Carbohydrate Research, 35 (1974) 15–31

CONFORMATIONAL ANALYSIS OF ACYLATED 1,1-BIS(ACYLAMIDO)-1-DEOXYPENTITOLS BY FOURIER-TRANSFORM, P.M.R. SPECTROSCOPY*

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(Received November 6th, 1973; accepted with revisions, February 4th, 1974)

ABSTRACT

The conformations of eight acylated 1,1-bis(acylamido)-1-deoxypentitols in solution have been studied by pulse, Fourier-transform, p.m.r. spectroscopy at 90 MHz. The *arabino* and *lyxo* derivatives adopt the zigzag conformation, whereas the *ribo* and *xylo* derivatives favor different sickle conformations. The validity of the conformational assignments of these derivatives by the p.m.r. method is discussed. The relative merits and accuracy of the continuous-wave and pulse-Fourier p.m.r. spectroscopic methods in the conformational analysis of carbohydrates are appraised, and the applicability of the exponential-filtering technique to enhancement of either the sensitivity or the resolution of their spectra is demonstrated.

INTRODUCTION

Investigations of *solutions* of (polyhydroxyalkyl)quinoxaline derivatives[1,2], acetylated[3] and nonacetylated[4] glyculose arylosotriazoles, polyacetoxy-*trans*-1-nitro-1-alkenes[5], acetylated alditols[6], diethyl[7] and diphenyl[8] dithioacetal, dimethyl acetal[9], and *aldehydo*[10] derivatives of aldoses, pentononitriles[11,12], (polyhydroxyalkyl)-thioamides and -thiazoles[12], methyl 5-hexulosonates and *keto*-hexuloses[13], and unsubstituted aldose diethyl and diphenyl dithioacetals[14] by continuous-wave, p.m.r. spectroscopy have shown that these derivatives usually favor a conformation that has the carbon atoms of the sugar chain in a planar, zigzag arrangement, unless this conformation contains an eclipsed, 1,3-interaction between substituent oxygen atoms. Relief of this steric interaction, which is generally assumed to be repulsive, normally occurs by distortion of the zigzag conformation to a sickle conformation in which one of the carbon atoms of the chain lies outside the plane containing the rest of the carbon atoms in the chain.

*Dedicated to Dr. Horace S. Isbell, in honor of his 75th birthday.
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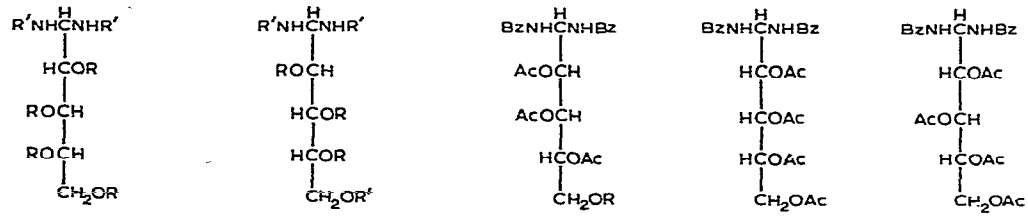
For *crystalline* alditols, similar results have been obtained by X-ray crystallography[15], although the observation of a planar, zigzag form for anhydrous[16] and hydrated[17] D-gluconate ion in the solid state is an exception to the general rule and has been explained[17] in terms of an intramolecular hydrogen-bond between O-2 and O-4. The p.m.r. interpretations for D-lyxononitrile tetraacetate are unexpected, in that they are apparently consistent with either a nonstaggered, sickle conformation or a fully staggered "U"-shaped conformation[11], despite the fact that the zigzag conformation thereof cannot have a 1,3-interaction of oxygen atoms.

Current interest in the conformations of acyclic carbohydrate derivatives and in the factors that determine these conformations prompted us to examine a complete series of peracetylated 1,1-bis(benzamido)-1-deoxypentitols and some related derivatives by Fourier-transform, p.m.r. spectroscopy at 90 MHz, with the objectives of (*a*) determining the effect of the relatively large acylamido substituents on the conformations assumed by the pentitol derivatives, (*b*) establishing the relative merits of the pulse, Fourier-transform and continuous-wave techniques for determination of conformations, and (*c*) ascertaining whether the p.m.r. method provides a unique, conformational solution for these derivatives.

