CONFORMATION OF 3-ACETAMIDO-3,6-DIDEOXYHEXOPYRANOSIDES: CIRCULAR DICHROISM STUDY

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Dedicated to Professor F. Šorm on the occasion of his 80th birthday.

CD spectra of 15 stereoisomeric methyl 3-acetamido-3,6-dideoxyhexopyranosides were measured in methanol, 2,2,2-trifluoroethanol and acetonitrile. The data have been applied for estimation of probable conformations. The factor determining signs of the observed Cotton effects seems to be the spatial orientation of the acetamido group with respect to the pyranose ring. The possible role of a non-planar amide group is also discussed.

Since 1965, when Beychok and Kabat[1] published data on chiroptical properties of acetamido saccharides, many papers have been published dealing with amide chromophore bound to the $C_{(2)}$ atom of pyranoses[2]. Parameters of the characteristic $n-\pi^*$ band (at about 210—215 nm) have been correlated with structural features under assumption that the one-electron mechanism[3] is operating and, consequently, the amide quadrant rule[4] is valid. Later on, Weigang[5] suggested an octant rule with distorted yz nodal plane. With the aim to specify more exactly the shape of nodal surface Bartlett and coworkers[6] analyzed the chiroptical data of a large series of steroids bearing acetoxy and/or acetamido substituents. However, the analysis of substituent contributions did not result in unequivocal conclusions. It seems to be unlikely that empirical sector rules are satisfactory for the interpretation of CD data of these compounds in which the amide chromophore is located in an acyclic (flexible) section of the skeleton. In the present form, these rules are unable to respect all structural details of the amide chromophore. Our knowledge of the spatial arrangement of acetamido saccharides is based on the one hand on X-ray structure determinations[7–9], on the other hand on the ^{1}H-NMR spectra[10,11]. Mutual orientation of the acetamido group and the pyranose ring, detected in all these studies, is characterized by an anti-periplanar arrangement of hydrogen atoms in $C_{(x)}$—H (pyranose ring) and N—H groups. In our preceding paper[12] dealing with quantum chemical calculations (CNDO) on the 2-acet-amido-1,3-propanediol, we considered for the case of 3-acetamidohexopyranoses also an arrangement deviating substantially from the true antiperiplanar partial conformation. Moreover, the calculations showed that a non-planar amide grouping may be present in this case.

In the present paper, we collected experimental data which could be confronted with results earned from quantum chemical calculations[12]. We measured the CD curves

of all existing methyl 3-acetamido-3,6-dideoxyhexopyranosides (excepting β-*ido* isomer) in solvents of different solvation abilities: in 2,2,2-trifluoroethanol interacting with amide C=O group[13], in acetonitrile interacting with N—H group[13] and in methanol which is able to interact with both groups. Differences in CD curves of systems differing in relative configuration and/or solvation could offer a new information as to the conformation of compounds studied[14] and, more generally, of the amide chromophore as such[15,16].

EXPERIMENTAL

Materials: For measurements following compounds were used: Methyl 3-acetamido-3,6-dideoxy-α-L-glucopyranoside[17,18] (*I*), -β-D-glucopyranoside[19,20] (*II*),-α-D-talopyranoside[21] (*III*), -β-D-talopyranoside[19] (*IV*), -α-D-galactopyranoside[17,18] (*V*), -β-D-galactopyranoside[19] (*VI*), -α-L-mannopyranoside[17,22] (*VII*), -β-D-mannopyranoside[19,20] (*VIII*), -α-L-allopyranoside[23] (*IX*), -β-D-allopyranoside[24] (*X*), -α-L-idopyranoside[25] (*XI*), -α-D-gulopyranoside[23] (*XII*), -β-D-gulopyranoside[24] (*XIII*), -α-D-altropyranoside[26] (*XIV*), and -β-D-altropyranoside[24] (*XV*).

