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CONFORMATIONS OF METHYL 3,4-DIDEOXY-DL-GLYC-3-ENOPYRANOSIDES*

OSMAN ACHMATOWICZ, JR., ANNA BANASZEK, MAREK CHMIELEWSKI, ALEKSANDER ZAMOJSKI,
Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warszawa (Poland)
AND WOJCIECH LOBODZINSKI
Industrial Institute of Electronics, 00-241 Warszawa (Poland)
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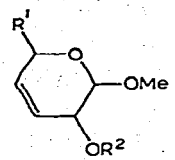
ABSTRACT

The conformational equilibrium (${}^{0}H_{1} \rightleftharpoons {}^{1}H_{0}$) has been established for 26 diastereoisomeric methyl 3,4-dideoxy-DL-glyc-3-enopyranosides on the basis of the coupling constant $J_{1,2}$. The position of equilibrium depends on the interplay of steric and polar factors. The concept of the allylic effect is useful in explaining some conformational phenomena.

INTRODUCTION

Methyl 3,4-dideoxy-pent- and -hex-3-enopyranosides (**1**) are a class of unsaturated monosaccharides which are of interest in carbohydrate chemistry as intermediates in the synthesis and chemical modification of sugars[2], but little is



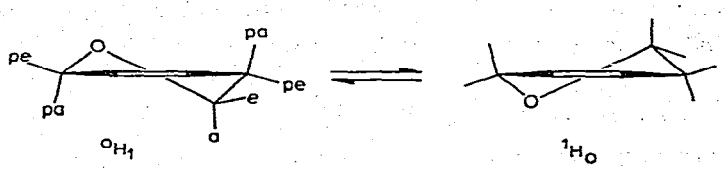
1 $R^1 = H, Me, CH_2OH$
$R^2 = H, Ac, CH_2Ph$

known about their stereochemistry. As part of a programme aimed at the evaluation of the chemical and physical properties of compounds of type **1**, we have studied their conformation and now report on p.m.r. data for 26 diastereoisomeric compounds in this category (see Tables I and III for formulae).

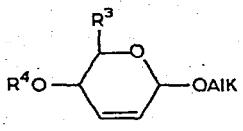
*Part V of the series: The n.m.r. spectra and conformations of dihydropyran derivatives[1].

RESULTS

Derivatives of 5,6-dihydro-α-pyran are generally considered to exist as equilibria of half-chair conformations:

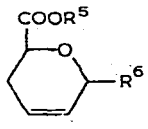


The position of each equilibrium depends on the mutual disposition and character of the substituents as well as on solvent and temperature. This conclusion was derived from the analysis of coupling constants in the p.m.r. spectra of various 5,6-dihydro-α-pyrans, mostly alkyl 2,3-dideoxyglyc-2-enopyranosides[3] (**2**) and esters of 5,6-dihydro-α-pyran 6-carboxylic acids[4] (**3**).



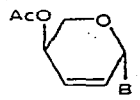
2

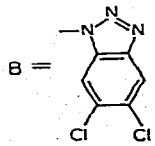
R^3 = H, Me, CH_2OH
R^4 = H, Ac



3

R^5 = Me, Bu
R^6 = H, OMe





A recent X-ray analysis of 2-(4-*O*-acetyl-2,3-dideoxy-β-L-pent-2-enopyranosyl)-5,6-dichlorobenzotriazole (**4**) confirmed the half-chair form of the sugar moiety[5].

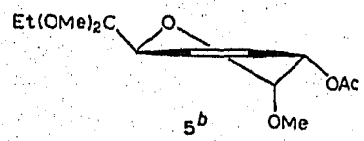
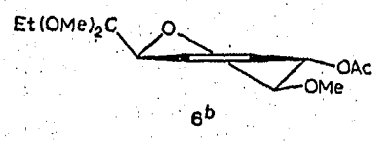
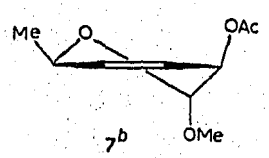
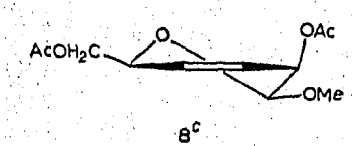
The p.m.r. data of four selected diastereoisomeric methyl 3,4-dideoxyglyc-3-enopyranosides are recorded in Table I.

