Carbohydrate Research, 79 (1980) 29–37

CONFORMATIONAL ANALYSIS OF 1,2:3,4-DI-*O*-ISOPROPYLIDENE-α-D-*galacto*-OCTOPYRANOSE DERIVATIVES: A ^{1}H- AND ^{13}C-N.M.R.-SPECTRAL AND X-RAY COMPARATIVE STUDY

KLAUS G. R. PACHLER*, ELNER B. RATHBONE**, GRAHAM R. WOOLARD***, AND MARIANNE WOUDENBERG

National Chemical Research Laboratory, Council for Scientific and Industrial Research, Pretoria 0001 (South Africa)

(Received July 30th, 1979; accepted for publication, September 4th, 1979)

ABSTRACT

The pyranoid conformations of 7-acetamido-6,7,8-trideoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-octopyranose (3) and 7-acetamido-7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-L-*threo*-α-D-*galacto*-octopyranose (4) in solution have been determined by calculation of the dihedral angles from the vicinal, proton–proton coupling-constants, using three modifications of the Karplus equation. Of these, only the equation

$$^3J(\mathrm{HCCH})(\phi) = (7.48 - 0.74\ \Sigma\Delta \mathrm{E_X}) - (2.03 - 0.17\ \Sigma \mathrm{E_X})\cos\phi + (4.60 - 0.23\ \Sigma\Delta \mathrm{E_X})\cos 2\phi + 0.06\ (\Sigma \pm\Delta \mathrm{E_X})\sin\phi + 0.62\ (\Sigma \pm\Delta \mathrm{E_X})\sin 2\phi$$

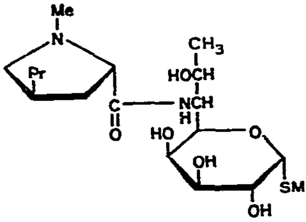
indicates that the pyranoid part of 3 and 4 has the $^OS_2$ conformation, very slightly distorted towards $^OH_5$, in agreement with the conformations determined for the crystalline state. Analysis of the ^{1}H-n.m.r. data for a series of 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-octopyranose derivatives shows that the pyranoid parts of these compounds adopt the same conformation as that found for 3 and 4.

INTRODUCTION

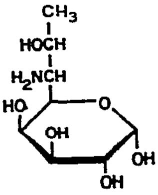
The antibiotic lincomycin (1) contains a sugar moiety, methyl 6-amino-6,8-dideoxy-1-thio-D-*erythro*-α-D-*galacto*-octopyranoside[1], coupled by an amide linkage to L-*trans*-4-propylhygric acid[2]. Lincosamine (2), an intermediate in the synthesis of lincomycin, has been the subject of several reports[3–10]. This has resulted in the preparation of a series of di-*O*-isopropylidene-α-D-*galacto*-octopyranose derivatives. Recently, the synthesis and crystal structure of 7-acetamido-6,7,8-trideoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-octopyranose (3), a compound related

---

*E. Merck, Analytisches Zentrallaboratorium, Postfach 4119, D-6100 Darmstadt, West Germany.
**Tate and Lyle Ltd., Group Research and Development, P.O. Box 68, Reading RG6 2BX, U.K.
***Dextran Products, 421 Constock Road, Scarborough, Ontario M1L 2H5, Canada; to whom correspondence should be addressed.



1 [Pr = $Me(CH_2)_2$—]



2

to lincosamine, were reported[11]. The synthesis and crystal structure of 7-acetamido-7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-L-*threo*-α-D-*galacto*-octopyranose (**4**), and the synthesis of 7-acetamido-7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*erythro*-α-D-*galacto*-octopyranose (**5**) have also been described[12].

A knowledge of the conformation of biologically active compounds in solution is essential in assessing their mode of action, and in the development of syntheses of new, physiologically active compounds. Although X-ray crystallography provides the spatial structures of molecules in the crystal lattice, these conformations are not necessarily identical with those in solution. The Karplus equation[13], which relates the vicinal, proton–proton coupling-constants to the dihedral angles between the coupling protons, has been modified[14] by the introduction of an empirical, proportionality constant for application to six-membered carbohydrate rings. This modified equation may be written as follows.

$$^{3}J(\mathrm{HCCH})(\phi) = 4.13 - 0.55\cos\phi + 4.41\cos 2\phi \qquad (1)$$

Equation *1* has been applied in a ^{1}H-n.m.r. study of the conformation of some di-*O*-isopropylidenearabinopyranose derivatives[15].