Methods: The CD spectra were measured on a Roussell-Jouan CD 185/II Dichrographe in solutions of concentration 0·5—1·5 mg per ml; cell thickness 0·5 and 2 mm. Quantum chemical calculations were performed on a CDC 3300 computer, curve analyses on a Hewlett–Packard 9830 A calculator equipped with digital $x — y$ plotter HP 9862 A.

RESULTS AND DISCUSSION

Selected CD data of compounds under study are collected in Table I. For the sake of easier interpretation, only data of D-enantiomers are given even in those cases in which L-enantiomers were actually measured (*cf.* Experimental). The values in Table I characterize Cotton effects corresponding to the n-π^* electronic transitions within the acetamido groupings. This assignment is corroborated by the observed red shift of these maxima in the solvent series 2,2,2-trifluoroethanol — methanol — acetonitrile. The electronic π-π^* transition, located at about 195 nm, was measured with lower accuracy and was not explicitly considered in the discussion. The participation of other chromophores seems to be unimportant in the accessible spectral region.
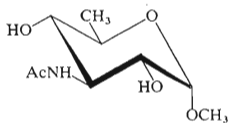
For a more detailed correlation of the CD spectra with the spatial arrangement of 3-acetamidohexopyranosides[14], it is necessary to consider on the one side the present knowledge of stereochemistry of these compounds, on the other side the possible solvation effects which might influence the conformation on several levels: i) They may shift the $^4C_1 \rightleftharpoons {}^1C_4$ equilibrium between two pyranose forms, ii) they may alter the orientation of the acetamido group with respect to the rest of the molecule (*i.e.* the dihedral angle on the N—C$_{(3)}$ bond) and, finally, iii) they may influence also the possible non-planarity of the amide grouping[15].

A greater population of the $^1C_4$ (D) conformer in solvents mentioned above may be expected only with β-D-anomers of those compounds which expose in the $^4C_1$ (D) conformer the 3-acetamido group in axial position[26] (*X, XIII, XV*). Chiroptical phenomena of these isomers should have, in the case of prevailing $^1C_4$ (D) form (with equatorial 3-acetamido group), a pseudoenantiomeric character when compared with chiroptical phenomena of those diastereoisomers in which the absolute configuration is reversed at all chiral centres with the exception of the $C_{(5)}$ centre and in which, consequently, the acetamido group in the $^4C_1$ (D) conformer is also equatorial. In other words, the configurational isomer β-D-*allo* (*X*) in $^1C_4$ conformation should behave as a pseudoenantiomer of the α-D-*talo* (*III*) isomer in the $^4C_1$ conformation and *vice versa*. Similarly, β-D-*ido* isomer should be, as regards the CD data, pseudo-
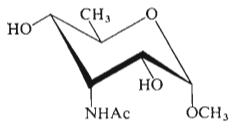
TABLE I

CD Data of Methyl 3-Acetamido-3,6-dideoxyhexopyranosides

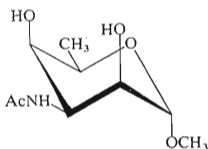| Compound[a]	$\Delta\varepsilon \cdot 10^{-3}$ (λ, nm)		
	CH_3OH	TFE^b	CH_3CN
I	−0·15 (219·0)	−2·24 (211·0)	−1·16 (217·0)
II	−1·02 (216·0)	−1·85 (213·0)	−1·99 (217·0)
III	−2·18 (215·0)	−0·61 (225·0)	1·10 (222·0)^c
IV	−0·43 (219·0)	—	
V	−2·70 (214·5)^c	0·90 (216·5)^c	1·65 (216·5)^c
VI	−7·00 (214·0)	3·05 (210·5)^c	−0·50 (232·5)^c
			1·00 (215·0)^c
VII	3·83 (215·0)	−7·93 (209·0)	0·30 (235·5)^c
			−1·40 (215·0)^c
VIII	7·39 (212·5)	−4·93 (210·0)	−3·96 (216·0)
IX	7·41 (214·0)	12·00 (211·0)	9·25 (217·5)
X	1·80 (214·0)	—	0·75 (223·0)^c
			0·70 (215·0)^c
XI	4·13 (215·0)	10·35 (210·0)	3·54 (218·0)
XII	8·33 (214·0)	11·40 (209·0)	9·72 (218·0)
XIII	4·18 (212·0)	−0·15 (233·0)^c	1·60 (217·0)^c
XIV	1·72 (215·0)	7·18 (212·0)	6·96 (218·0)
XV	—	−0·20 (215·0)^c	−0·80 (217·0)^c