In principle, the conformational equilibria of compounds of type **1** might be determined by evaluation of the following p.m.r. data: (*a*) vicinal and allylic coupling constants, $J_{2,3}$, $J_{2,4}$, and $J_{4,5}$, $J_{3,5}$, on the basis of Garbisch[6a] equations: $J_{vic} = 6.6\cos^2\phi + 2.6\sin^2\phi$, and $J_{allyl} = 1.3\cos^2\phi - 2.6\sin^2\phi$ for dihedral angles (ϕ) between 0° and 90°; (*b*) homoallylic coupling constant, $J_{2,5}$; (*c*) vicinal coupling constant, $J_{1,2}$.

It has been observed[6b] that, in 5,6-dihydro-α-pyran systems, the vicinal and allylic coupling constants of H-2 and H-5 showed deviations from the Garbisch equations. This is not unexpected, since these relations are semiempirical and their parameters were obtained from numerical data associated with carbocyclic systems. Therefore, they can only be used for qualitative analyses. The magnitude of

TABLE I

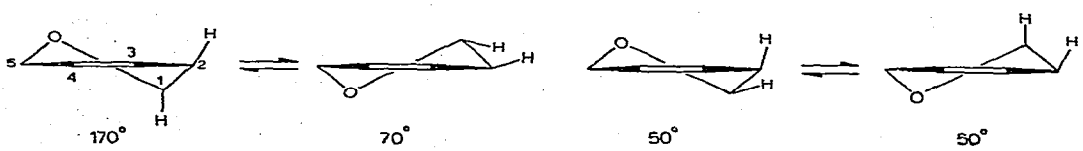
P.M.R. DATA OF METHYL 3,4-DIDEOXYGLYC-3-ENOPYRANOSIDES[a]

Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	$J_{1,2}$	$J_{1,3}$	$J_{1,4}$	$J_{1,5}$	$J_{2,3}$	$J_{2,4}$	$J_{2,5}$	$J_{3,4}$	$J_{3,5}$	$J_{4,5}$
 5[b]	5.18	5.35	5.64	6.08	4.37	4.2	−1.4	0.4	−0.7	1.7	−2.1	3.9	10.6	−2.6	1.9
 6[b]	4.51	5.28	5.63	6.07	4.38	7.0	−0.1	0.3	−0.3	2.0	−1.9	3.1	10.3	−2.7	1.6
 7[b]	4.76	4.91	5.81	5.99	4.33	1.1	−1.3	0.4	−0.8	4.9	−0.6	2.1	10.0	−2.0	1.3
 8[c]	4.48	5.20	5.71	5.58	—	2.9	—	—	—	3.6	0.6	1.6	10.1	1.5	1.2

[a] $CDCl_3$ solution, δ scale, J in Hz. [b] Using these data, a good correlation of the simulated spectrum and the experimental spectrum was obtained. [c] In $CDCl_3$–C_6D_6 (1:1) solution: data taken from K. Bock and Ch. Pedersen, *Acta Chem. Scand.*, 25 (1971) 1021.

homoallylic coupling in the 5,6-dihydro-α-pyran ring depends on the mutual orientation of the protons involved. For both pseudo-*ax* protons, it has the largest (~3 Hz), for pseudo-*ax*–pseudo-*eq* protons medium (1.5–2.5 Hz), and for both pseudo-*eq* protons the smallest (<1 Hz) value[6c]. This coupling constant also can serve only for qualitative estimations. The p.m.r. data of four selected, diastereoisomeric methyl 3,4-dideoxyglyc-3-enopyranosides shown in Table I indicate that all these compounds occur exclusively, or, at least, preferentially in the $^{\circ}H_1$ conformations.