One of us, with coworkers, has previously studied the structures of a large series of both cyclic and acyclic 1,1-bis(acylamido)-1-deoxy derivatives of sugars and alditols by means of infrared spectroscopy[18].

SCOPE OF THE WORK

The following derivatives were studied: tetra-*O*-acetyl-1,1-bis(benzamido)-1-deoxy-L-arabinitol[19] (**1**), tri-*O*-acetyl-1,1-bis(benzamido)-5-*O*-benzoyl-1-deoxy-D-arabinitol[20] (**2**), 1,1-bis(benzamido)-tetra-*O*-benzoyl-1-deoxy-D-arabinitol[19] (**3**), 1,1-bis(acetamido)-tetra-*O*-acetyl-1-deoxy-L-arabinitol[21] (**4**), tetra-*O*-acetyl-1,1-bis(benzamido)-1-deoxy-D-lyxitol[22] (**5**), tri-*O*-acetyl-1,1-bis(benzamido)-5-*O*-benzoyl-1-deoxy-D-lyxitol[20] (**6**), tetra-*O*-acetyl-1,1-bis(benzamido)-1-deoxy-D-ribitol[19] (**7**), and tetra-*O*-acetyl-1,1-bis(benzamido)-1-deoxy-D-xylitol[19] (**8**).



1 R = Ac; R' = Bz
4 R = R' = Ac

2 R = Ac; R' = Bz
3 R = R' = Bz

5 R = Ac
6 R = Bz

7

8

RESULTS AND DISCUSSION

P.m.r. spectroscopy. — Compounds **1**, **5**, **7**, and **8** constitute a complete series of tetra-*O*-acetyl-1,1-bis(benzamido)-1-deoxypentitols, and derivatives of this type

were found generally to yield the best-resolved p.m.r. spectra at 90 MHz, particularly when the derivatives were examined as their solutions in pyridine-d_5–hexafluorobenzene. The pulse, Fourier-transform technique rapidly provides spectra of excellent signal:noise ratio, even from relatively small quantities of material[23,24], and the associated computer equipment allows automatic measurements of line frequencies and chemical shifts in p.p.m. from tetramethylsilane (see Table I).

Exchange of the NH protons of the bis(acylamido) derivatives with deuterium was not achieved by mere shaking or ultrasonic mixing of the solutions of the derivatives with deuterium oxide; catalysis of the exchange process by the addition of a drop of pyridine-d_5 was found necessary. However, even in pure pyridine-d_5, proton exchange was insufficiently rapid to remove the effects of spin coupling between H-1 and the NH and NH′ protons. The NH and NH′ signals therefore appeared as doublets at low field that disappeared on deuterium exchange (see, for example, Fig. 1b). These doublets were ~2 p.p.m. to lower field for solutions that contained