The original Karplus equation, which does not account for the electronegativities[16] (E) and spatial arrangements of the substituents[17–19], was extensively modified by Pachler[20]. An analysis[20] of experimentally determined, vicinal, proton–proton coupling-constants gave the empirical parameters for equation *2*.

$$^{3}J(\mathrm{HCCH})(\phi) = (7.48 - 0.74\,\Sigma\Delta E_{\mathrm{X}}) - (2.03 - 0.17\,\Sigma E_{\mathrm{X}})\cos\phi + (4.60 - 0.23\,\Sigma\Delta E_{\mathrm{X}})\cos 2\phi + 0.06\,(\Sigma \pm\Delta E_{\mathrm{X}})\sin\phi + 0.62\,(\Sigma \pm\Delta E_{\mathrm{X}})\sin 2\phi, \qquad (2)$$

where $\Delta E_{\mathrm{X}} = E_{\mathrm{X}} - E_{\mathrm{H}}$. The sign of $\pm\Delta E_{\mathrm{X}}$ depends on the spatial arrangement of the substituent (X) relative to the coupling protons. Recently, Jankowski[21] proposed yet another type of Karplus equation; this accounts for structural modifications on the HCCH fragments through the directly bonded (C,H), coupling constants, as follows.

$$^{3}J(\mathrm{H}_i\mathrm{C}_i\mathrm{C}_j\mathrm{H}_j)(\phi) = 8.79\cos^2\phi + 0.004[^{1}J(\mathrm{C}_i,\mathrm{H}_i) + {}^{1}J(\mathrm{C}_j,\mathrm{H}_j)] \qquad (3)$$

In the present article, the pyranoid conformations of **3** and **4** in the crystal lattice are compared with those in solution (as derived from their ^{1}H-n.m.r. data, using equations *1–3*).

RESULTS AND DISCUSSION

The dihedral angles of the hydrogen substituents of compounds **3** and **4**, as determined[11,12] by X-ray crystallography, are listed in Table I. The pyranoid conformation of compound **3** is $^{O}S_2$ very slightly distorted towards $^{O}H_5$. Compound **4** also has the $^{O}S_2$ conformation in the crystal lattice[12], but with greater distortion towards $^{O}H_5$ compared to **3**. All hydrogen atoms were located in determining the crystal structure of these compounds, and the proton–proton, dihedral angles obtained from the fractional, atomic coordinates are only accurate to within ±5°. Just 20 years ago, it was pointed out[22] that 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose has a non-chair conformation.

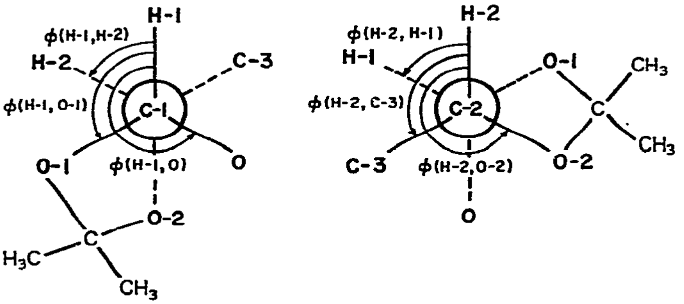
The electronegativity scale of Huggins[23] was used in the application of equation *2*. The ΔE_X values for carbon, nitrogen, and oxygen are 0.4, 0.85, and 1.3,

TABLE I

DIHEDRAL ANGLES BETWEEN HYDROGEN ATOMS OF COMPOUNDS **3** AND **4**, DETERMINED BY X-RAY CRYSTALLOGRAPHY, AND CALCULATED FROM THE OBSERVED COUPLING-CONSTANTS BY USE OF EQUATIONS *1*, *2*, AND *3*