Conformational equilibria of compounds **7–30** (for formulae, see Table III) can be determined within reasonable limits of accuracy from the magnitude of $J_{1,2}$. Values of $J_{1,2}$ are weighted averages of the corresponding coupling constants of two conformers present in the equilibrium mixture. For compounds with *trans*-related substituents at C-1 and C-2, the coupling constants contributing to the measured $J_{1,2}$ value are of *ax*–pseudo-*ax* ($J_{1a,2pa}$) and *eq*–pseudo-*eq* ($J_{1e,2pe}$) protons, and for those with *cis* substituents, of *eq*–pseudo-*ax* ($J_{1e,2pa}$) and *ax*–pseudo-*eq* ($J_{1a,2pe}$) protons. The corresponding dihedral angles of H-1 and H-2 are shown below.



In order to determine the conformational equilibria, the numerical values of all four couplings should be known ($J_{a,e}$ is not necessarily equal to $J_{e,a}$ in saturated pyranoid rings[6d]). Coupling constants of separate conformers are usually obtained in one of the following ways: (1) freezing-out of conformers and measuring their p.m.r. spectra directly; (2) taking coupling constants from the appropriate model compounds of fixed conformation; (3) using the known dependence of coupling constants on dihedral angles which, in turn, may be obtained from Dreiding models. Methods 1 and 3 could not be applied to the compounds studied herein. Because of the very low energy-barrier to ring inversion of unsaturated six-membered rings[7], the freezing-out of conformers is not practicable. The Karplus equation gives only a rough approximation and may even be misleading; for instance, the dihedral angles H_{1e}/H_{2pa} and H_{1a}/H_{2pe} are equal (50°), therefore $J_{1e,2pa}$ and $J_{1a,2pe}$ should also be equal but this was shown not to be the case (*cf.* Table I, compounds **5** and **6**).

From the available model compounds*, only two of the required coupling constants [$J_{1e,2pa}$ (**5**) and $J_{1a,2pa}$ (**6**)] were available. The remaining two were calculated as follows. Any coupling constant J which is a weighted average of J' and J'', corresponding to two conformers in an equilibrium mixture, is a function of temperature: $J = f(T)$. From known thermodynamic relations, the following equations may

*We believe that the steric bulk of the 1,1-dimethoxypropyl group, $Et(MeO)_2C$ is comparable to that of the *tert*-butyl group. Hence, compounds **5** and **6** exist exclusively in the $^{\circ}H_1$ conformation.

be evolved:

$$J'x+J''(1-x)=J \qquad K=e^{-\Delta G/RT},$$

$$K=\frac{1-x}{x}=\frac{J'-J}{J-J''}, \qquad K=e^{-\Delta H/RT}\times e^{\Delta S/R},$$

$$\Delta G=-RT\ln K, \qquad \frac{J'-J}{J-J''}=e^{-\Delta H/RT}\times e^{\Delta S/R},$$

$$\Delta G=\Delta H-T\Delta S, \qquad J=\frac{J'e^{\Delta H/RT}+J''e^{\Delta S/R}}{e^{\Delta H/RT}+e^{\Delta S/R}},$$

where ΔH and ΔS are enthalpy and entropy differences, respectively, of the two conformers, T = absolute temperature, R = gas constant, and K = equilibrium constant.

Assuming that thermodynamic (ΔH, ΔS) and coupling (J', J'') constants are temperature-independent, they may, in principle, be calculated from the above equation for J by using J values obtained at various temperatures. However, as shown by Garbisch[8], computer programs will converge to correct solutions regardless of the initial estimates of ΔH, ΔS, J', and J'', if J is measured with an accuracy of ~0.002 Hz. It was also indicated that this type of calculation can be carried out successfully with the generally available accuracy of coupling-constant measurement, provided that some of the other parameters are known. The $J_{1,2}$ values of compounds **8** and **25** have been measured at temperatures between 181.6° and 372.0°K (Table II). The coupling constants $J_{1e,2pa}$ and $J_{1a,2pa}$ were taken from the model compounds **5** and **6**, respectively. The entropy change of conformational equilibria of compounds **8**