^{a} For easier interpretation data of D enantiomers are given in all cases; ^{b} TFE 2,2,2-trifluoro-ethanol; ^{c} values calculated by fitting the sum of Gaussian bands. A further band in the short wave-length region (not measured) was considered for this analysis. The calculated parameters of this band are as follows: for *V* in CH_3OH $\Delta\varepsilon = 8\cdot0 \cdot 10^{-3}$ (λ_{max} 197 nm), in TFE 4·7 (201), in CH_3CN 5·0 (190); for *VI* in TFE 6·0 (193), in CH_3CN 4·5 (199); for *XIII* in TFE 3·4 (200), in CH_3CN 3·0 (200), for *XV* in TFE −1·2 (190), in CH_3CN (195).

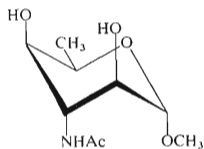$^1C_1(D)$ conformations of methyl 3-acetamido-3,6-dideoxy-α-D-hexopyranosides
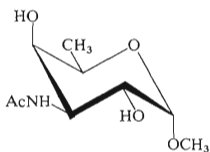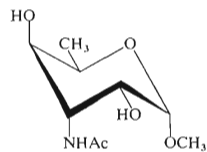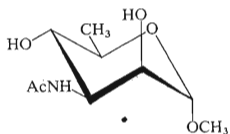

I
α-D-*gluco*

IX
α-D-*allo*

III
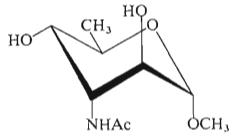α-D-*talo*

XI
α-D-*ido*

V
α-D-*galacto*

XII
α-D-*gulo*

VII
α-D-*manno*

XIV
α-D-*altro*

enantiomeric to α-D-*gluco* (*I*), β-D-*gulo* (*XIII*) to α-D-*manno* (*VII*) and β-D-*altro* (*XV*) to α-D-*galacto* (*V*), because in these pairs the environment of the acetamido chromophore is in principle enantiomeric. However, the experimental spectra testify that this relation is fulfilled only with the pair involving β-D-*altro* isomer *XV* when measured in 2,2,2-trifluoroethanol and acetonitrile. Therefore, we do not consider a shift in the $^4C_1 \rightleftarrows {}^1C_4$ equilibrium as the main source of the enantiomeric nature of some CD curves in the series of methyl 3-acetamido-3,6-dideoxyhexopyranosides. Furthermore, it also seems to be improbable that the solvents used might change dramatically this conformational equilibrium (estimated using ^{1}H-NMR spectroscopy[11]).

