EFFECT OF TEMPERATURE ON CHIROPTICAL AND CONFORMATIONAL PROPERTIES OF ACYCLIC KETOSES*

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Conformational mobility of tetruloses, 2-pentuloses, D-3-pentulose and 4-deoxy-L-pentulose was studied by measuring temperature dependences of CD spectra in the region +40°C to —140°C in a methanol–ethanol (1 : 4) mixture. The changes in spectra reflect the population of rotamers around bonds to the carbonyl chromophore. The most stable conformers were determined by PCILO quantum chemical calculation.

In our previous paper[2] we studied the effect of various solvents on the spectra of acyclic ketoses. We found different behaviour of these compounds in proton-donating and proton-accepting solvents, manifesting itself by intensity change of two overlapping bands in the carbonyl $n-\pi^*$ transition region. Two bands of opposite sign led to the assumption that, at room temperature, ketoses of this type exist in two predominating rotamers. The signs of their Cotton effects were interpreted using the Octant rule[3]. Recently, an effort has been made to make this rule more accurate in order to clarify some discrepancies[4]. Thus, α-fluoro derivatives are well known to exhibit an antioctant behaviour[5,6] whereas the role of other polar substituents on the α-carbon is hitherto not clear[7,8]. The symmetry of the carbonyl group undoubtedly determines the at least quadrant division of space by two nodal planes. Further division into octants is not unequivocal and can be influenced by interactions with closely located polar groups. The ketoses, investigated by us, contain two different groups on the asymmetric α-carbon: the polar hydroxyl group and the hydroxymethyl group which, according to the Octant rule, could behave similarly as an alkyl group.

In this paper we try to explain the conformational behaviour of acyclic ketoses, as well as to add to the existing knowledge data following from the temperature dependence of CD spectra. We studied eight acyclic ketoses: D-*glycero*-tetrulose (*I*), L-*glycero*-tetrulose (*II*), D-*threo*-pentulose (*III*), L-*threo*-pentulose (*IV*), D-*erythro*-pentulose (*V*), L-*erythro*-pentulose (*VI*), D-*threo*-3-pentulose (*VII*), and 4-deoxy-L-*glycero*-pentulose (*VIII*).

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EXPERIMENTAL

The compounds *I*—*VIII*, prepared according to methods described in the references in the previous communication[2], were syrupy substances whose physico-chemical constants agreed with the reported values. The temperature dependences were measured on a Roussel–Jouan Dichrograph CD 185 model using a cryostate. The compounds were measured in methanol–ethanol (1 : 4) mixture, concentration 1—2 mg/ml, 1 cm cells, temperature range +40°C to —140°C. The mixture employed afforded perfectly transparent liquid solutions even at —150°C. The experimental values were corrected for concentration changes due to temperature prior to the calculations. The value of 0·001 was used as the mean dilatation coefficient of the solution[9], γ. The calculations were executed on a CDC 3300 computer.

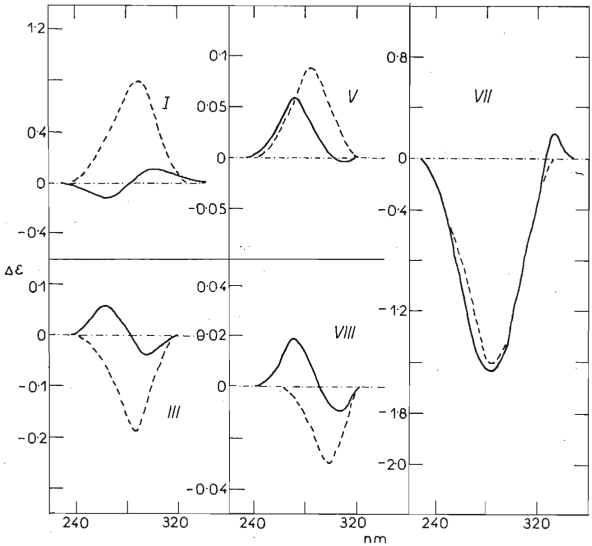

FIG. 1

CD Spectra of Acyclic Ketoses *I*, *III*, *V*, *VII* and *VIII* at Room Temperature (———) and at —140°C (-----) in Methanol–Ethanol Mixture (1 : 4).

RESULTS AND DISCUSSION

CD spectra of the studied acyclic ketoses showed that intensity of the two dichroic bands due to the carbonyl $n \rightarrow \pi^*$ transition depends strongly on temperature. Fig. 1 depicts CD spectra at room temperature and at −140°C (the lowest temperature). The relation between two overlapping bands measured at room temperature is evident. Although at room temperature the long wavelength band (at about 300 nm) is for all the compounds (except the compound *VII*) less intense than that at shorter wavelength (about 270 nm), at low temperatures the first band grows stronger and finally it becomes the only characteristic band.