TABLE II

J VALUES FOR COMPOUNDS **8** AND **25**[a]

T (°K)	$J_{1,2}$		*T* (°K)	$J_{1,2}$	
	8	**25**		**8**	**25**
181.6	—	6.49	287.2	2.98	5.68
204.1	—	6.40	295.8	2.98	5.63
221.3	2.50	6.17	306.0	3.00	5.60
227.6	2.55	6.07	318.0	3.02	5.58
238.6	2.60	5.98	326.8	3.05	5.55
245.1	2.63	5.93	343.0	3.06	5.52
256.6	2.83	5.90	352.0	3.09	5.50
262.6	2.85	5.80	362.0	3.16	5.47
277.7	2.90	5.78	372.0	3.19	5.45
279.2	2.95	5.78			

[a]For formulae, see Table III.

TABLE III

CONFORMATIONAL EQUILIBRIA OF METHYL 3,4-DIDEOXYGLYC-3-ENOPYRANOSIDES

Compound	R^1	R^2	R^3	$J_{1,2}$[a] (*Hz*)	$^0H_1$ (%)	$^1H_0$ (%)	$-\Delta G^{298}$ (*kJ/mole*)
α-DL-*glycero*							
9	H	H	OH	3.75	75	25	2.72
10	H	H	OAc	3.75	75	25	2.72
11	H	H	OCH_2Ph	2.87	26	74	−2.60
α-DL-*erythro*							
12	Me	H	OH	3.7	72	28	2.34
13	Me	H	OAc	4.2	100	0	...
14	CH_2OH	H	OH	3.8	78	22	3.14
15	CH_2OAc	H	OH	4.1	94	6	6.82
16	CH_2OAc	H	OAc	4.2	100	0	...
α-DL-*threo*							
7	Me	OAc	H	[b]	100[c]	0	...
17	Me	OH	H	[b]	100	0	...
18	CH_2OH	OH	H	[b]	100	0	...
19	CH_2OAc	OH	H	[b]	100	0	...
20	CH_2OAc	OAc	H	[b]	100	0	...

β-DL-*glycero*							
21	H	H	OH	2.75	36	64	−1.43
22	H	H	OAc	0.75	6	94	−6.82
23	H	H	OCH_2Ph	2.60	34	66	−1.64
β-DL-*erythro*							
24	Me	H	OH	6.0	85	15	4.30
25	Me	H	OAc	5.63	78	22	3.14
26	CH_2OH	H	OH	5.95	84	16	4.11
27	CH_2OAc	H	OAc	4.75	66	34	1.64
β-DL-*threo*							
8	CH_2OAc	OAc	H	2.98	73	27	2.46
28	Me	OH	H	2.6	89	11	5.18
29	Me	OAc	H	2.7	83	17	3.93
30	CH_2OH	OH	H	2.4	100	0	...

[a] $CDCl_3$ solution, 298 °K. Coupling constants were obtained by first-order analysis.
[b] Singlet, below resolution. [c] The calculated value (1.1 Hz, Table I) of $J_{1,2}$ indicates only 89% of the $^0H_1$ conformer.

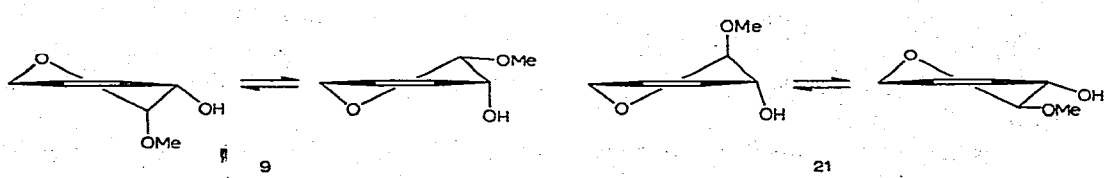
and **25** was neglected[9]. Taking the $J_{1,2}$ values from Table II and employing the above equation for J, the coupling constants $J_{1e,2pe}$ and $J_{1a,2pe}$, as well as the respective ΔH values, were calculated with the aid of a computer program for the evaluation of parameters of one variable function approximating a set of experimental data[10]. The following values were obtained: $J_{1e,2pe}$ 0.34 Hz, ΔH 3.14 kJ/mole; $J_{1a,2pe}$ 2.4 Hz, ΔH 2.0 kJ/mole. On the basis of the foregoing data, conformational equilibria and energies of compounds **7–30** were calculated. The results are given in Table III.

