon skeleton of the molecule. This concept was used in the study[4] of D-glyceraldehyde which also presents direct quantum-chemical calculation of the dependence of the rotational strength on the bond rotation.

The content of acyclic form of ketohexoses does not exceed 1% in aqueous solution. The values derived from spectroscopic data are 0·7, 0·2, and 0·6% for D-fructose, L-sorbose, and D-tagatose, respectively[2]. The corresponding content observed with the 1-deoxy derivatives is 20 times greater. The amount of the acyclic form increases with increasing temperature. The CD spectra of non-aqueous solutions of D-fructose showed double-sign curves in the region of the $n \rightarrow \pi^*$ transition which can be due to the conformational equilibrium[5].

The aim of this work was to study the conformational equilibrium of acyclic form of ketohexoses under various conditions. For this purpose we chose 2-ketohexose derivatives with identical absolute configuration at $C_{(3)}$ carbon atom.

EXPERIMENTAL

1-Deoxy-D-fructose was prepared according to ref.[6]. Preparation of 3-deoxy-, 4-deoxy-, and 6-deoxy-D-fructose is given in refs[7–9]. Dimethyl sulphoxide (Fluka) was dried over Potasit 3 molecular sieve (Dimitrov Chemical Works, Bratislava). The CD spectra were measured in redistilled water 90—120 min after dissolution, *i.e.* after mutarotation[10] and establishing of the equilibrium. The non-aqueous solutions were temperated at 50°C for 24 h before the measurements. The measurements in methanol–ethanol (1 : 4) were carried out also at low temperatures down to —160°C, those in water and dimethyl sulphoxide also at 50°C. The measurements were carried out with a Dichrograph III Jobin–Yvon equipped with cryostat. The compounds were measured in 5—10 mm cells, the concentrations of the solutions being 2—10 mg/ml.

TABLE I

Parameters of circular dichroism of ketohexoses

Compound	Water		Dimethyl sulphoxide	
	λ, nm ($\Delta\varepsilon . 10^3$)	ratio[a]	λ, nm ($\Delta\varepsilon . 10^3$)	
L-Sorbose	278 (+2·6)	0·39	270 (+1·1)	300 (−8·0)
D-Tagatose	282 (+3·5)	0·41	285 (+12·8)	319 (−0·9)
D-Fructose	275 (+8·4)	1·00	267 (+5·6)	300 (−11·7)
1-Deoxy-D-fructose	314 (−2·0)	—	—	—
	278 (+133·0)	15·83	275 (+15·0)	313 (−3·8)
3-Deoxy-D-fructose	276 (+9·5)	1·13	—	—
4-Deoxy-D-fructose	278 (+13·8)	1·64	—	—
6-Deoxy-D-fructose	273 (+19·6)	2·33	—	—

[a] $\Delta\varepsilon$(ketose)/$\Delta\varepsilon$(D-fructose).

RESULTS AND DISCUSSION

The basic spectral parameters obtained for the aqueous solutions are given in Table I. All the compounds exhibited positive Cotton effect in the region of 280 nm, which agrees with the statement[2] that compounds with S absolute configuration at the asymmetric centre adjacent to chromophore should have positive circular dichroism of the $n \rightarrow \pi^*$ transition.

With 1-deoxy-D-fructose we observed another dichroic band of opposite sign (negative) in the long-wave region of $n \rightarrow \pi^*$ absorption (Table I). So far this band has not been observed with other ketoses or aldoses in aqueous solution. High intensity of the positive band also reflects the relatively highest content of the acyclic form. The UV absorption spectrum shows a gaussian band ($\varepsilon = 213$, 264 nm) in contrast to shoulders of other ketoses. The increased proportion of the acyclic form is due to changed nucleophilicity of the carbonyl carbon atom. The values of elipticity ratios (Table I) of the deoxyfructoses reflect the content of the acyclic form with respect to D-fructose.