Conformational equilibria were investigated by studying the temperature dependence of the $\Delta\varepsilon$ value at two different wavelengths and also the dependence of the sum of areas of both bands on temperature for enantiomeric pairs. The curves of these dependences exhibit an S-like shape (*e.g.* compound *I*, Fig. 2) which allowed a two-state equilibrium approximation. Mathematical evaluation, based on this approximation, afforded thermodynamic parameters listed in Table I. Thus-obtained energy values reflect the population of the extreme conformations with different chiroptical manifestation. In some cases the employed iterative calculation procedure

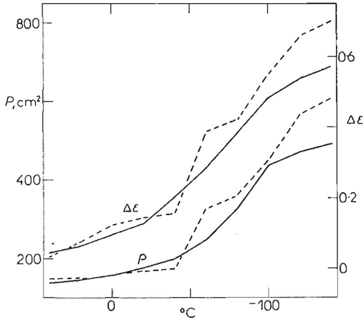

FIG. 2

Dependence of $\Delta\varepsilon$ (at 290 nm) and Sum of Areas (P) of Dichroic Bands on Temperature for D-*glycero*-Tetrulose (*I*)

Measured (------) and calculated (———) values.

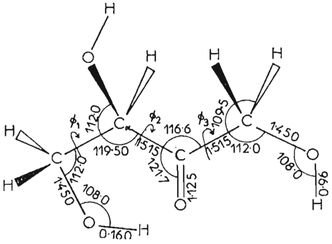

FIG. 3

Structure of the Model D-*glycero*-Tetrulose $\phi_1 = \phi_2 = \phi_3 = 0$ with Bond Lengths and Angles.

was not convergent and it was not possible to obtain the desired data. The inconsistency of the listed values indicates that the fitting procedure is very sensitive to the input experimental data. The two-state equilibrium approximation represents obviously an oversimplification. Also the presence of cyclic conformers of 2-pentuloses can represent a disturbing factor.

The existing studies[2,10,11] concerned the correlation of sign of the chromophore Cotton effect with the absolute configuration of the neighbouring chiral center. D-*threo*-Pentulose (*III*) in which the α-carbon atom has the *S*-configuration, exhibited in aqueous solution a positive Cotton effect superimposed on the negative background ORD curve[10]; this Cotton effect was observed also in the CD spectrum[11]. Our measurements[2] in 1,1,1,3,3,3-hexafluoro-2-propanol and dioxane revealed another

TABLE I

Temperature Dependence for Various Parameters Observed for the Acyclic Ketoses in the Interval +20°C to —140°C (*a*, *b* temperature dependence of Δε at 300 and 290 nm, respectively; *c* temperature dependence of the area of both bands; *d* values in parentheses are standard deviations)

Compound	Dependence	ΔH^d kJ/mol	ΔS^d J/mol deg
I	*a*	—10·0 (7·5)	—45·2 (40·6)
	b	—12·1 (3·7)	—57·7 (20·0)
	c	—14·6 (4·1)	—75·6 (21·7)
II	*a*	— 8·3 (5·0)	—34·3 (31·3)
	b	— 5·8 (5·0)	—21·3 (36·4)
	c	— 7·5 (3·6)	—38·0 (26·7)
III	*a*	— 8·7 (0·4)	—34·7 (10·8)
	b	—10·4 (4·1)	—44·7 (23·4)
	c	— 7·1 (2·5)	—28·4 (16·3)
IV	*a*	—19·2 (2·3)	—90·8 (13·3)
	b	—12·9 (2·5)	—58·1 (13·3)
	c	—18·4 (7·9)	—88·7 (40·1)
VI	*b*	— 6·2 (1·6)	—28·4 (12·1)
VIII	*a*	—15·6 (2·9)	—69·9 (14·2)

very weak negative band in the long wavelength region (about 300 nm). In methanol or in a methanol–ethanol (1 : 4) mixture at room temperature this negative dichroic band is stronger and at low temperature it is even the dominant one (Fig. 1). This markedly high sensitivity of chiroptical properties of acyclic ketoses towards the solvent type and temperature leads to the conclusion that the validity of the recently formulated[11] so called "symmetry rule" which relates the Cotton effect sign with absolute configuration is restricted only to some specific conditions.

Stereochemical interpretation of CD curves with two signs is based on the assignment of rotamers around the carbonyl carbon–α-carbon bond to the single Cotton effects. The preferred three rotamers involve eclipsing of the C=O bond with substituents bonded to the α-carbon. These conformations were derived empirically[12,13]. Since no quantum chemical verification for α-hydroxy ketones exists, we made use of the PCILO semiempirical method[14] in order to clarify the conformational behaviour of acyclic ketoses.