Compound	*X-ray, or equation number*	*Dihedral angle (degrees)*							
		ϕ(*H-1,2*)	ϕ(*H-2,3*)	ϕ(*H-3,4*)	ϕ(*H-4,5*)	ϕ(*H-5,6*)	ϕ(*H-5,6′*)	ϕ(*H-6,7*)	ϕ(*H-6′,7*)
3	X-ray	14.9	62.4	26.1	50.6	79.4	171.4	175.3	67.5
	1	41.0	57.5	21.0	61.0	38.5	147.0	158.6	29.8
	2	21.5	68.5	[a]	51.0	41.8	138.9	139.2	31.1
	3	48.5	68.5	28.8	72.7	50.1	152.1	135.9	9.2
4	X-ray	12.3	71.7	17.6	49.6		178.7		59.2
	1	39.7	58.9	21.0	63.2		160.3		58.2
	2	22.7	69.7	[a]	52.0		156.6		54.5

[a] Observed coupling slightly larger than largest *J* in the angle range. From model, ~14.5° for **3**.



$$\Sigma\Delta E = +\Delta E_{O\text{-}1} - \Delta E_{O} \qquad +\Delta E_{C\text{-}2} - \Delta E_{O\text{-}2}$$

Fig. 1. Derivation of the electronegativity term for the H-1–C-1–C-2–H-2 dihedral angles of compounds **3** and **4**, from the "Newman" projection along C-1–C-2 and C-2–C-1.

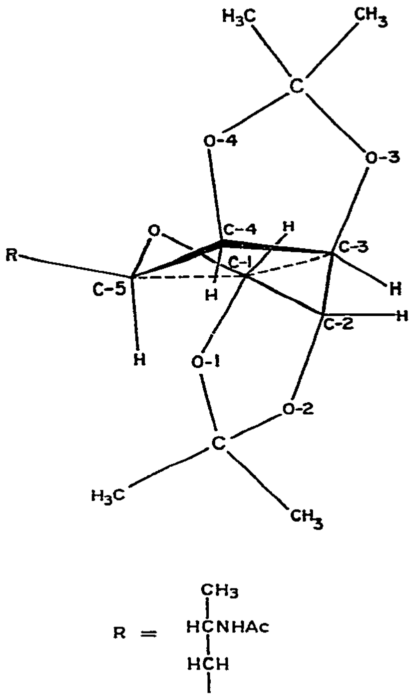


Fig. 2. A perspective diagram showing the conformation of compound 3 in solution. The reference plane, C-1–C-3–C-4–C-5, is indicated by the broken line.

respectively. The derivation of the $\Sigma \pm \Delta E_X$ electronegativity term[20] for C-1–C-2 of compounds **3** and **4** is illustrated in Fig. 1. Other electronegativity terms were calculated in a similar way.

The dihedral angles calculated for compound **3** from the observed coupling-constants by using equations *1–3*, and the corresponding values for compound **4** using equations *1* and *2*, are given in Table I. In the application of equation *2*, the relevant graphs of J *versus* the dihedral angle (ϕ) yielded the dihedral angles given in Table I.

The dihedral angle ϕ(H-3,H-4) could not be determined from equation *2*, as the graph of J *vs.* ϕ has a maximum of $J = 7.3$ Hz at $\phi = 0°$. A perspective diagram of compound **3** is shown in Fig. 2 (X-ray, bond angles and bond lengths). The model constructed from the values of ϕ(H-1,H-2), ϕ(H-2,H-3), and ϕ(H-4,H-5), determined from equation *2*, showed ϕ(H-3,H-4) = 14.5°.

Comparison of the dihedral angles for compounds **3** and **4** (equations *1* and *3*, and Table I) with those for the ${}^{O}S_2$ and $B_{2,5}$ conformers[15] indicates that the conformations of these sugars in solution are all ${}^{O}S_2$, each distorted to different extents towards $B_{2,5}$. A similar conformation was proposed[15] for various di-*O*-isopropylidene-arabinopyranose derivatives in solution by using equation *1*. These results differ from the conformations determined by X-ray crystallography[11,12].