Selected derivatives were also measured in dimethyl sulphoxide (Table I). The spectrum of D-fructose exhibits two dichroic bands in the absorption region of $n \rightarrow \pi^*$ transition. The long-wave band with negative sign reaches double intensity value as compared with the positic dichroic band. With 1-deoxy-D-fructose this ratio is reversed in favour of the positive band in the ratio 4 : 1. Increasing temperature (50°C) causes intensity increase of the dichroic bands of the both compounds, their ratio being changed in favour of the positive band. L-Sorbose in dimethyl sulphoxide shows two dichroic bands of opposite signs with the intensity ratio 1 : 7 in favour of the negative long-wave band. D-Tagatose also has double-sign CD transition $n \rightarrow \pi^*$. The negative dichroic band is of very low intensity, being 14 times weaker than the positive band. Increasing temperature causes, in the both compounds, an intensity increase of mainly the positive dichroic band.

The measurements in water and in dimethyl sulphoxide indicate different effects of protic and aprotic solvents. The increase of the values due to heating to 50°C reflects the increase of content of the acyclic form and is greater in aqueous solutions. In contrast to water, in dimethylsulphoxide all the measured compounds exhibit double-sign dichroic curves. The conformaional equilibrium is shifted in favour of the rotamers whose CD was not recordedt in aqueous solution. The most distinct shift is observed with D-fructose and L-sorbose, the negative CD reaching 2 and 7 times greater elipticity values, respectively, as compared with the positive CD.

We tried to obtain further information on the conformational equilibrium with the use of low-temperature measurements in the mixture ethanol–methanol (4 : 1). Alcoholic solution of D-fructose shows two dichroic bands (Fig. 1). The positive band is more intensive than the negative band at room temperature. Lowering temperature causes intensity decrease of the positive band down to its disappearance, whereas intensity of the negative band increases. With 1-deoxy-D-fructose the both dichroic bands were changed (Fig. 1). On lowering the temperature to −60°C the intensity of the both bands decreased at the same rate. Further temperature lowering caused an increase of the positive band in 275 nm region, whereas the negative long-wave band at 313 nm slowly decreased. With 3-deoxy-D-fructose no circular dichroism was observed at the given measurement conditions. With L-sorbose the CD spectra showed 2 dichroic bands which decreased with temperature (Fig. 2). L-Tagatose in alcoholic mixture showed only the positive dichroic band whose value decreaes until it completely disappears at −70°C (Fig. 2). All the mentioned temperature changes are reversible.

The lowering of CD values of all the ketohexoses with decreasing temperature reflects formation of the more stable cyclic form. When lowering the temperature we can observe a change in the intensity ratio of the negative and the positive dichroic bands. The shift in favour of the long-wave band is marked with D-fructose and slight with L-sorbose. The both compounds also show a marked negative circular dichroism in dimethyl sulphoxide. The similarity in the chiroptical properties can be considered as a consequence of structural similarity of these compounds. The both compounds are analogues of D-*threo*-pentulose which shows the same CD properties[3]. With 1-deoxy-D-fructose the behaviour at low temperatures as well as the mentioned solvent effect (negative CD in water) are different. Here the CD reflects a more complex conformational equilibrium.

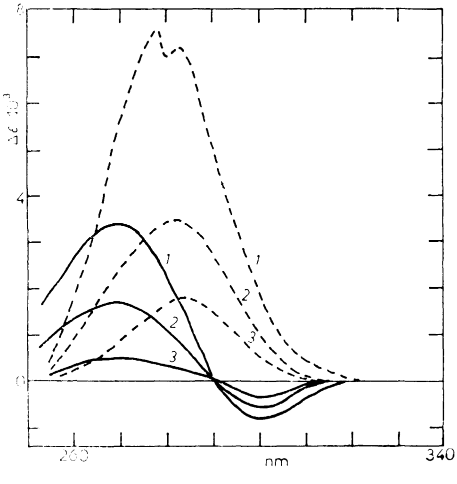

FIG. 1

Circular dichroism spectra of D-fructose, $\Delta\varepsilon \cdot 10^2$ (———) and 1-deoxy-D-fructose $\Delta\varepsilon \cdot 10^3$ (- - - - -) at 20°C (*1*), −40°C (*2*), and −160°C (*3*)