We can achieve some thoughts of the spatial relation between the acetamido group and pyranose ring by comparison of the CD spectra of various stereoisomers in the same solvent. Due to symmetrical localization of hydroxy groups in the immediate neighbourhood of the amide chromophore the rotatory strength is very low with D-*gluco* (*I, II*) and D-*talo* (*III, IV*) isomers. Using the amide quadrant rule[4] for interpretation of the negative dichroic band in the CD spectra of these compounds we have to place the pyranose ring in the upper right quadrant. In this conformation, the amide group deviates by 40−50° from the *trans*-arrangement on the N—$C_{(3)}$ bond. This value is in agreement with quantum chemical calculations on the model compound (2-acetamido-1,3-propanediol)[12], however in disagreement with ^{1}H-NMR measurements[11]. The solvent effect is manifested only by shifting the maxima of the *n-π** dichroic bands. It reflects the strength of the proton-donor interaction of the solvent with lone electron pairs on the carbonyl oxygen atom. With D-*galacto* (*V, VI*) and D-*manno* (*VII, VIII*) isomers we can observe an enantiomeric relationship of the Cotton effects which is, presumably, related to the mirror orientation of the chromophoric system with respect to the pyranose ring in compounds under comparison. This orientation is governed by intramolecular hydrogen bonds between the acetamido group and vicinal hydroxy groups, mainly by interaction of a hydroxy group in the equatorial position (at $C_{(2)}$ atom in D-*galacto* isomers *V, VI* and at $C_{(4)}$ atom in D-*manno* isomers *VII, VIII*) with the carbonyl oxygen atom and by interaction of the NH group with a hydroxy group in the axial position (at $C_{(4)}$ atom in D-*galacto* and at $C_{(2)}$ atom in D-*manno* isomers). The existence of these interactions follows not only from the infra-red spectra[14,27], but also from quantum chemical calculations on model compounds[12]. The pronounced solvent dependence of the CD curves of D-*galacto* and D-*manno* isomers is documented in Fig. 1. Both isomers exhibit in methanol oppositley signed Cotton effects when compared with those in 2,2,2-trifluoroethanol and acetonitrile. Acetonitrile and, mainly, 2,2,2-trifluoroethanol are able, owing to their specific solvation properties, to perturb the intramolecular interactions. On the contrary, methanol with a hydroxy group very similar to hydroxy groups in saccharides need not interfere seriously with intramolecular hydrogen bonds in structures studied. Application of the amide quadrant rule[4] on

D-*galacto* isomers *V*, *VI* and D-*manno* isomers *VII*, *VIII* in conformations considered above predicts in the first case a positive in the second case a negative n-π^* dichroic band, in agreement with experimental data estimated in methanol. In the CD spectra of β-D-*galacto* (*VI*) and α-D-*manno* (*VII*) isomers measured in acetonitrile two n-π^* bands are discernible. Therefore, the presence of two conformers with different mutual orientation of the amide chromophore and pyranose ring could be considered.

With all four α-D anomers *IX*, *XI*, *XII*, and *XIV*, which expose in the $^4C_1$ conformation the acetamido group in the axial position, we can find only one strong and positive n-π^* band in all solvents used. The uniform orientation of the chromophoric group in these compounds can be stabilized by a hydrogen bond between the anomeric methoxy group and hydrogen atom of the N—H group[27,28] the attack of which by solvent molecules must be seriously sterically hindered. According to the amide quadrant rule[4], the nodal plane comprising the plane of the amide grouping divides the pyranose skeleton of these structures in two equivalent, but enantiomeric parts compensating each other. In spite of this, the α-D anomers *IX*, *XI*, *XII*, and *XIV* exhibit relatively high ellipticity values.

It follows from the description given above that the application of the amide quadrant rule[4] does not afford a fully satisfactory reasoning of all the observed data. We suppose that a more consistent interpretation could be approached using the

FIG. 1

CD Spectra of Methyl 3-Acetamido-3,6-dideoxy-α-D- (– – – –) and -β-D- (– – –) -*manno*-Hexopyranosides in 2,2,2-Trifluoroethanol *1*, in Methanol *2*, and in Acetonitrile *3*
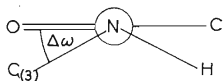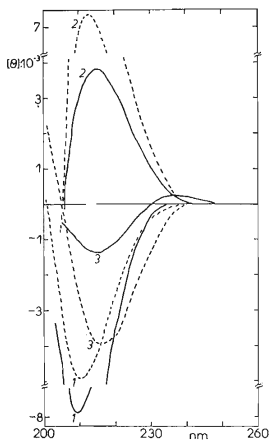

FIG. 2

Non-Planar Amide Group with *R* Chirality Viewed along the N—C' Bond.