An examination of the dihedral angles for compounds **3** and **4**, derived from equation *2* (see Table I), shows that the pyranoid parts in these sugar derivatives are similar to each other, and adopt the ${}^{O}S_2$ conformation, distorted towards ${}^{O}H_5$. The conformations of compounds **3** and **4** in solution, determined from the coupling constants by using equation *2*, agree better with those obtained by X-ray crystallography. Assuming that the conformations of compounds **3** and **4** in the solid and in solution do not differ significantly (which is a reasonable assumption, because of the rigidity of the ring system), these results indicate that equation *2* is superior to equations *1* and *3* in determining conformations in solution from vicinal, proton–proton coupling-constants.

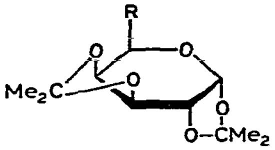
The similarities in the vicinal, proton–proton coupling-constants of the protons on the pyranose rings of 7-acetamido-7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*erythro*-α-D-*galacto*-octopyranose (compound **5**; see Experimental section) and other 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-octopyranose derivatives (compounds **6**–**18**; see Table II) indicate that these sugars each adopt a conformation closely related to those found for compounds **3** and **4**. The dihedral angles for the ring protons of compounds **5**–**18**, determined from equation *2* (see Table II), show that the conformations of these sugars are distorted to different degrees from ${}^{O}S_2$.

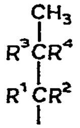
In solution, the side-chains of compounds **3** and **4** can exist in different, staggered conformations. Rotation around the C-5–C-6 bond in compound **3** resulted in the three possible conformations I, II, and III. Rotamer III, with gauche interactions between the three bulky groups, should have a much higher energy than I and II. Compound **3** exists in the crystalline state as I only. In solution, the vicinal

TABLE II

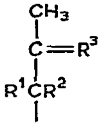
COUPLING CONSTANTS OF SOME 1,2:3,4-DI-*O*-ISOPROPYLIDENE-α-D-*galacto*-OCTOPYRANOSE DERIVATIVES

Compound	*Coupling constant (Hz)*				*Dihedral angle (degrees)*			*References*
	J(*H-1,2*)	J(*H-2,3*)	J(*H-3,4*)	J(*H-4,5*)	φ(*H-1,2*)	φ(*H-2,3*)	φ(*H-4,5*)	
5	5.1	2.4	7.9	1.9	22.5	69.6	51.5	This work
6	5.0	2.4	7.7	1.8	23.5	69.6	52.5	11
7	5.0	2.1	7.8	1.5	23.5	73.0	55.6	10
8	5.0	2.0	8.0	1.5	23.5	74.3	55.6	10
9	5.0	2.2	8.0	1.6	23.5	71.8	54.6	10
10	5.0	2.1	8.0	1.0	23.5	73.0	62.3	10
11	4.9	2.2	8.0	1.5	24.5	71.8	55.6	10
12	5.0	2.0	8.0	1.0	23.5	74.3	62.3	10
13	5.0	2.5	7.8	1.6	23.5	68.5	54.6	10
14	5.0	2.5	7.7	1.5	23.5	68.5	55.6	10
15	5.1	2.4	7.8	1.8	22.5	69.6	52.5	11
16	5.0	2.5	8.0	2.0	23.5	68.5	50.6	7
17	5.0	2.4	8.0	1.8	23.5	69.6	52.5	10
18	5.0	2.6	7.8	1.9	23.5	67.5	51.5	10



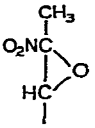
R =  $CH_3-CR^3R^4-CR^1R^2-$

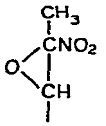
	R^1	R^2	R^3	R^4
3	H	H	NHAc	H
4	OH	H	H	NHAc
5	OH	H	NHAc	H
6	H	H	H	NHAc
7	NHBz	Me	OH	Me
8	NHBz	Me	Me	OH
9	NH_2	Me	OH	Me
10	NHAc	Me	OH	Me
11	NHAc	Me	Me	OH