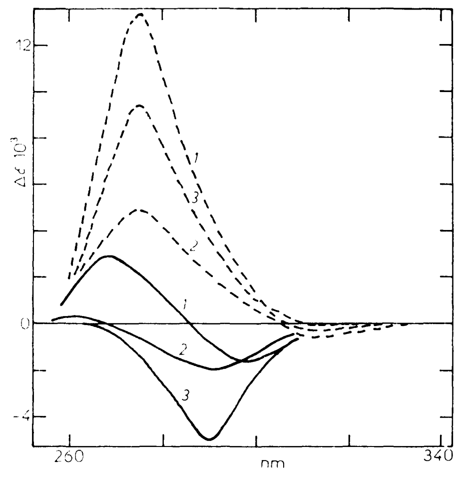

FIG. 2

Circular dichroism spectra of L-sorbose (———) and D-tagatose (- - - - -) at 40°C (*1*), 20°C (*2*), and −40°C (*3*)

D-Tagatose is analogous to L-*erythro*-pentulose, and their chiroptical properties are similar[3]. The chiroptical properties of the structures with *erythro*-configuration differ from those of *threo*-configuration by their negative CD being suppresssed down to the minimum. In contrast to other ketoses, with D-tagatose in alcoholic solution the positive Cotton effect only is observed at 282 nm even at low temperatures.

The shape of the spectrum reflects the conformational equilibrium of the rotamers around the bond of the chromophore to the chiral residue of the molecule. The positive dichroic band lies in the region of shorter wavelengths with an apparent maximum at 282 nm. With respect to the corresponding energy of the $n \rightarrow \pi^*$ transition it can be concluded that it is due to the conformers with hydrogen bonds to the non-bonding orbitals of the carbonyl oxygen atom. This behaviour is most distinct in aqueous solutions. Strong intermolecular interactions cancel out any possible intramolecular interactions. Most probably the compounds exist in a stretched "zig-zag" conformational arrangement. (In L-sorbose it is destabilized by synaxial interaction of OH groups at $C_{(3)}$ and $C_{(5)}$.) The vicinal hydroxyl group at $C_{(3)}$ atom is oriented anticlinally with respect to the carbonyl group. For glyceraldehyde it was calculated[4] that this conformational region exhibits positive CD. In aprotic medium this arrangement is present ,too, and it can be supported by intramolecular hydrogen bond to the hydroxyl group at $C_{(4)}$.

The negative long-wave dichroic band lies in the region above 280 nm. It can be considered to be due to the conformational arrangement in which the hydrogen interactions of the chromophore are absent. The mutual orientation of carbonyl group and the hydroxyl group at $C_{(3)}$ can be expressed by a torsion angle in synclinal region. This orientation region exhibits negative CD in glyceraldehyde[4]. Rotation around the $C_{(2)}$—$C_{(3)}$ bond disturbs the regular "zig-zag" arrangement. In D-tagatose the hydroxymethyl group at $C_{(1)}$ approaches the hydroxyl group at $C_{(4)}$. No such interaction is observed in D-fructose and L-sorbose. These compounds show a more distinct presence of the conformers with negative CD. In 1-deoxy-D-fructose, which has no hydroxyl group at $C_{(1)}$, this conformational arrangement can be considered more favourable as compared with other ketoses. The CD spectrum exhibits negative Cotton effect even in aqueous medium.

Thus the double-sign circular dichroism of acyclic forms of 2-ketohexoses can be interpreted as a consequence of the conformational equilibrium *syn* $\rightleftharpoons$ *anti* of the rotamers at the $C_{(2)}$—$C_{(3)}$ bond. The anticlinal rotamers contributing with negative CD (which disagrees with the symmetry rule[2]) are characterized by relatively low rotational strength. These rotamers appear to be more favourable energetically in aprotic solvent. Their preference in the alcoholic mixture is especially distinct with D-fructose and L-sorbose, *i.e.* compounds with *threo*-configuration of the hydroxyl groups at the chiral centres adjacent to the chromophore.

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