concept of a non-planar amide group with pyramidal arrangement of bonds on the nitrogen atom[15,16,28−31]. One of the enantiomeric arrangements of this kind can prevail in the measured system due to non-bonding interactions and determine the chiroptical properties. Because of the inherently chiral nature of non-planar amide groups we have to expect higher rotatory strength than with planar chromophore. Even a small overpopulation of a conformer with definite inherently chiral chromophoric system could be sufficient to determine the resulting sign of optical activity. At present, experimental data are lacking on the basis of which we could correlate unequivocally the inherent chirality of the amide group with the sign of its chiroptical phenomena[16,29,30]. In the preceding paper[12] we calculated quantum chemically conformational energy maps $E(\Phi, \Psi)$ for such conformers of the 2-acetamido-1,3-propanediol which can serve as models for configurational isomers of hexopyranoses. The most stable spatial arrangements derived in this way and spectroscopic parameters calculated for them are given in Table II. They could be used for a tentative correlation of the experimental CD data of methyl 3-acetamido-3,6-dideoxyhexopyranosides.

Table II shows that the positive sign of the n-π^* dichroic band should be related to the non-planar amide group with S chirality (characterized by a negative $\Delta\omega$ angle, see Fig. 2). Conversely, the sign of the n-π^* band should be positive for the R absolute configuration. Simple comparison of these (calculated) relations with our experi-

TABLE II

Calculated Oscillator (f) and Rotatory (R) Strengths in Conformations of 2-Acetamido-1,3-propanediol Considered as Models for the Equatorial Acetamido Group on the $C_{(3)}$ Atom of Pyranoses

Configuration	Φ	$\Delta\omega^a$	Chirality of the amide group	λ, nm	f	$R \cdot 10^{40b}$
gluco	−30°	−25°	S	296·9	0·0028	7·3
	50°	−25°	S	296·7	0·0048	10·4
talo	−40°	−25°	S	298·9	0·0034	10·9
	50°	−25°	S	299·1	0·0052	13·8
galacto	50°	−25°	S	296·2	0·0047	3·4
	−40°	−25°	S	300·1	0·0035	9·7
	30°	25°	R	304·8	0·0015	− 6·9
	−50°	25°	R	299·1	0·0038	−12·8

^{a} Φ Dihedral angle H—$C_{(3)}$—N—C′, $\Delta\omega$ $C_{(3)}$—N—C′—O (ref.[12]); ^{b} in esu^2 cm^2 units.

mental data suggests the following hypothesis: Negative Cotton effects observed with D-*gluco* isomers *I*, *II* are related to the *R* chirality of the amide group. The amide geometry with this chirality intensifies the interactions with vicinal substituents in compounds *I* and *II*. Two local conformations seem to be permissible. The first one, with anticlinal orientation of hydrogen atoms in the fragment H—$C_{(3)}$—N—H, is not consistent with ^{1}H-NMR data[11]. The second one, however, with antiperiplanar orientation of the mentioned hydrogen atoms brings the carbonyl oxygen atom in proximity of the $C_{(4)}$ hydroxy group which exhibits an enhanced nucleophility when compared with $C_{(2)}$ hydroxy group also in chemical reactions[17,32,33]. Chirality of the *S* type is also preferred in D-*talo* isomers due to the hydrogen bond between the N—H proton and $C_{(4)}$—OH oxygen atom. Several stable conformations with *R* or *S* chirality have been calculated for D-*galacto* and D-*manno* isomers. From experimental data it follows that it is in these compounds where the sign of the n-π* dichroic band is solvent dependent, *i.e.* solvent induced changes in local conformation could be envisaged. To the acetamido group located axially in α-anomers, we can directly assign the *S* chirality which is determined by the interaction of the N—H proton with the anomeric oxygen atom, in agreement with experimentally observed positive n-π* bands. We can conclude, with some emphasis, that the presented data are not in controversy with the concept of a non-planar amide group existing in two enantiomeric unequally populated conformations in the series of compounds under study.

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