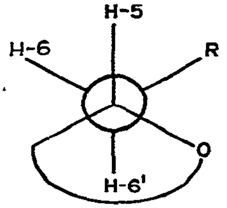
R =  $CH_3-C(=R^3)-CR^1R^2-$

	R^1	R^2	R^3
12	NHBz	Me	O
13	N_3	Me	O
14	Me	N_3	O
15	H	H	NHOH

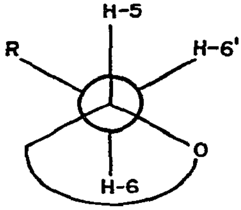
16 R = $-CH{=}C(NO_2)CH_3$

17 R = 

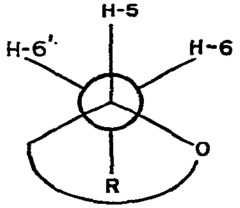
18 R = 



I



II



III

coupling-constants observed are the weighted average of the corresponding coupling-constants for the different rotamers. Any contribution of II would result in a decrease of the H-5,H-6′ coupling, and ${}^3J$(H-5,H-6) should increase. It is, therefore, not surprising that the proton–proton dihedral angles between H-5, H-6, H-6′, and H-7 calculated by use of equation *2* (and, also, equations *1* and *3*) are substantially different from those observed for the solid state.

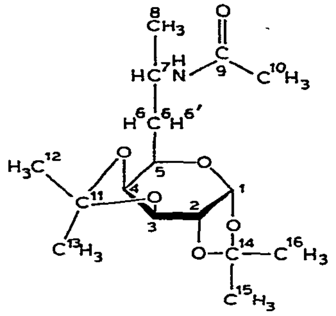


Fig. 3. Numbering system used for compounds **3–5** in ^1H- and ^{13}C-n.m.r. analysis.

TABLE III

^{1}H-N.M.R. DATA FOR COMPOUNDS **3**, **4**, AND **5**

Hydrogen atom	*δ$_H$ (p.p.m.)*		
	3	**4**	**5**
1	5.52	5.51	5.51
2	4.31	4.30	4.30
3	4.62	4.61	4.61
4	4.24	4.46	4.46
5	3.84	3.67	3.63
6	1.81	—	—
6′	1.70	3.77	3.88
7	4.14	4.02	4.18
8	1.18	1.30	1.23
10	1.94	1.96	1.98
12	1.48	1.49	1.51
13	1.44	1.45	1.44
15	1.33	1.36	1.36
16	1.31	1.32	1.32
Coupling constant	*J(Hz)*		
	3	**4**	**5**
J(1,2)	5.19	5.08	5.09
J(2,3)	2.40	2.39	2.40
J(3,4)	7.98	8.00	7.94
J(4,5)	1.96	1.86	1.93
J(5,6)	4.70	—	—
J(5,6′)	7.95	8.88	8.97
J(6,6′)	−14.91	—	—
J(6,7)	5.60	—	—
J(6,7′)	9.63	2.70	2.82
J(7,8)	6.45	7.04	6.93

TABLE IV

^{13}C-N.M.R. DATA FOR COMPOUND 3

Carbon atom	*δ_C (p.p.m.)*	*J (CH) (Hz)*
1	96.5 Ddt	178.9, 4.6, 2.3
2	70.4 Dm	152.1
3	70.8 Dd	153.9, 3.6
4	72.9 Dm	152
5	66.0 Dm	142.5
6	36.4 Tm	127.9
7	43.8 Dm	137.8
8	21.9 Qm	126.4
9	169.5 Sm	—
10	23.5 Qm	127.6
11	109.0 Sm	—
14	108.4 Sm	—
12	25.9 Qm	127.0
13	25.8 Qm	127.1
15	24.8 Qm	126.3
16	24.5 Qm	126.1

EXPERIMENTAL

^{1}H-N.m.r. spectra were recorded at 33° with a Varian EM-390 spectrometer, for degassed solutions in deuteriochloroform, with tetramethylsilane as the internal, reference standard. ^{13}C-N.m.r. spectra of **3** in deuteriochloroform were recorded with Varian CFT-20 and XL-100-15 spectrometers. Fig. 3 gives the numbering employed herein.