DISCUSSION

The position of the conformational equilibrium for methyl 3,4-dideoxyglyc-3-enopyranosides is dependent on the interaction of such steric and polar factors as 1,3-*ax*–pseudo-*ax* repulsion, the anomeric effect, and, as shown below, the allylic effect. In the methyl 3,4-dideoxypent-3-enopyranosides, **9** (α-DL-*glycero*, *cis*) and **21** (β-DL-*glycero*, *trans*), the anomeric effect plays the decisive role; the equilibrium is shifted toward conformers with an *ax* methoxyl group (Table III, **9** and **14**). The magnitude of the anomeric effect increases with the decreasing polarity of the solvent[11]. This effect was illustrated by the data on the conformational equilibria of **9** and **21** in several solvents. The preponderance of conformers with an *ax* methoxyl group is greatest in benzene (Table IV). The especially high contribution of this conformer observed for **9** can also be accounted for by the unfavourable Reeves Δ^2-effect in the alternative conformation.

TABLE IV

CONFORMATIONAL EQUILIBRIA OF METHYL 3,4-DIDEOXY-α- AND -β-DL-PENT-3-ENOPYRANOSIDES (**9** AND **21**) IN FOUR SOLVENTS

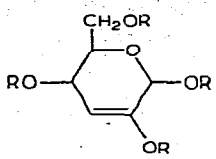


9 21

Solvent	**9**			**21**		
	$J_{1,2}$ (*Hz*)	$^oH_1$	^1H_o	$J_{1,2}$ (*Hz*)	^1H_o	$^oH_1$
C_6D_6	4.2	100	0	1.75	79	21
$CDCl_3$	3.75	75	25	2.75	64	36
$(CD_3)_2SO$	3.55	64	36	3.15	58	42
D_2O	3.50	61	39	2.88	62	38

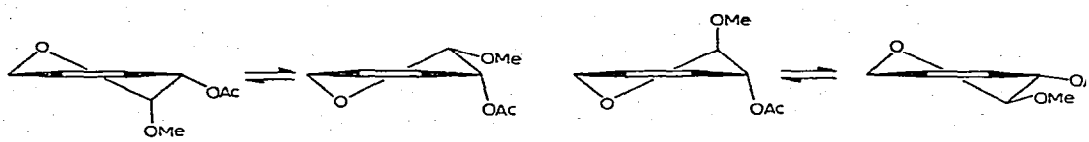
In the 2-*O*-acetyl compounds, **10** and **22**, the position of conformational equilibrium is also determined by the anomeric effect. The great preponderance (94 %) of the ^1H_o conformation of **22** having *ax* methoxyl and pseudo-*ax* acetate substituents is

noteworthy when compared to the 75% contribution of the $^{\circ}H_1$ conformer in **10**. This result can be explained by the so-called allylic effect[12], *i.e.*, the preference of polar substituents in allylic positions for the pseudo-*ax* orientation. The allylic effect has been invoked[12] to explain conformational phenomena in the esters of 2,3-unsaturated sugars, *i.e.*, 3-deoxyhex-2-enopyranoses (**31**). The origin of this effect is



31 R = Ac, Bz

uncertain but may be connected with steric (repulsion between pseudo-*eq* and adjacent vinylic substituents) and/or polar factors. The scope of the effect is also unclear. Although its operation can be observed in substituted dihydropyrans, there are some doubts as to its existence in cyclohexenes[13]. Conformer ratios of compounds **10** and **22** in benzene and deuteriochloroform solution are as follows:



C_6H_6	61	39	100	0
$CDCl_3$	75	25	94	6

Thus, in a benzene solution of **10**, the preponderance of the conformer with an *ax* methoxyl group is markedly decreased, whereas, for **22**, the preference for the ^1H_o conformer is increased. This result can be explained by an opposed or cumulative action of the anomeric and allylic effects, their magnitude being dependent on the nature of the solvent.