Structure of the model compound, D-*glycero*-tetrulose (*I*), together with description of the atoms and torsion angles and the values of bond angles and lengths used in the calculations, is depicted in Fig. 3. In the calculation of conformational energy we considered three degrees of freedom given by the torsion angles Φ_1, Φ_2 and Φ_3. The starting conformation (Fig. 3) corresponds to the values $\Phi_1 = 0$, $\Phi_2 = 0$ and $\Phi_3 = 0$, *i.e.* (0°, 0°, 0°). The three-dimensional space was studied in the form of a set of two-dimensional maps (Φ_i, Φ_j) with a step size of 30°, the value of the third angle being constant over the whole angular space. Fig. 4 shows the isoenergy contours ($\Phi_1, \Phi_2, \Phi_3 = 0$) relative to the absolute minimum A, characterized by angles (60°, 30°, 0°). Further two minima on the Φ_1, Φ_2 surface are represented by the conformations *B* (−60°, 0°, 0°) and *C* (180°, 0°, 0°) which are less stable than the conformation *A* by 2·71 kJ mol^{-1} and 4·352 kJ mol^{-1}, respectively. Calculation of the conformational spaces (Φ_1, Φ_2 = constant, Φ_3) and (Φ_1 = constant, Φ_2, Φ_3), where Φ_2 and Φ_1 were calculation parameters, led to other minima. With respect to CD spectra, the minimum (0°, −90°, 60°) of relative energy higher than 3·677 kJ mol^{-1} proved to be important. The above-mentioned energy minima are represented by the rotamers *A*, *B*, *C* and *D*, depicted in Fig. 5. From the calculated energy values we can determine the relative amount of the considered rotamers at room temperature ($A : B : C : D = 54 : 24 : 9 : 13$). At low temperatures, the mixture of conformers changes into the most stable conformer *A*.

The signs of the Cotton effects may be assigned to the theoretically calculated conformers according to the Octant rule as follows: In the conformer *A* (Fig. 5) the hydroxy group lies in the nodal plane and the hydroxymethyl group is in the rear left upper octant and hence it has a positive contribution. In conformers *B* and *C* the hydroxyl is in the rear left upper octant and the bond to the hydroxymethyl group lies in the nodal plane. The clear position of the hydroxymethyl group in the lower, left rear octant represents a decisive factor causing the negative Cotton effect

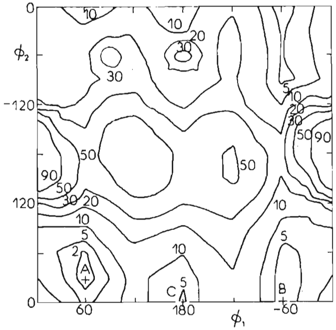

FIG. 4

Map of (ϕ_1, ϕ_2) Potential Energies

The contours 2, 5, 10, 20, 30, 50 and 90 kJ mol^{-1} relate to the minimum *A*.

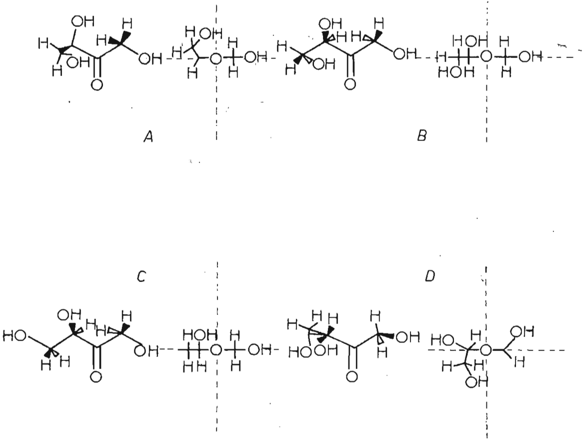

FIG. 5

Octant Projections of the Most Stable Conformations of D-*glycero*-Tetrulose (*I*) in the conformer *D*. The hydroxy group which lies near the nodal planes, can represent only a negligible contribution to the rotational strength.

It must be kept in mind that the calculations did not involve the effect of solvent. According to experimental data, the effect of hydrogen bonding is evident particularly when solvent character is changed. As mentioned in the case of compound *III*, change in the solvent character (water–hexafluoropropanol) results in a marked shift of conformational equilibrium, indicated even by a change of the Cotton effect sign. It is obvious that in the used alcoholic mixture intramolecular hydrogen bonds can arise which affect the molecular conformation and which are also involved in the PCILO calculation.

The conformational population at room temperature, as well as the preceding discussion of sign contributions, agree well with the experimentally found intensities of both bands. The increasing intensity of the positive band in the spectra of compounds *I*, *IV* and *V* with decreasing temperature is caused by decreasing population of the conformer *D* (with a marked negative contribution), and by an increasing content of conformers *A*, *B* and *C* (with a positive contribution to the rotational strength).

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