The interpretation of the ^{1}H-n.m.r. spectra of compounds **3**–**5** was hindered, due to strong coupling between labile and adjacent protons. The exchangeable protons were replaced by deuterium (by addition of deuterium oxide to a solution of these compounds in deuteriochloroform in the presence of a catalytic amount of triethylamine), and the solutions of the deuterated compounds were degassed, and sealed under vacuum. The chemical shifts and coupling constants of these deuterated compounds, as summarized in Table III, were determined by analyzing the ^{1}H-n.m.r. spectra by use of the computer program LAME[24]. Carbon-13 data for compound **3** are presented in Table IV. Off-resonance, proton-decoupled, ^{13}C-n.m.r. spectra aided in the assignment of the different ^{13}C-n.m.r. signals.

REFERENCES

1 W. SCHROEDER, B. BANNISTER, AND H. HOEKSEMA, *J. Am. Chem. Soc.*, 89 (1967) 2448–2453.
2 B. J. MAGERLEIN, R. D. BIRKENMEYER, R. R. HERR, AND F. KAGAN, *J. Am. Chem. Soc.*, 89 (1967) 2459–2464.
3 T. ATSUMI, T. FUKUMARU, T. OGAWA, AND M. MATSUI, *Agric. Biol. Chem.*, 37 (1973) 2621–2626.
4 T. ATSUMI, T. FUKUMARU, AND M. MATSUI, *Agric. Biol. Chem.*, 37 (1973) 2627–2630.

5 B. J. MAGERLEIN, *Tetrahedron Lett.*, (1970) 33–36.
6 H. SAEKI AND E. OHKI, *Chem. Pharm. Bull.*, 18 (1970) 789–802.
7 G. B. HOWARTH, D. G. LANCE, W. A. SZAREK, AND J. K. N. JONES, *Can. J. Chem.*, 47 (1969) 75–79.
8 G. B. HOWARTH, W. A. SZAREK, AND J. K. N. JONES, *Chem. Commun.*, (1969) 1339–1340.
9 G. B. HOWARTH, W. A. SZAREK, AND J. K. N. JONES, *J. Chem. Soc., C*, (1970) 2218–2224.
10 G. R. WOOLARD, E. B. RATHBONE, W. A. SZAREK, AND J. K. N. JONES, *J. Chem. Soc., Perkin Trans. 1*, (1976) 950–954.
11 J. C. A. BOEYENS, E. B. RATHBONE, AND G. R. WOOLARD, *Carbohydr. Res.*, 62 (1978) 39–47.
12 J. C. A. BOEYENS, M. J. NOLTE, AND G. R. WOOLARD, *Carbohydr. Res.*, 70 (1979) 103–115.
13 M. KARPLUS, *J. Chem. Phys.*, 30 (1959) 11–15.
14 R. W. LENZ AND J. P. HEESCHEN, *J. Polym. Sci.*, 51 (1961) 247–261.
15 C. CONE AND L. HOUGH, *Carbohydr. Res.*, 1 (1965) 1–9.
16 R. J. ABRAHAM AND G. GATTI, *J. Chem. Soc., B*, (1969) 961–968.
17 D. H. WILLIAMS AND N. S. BHACCA, *J. Am. Chem. Soc.*, 86 (1964) 2742–2743.
18 H. BOOTH, *Tetrahedron Lett.*, (1965) 411–416.
19 R. J. ABRAHAM, L. CAVALLI, AND K. G. R. PACHLER, *Mol. Phys.*, 11 (1966) 471–494.
20 K. G. R. PACHLER, *J. Chem. Soc., Perkin Trans. 2*, (1972) 1936–1940.
21 K. JANKOWSKI, *Org. Magn. Reson.*, 10 (1977) 50–51.
22 R. S. TIPSON, H. S. ISBELL, AND J. E. STEWART, *J. Res. Natl. Bur. Stand.*, 62 (1959) 257–282.
23 M. L. HUGGINS, *J. Am. Chem. Soc.*, 75 (1953) 4123–4126.
24 C. W. HAIGH, *Annu. Rep. NMR Spectrosc.*, 4 (1971) 311–362.