Whereas the conformational equilibrium of benzyl ether **23** (*trans*) is closely similar to that of the parent compound **21**, in the isomeric ether **11** (*cis*) the position of equilibrium is considerably shifted towards the conformer with an *eq* methoxyl group (Table III, **23** and **11**). At present, this observation is difficult to explain.

Replacement of a hydrogen atom at C-5 of compound **21** by a methyl, hydroxymethyl, or acetoxymethyl group, leading to a system with the α-*threo* configuration, causes (Table III, **7**, **17–20**) a complete shift of the conformational equilibrium towards the $^{\circ}H_1$ conformers, *i.e.*, those having an *ax* methoxyl group, a pseudo-*ax* C-2, and pseudo-*eq* C-5 substituents. In the series of compounds with α-*erythro* configuration (**12–16**), the $^{\circ}H_1$ conformers preponderate to a greater extent than in **9** or **10**. This indicates that, methyl, hydroxymethyl, or acetoxymethyl groups in position 5 prefer the pseudo-*eq* orientation. This conclusion somewhat invalidates the steric origin of the allylic effect.

In compounds with *β-threo* (**8**, **28–30**) and *β-erythro* (**24–27**) configurations a 1,3-*ax*–pseudo-*ax* interaction between the methoxyl and CH_2R (R = H, OH, or OAc) occurs in the $^1H_0$ conformation. Although it ought to be less strong than the 1,3-*syn*-axial repulsion in the tetrahydropyran ring, it is still sufficiently pronounced to destabilize this conformation. Consequently, compounds with *β-threo* or *β-erythro* configurations show a preponderance of the alternative conformation. In 2-*O*-acetyl derivatives of *β-erythro* configuration (**25** and **27**), the allylic effect opposes the 1,3-*ax*–pseudo-*ax* repulsion and, thus, the contributions of the $^1H_0$ conformations to the equilibria are somewhat higher than for the respective *β-threo* compounds (*cf.* **8** and **29**).

Assessment of the energies associated with the various effects in the systems studied is not possible at present. However, an approximate estimation can be made for the 1,3-*ax*–pseudo-*ax* interaction involving substituents at positions 1 and 5 of the glyc-3-enopyranose ring. Summing the conformational energies for compounds **21** and **24** or **26** gives values of 5.73 and 5.54 kJ/mole, respectively, which are far below the respective energies in the tetrahydropyran ring[14] (~10.5 kJ/mole).

Thus, the position of the conformational equilibrium in methyl 3,4-dideoxy-DL-glyc-3-enopyranosides is a compromise between the anomeric effect, 1,3-*ax*–pseudo-*ax* repulsion, and the preference of the CH_2R (R = H, OH, or OAc) group attached to the allylic carbon atom for the pseudo-*eq* position. It is interesting to note that the contribution of the allylic effect seems to be limited to the 2-*O*-acetyl compounds. The general importance of this phenomenon and its nature remain uncertain.

EXPERIMENTAL

Compounds **7–30** were obtained as described earlier[15,16]. The preparation of **5** and **6** will be described elsewhere[17]. P.m.r. spectra were recorded at 25° on a JEOL JNM-4H-100 spectrometer. The accuracy of J values determined at room temperature was ±0.05 Hz, and at variable temperatures ±0.02 Hz. The calculation of $J_{1e,2pe}$ and $J_{1a,2pe}$ was performed with DIXI (Fortran) program[10] on an ICL-1904 computer.

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