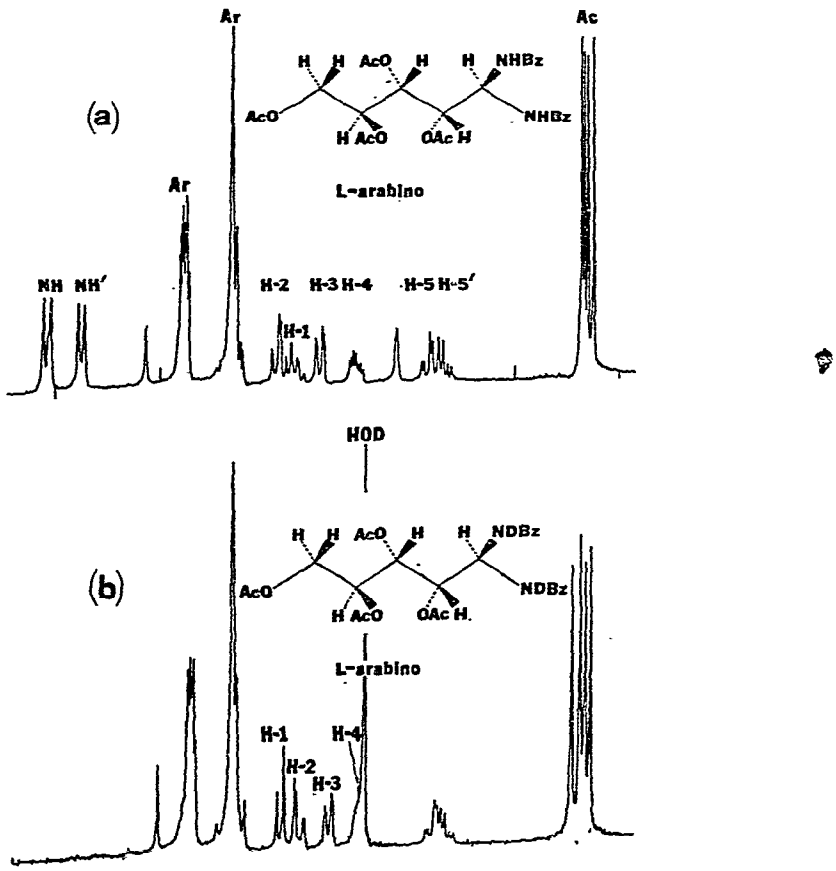


Fig. 1. Fourier-transform, p.m.r. spectra at 90 MHz: (*a*) tetra-*O*-acetyl-1,1-bis(benzamido)-1-deoxy-L-arabinitol (**1**) in 4:1 (v/v) pyridine-d_5–hexafluorobenzene, and (*b*) the *N*,*N*′-dideuterated derivative (**1**-d_2) in 12:5:3 (v/v) pyridine-d_5–deuterium oxide–hexafluorobenzene.

TABLE I

PROTON CHEMICAL-SHIFTS[a] OF ACYLATED 1,1-BIS(ACYLAMIDO)-1-DEOXYPENTITOLS

Compound	*Configuration*	*Solvent*[b]	*H-1*	*H-2*	*H-3*
1	*arabino*	C_5D_5N–C_6F_6 (4:1)	6.41q[d]	6.68q	6.02q
1-d_2[e]	*arabino*	C_5D_5N–D_2O–C_6F_6 (12:5:3)	6.77d	6.48q	6.05q
2	*arabino*	C_5D_5N–C_6F_6 (4:1)	6.46q	6.73q	6.16q
2-d_2[e]	*arabino*	C_5D_5N–D_2O–C_6F_6 (12:4:3)	6.77d	6.57q	6.20q
3	*arabino*	C_5D_5N–C_6F_6 (4:1)	6.68q[f]	~7.3[f]	6.82q
		$CDCl_3$–C_6D_6–C_5D_5N–C_6F_6 (4:4:2:1)	6.27q	~6.98[f]	6.51q
		$CDCl_3$–C_6F_6 (4:1)	~5.95q[f]	6.89d	6.27d
4	*arabino*	$CDCl_3$–C_6F_6 (9:1)	5.15[f]	5.90q	5.43q
		C_5D_5N–C_6F_6 (4:1)	6.09q[f]	6.26q[f]	5.89q
4-d_2[e]	*arabino*	C_5D_5N–C_6F_6–D_2O (20:5:3)	6.30d	6.07q	5.88q
5	*lyxo*	CD_3COCD_3–C_6F_6 (4:1)	6.55q	5.68q	5.46q[f]
		C_5D_5N–C_6F_6 (4:1)	6.85o	6.24q	5.86q[f]
5-d_2[e]	*lyxo*	C_5D_5N–D_2O–C_6F_6 (4:1:1)	7.13d	6.15q	5.78[f]
6	*lyxo*	C_5D_5N–C_6F_6 (4:1)	6.94o	6.33q	5.98m[f]
		C_6D_6–CD_3COCD_3–C_6F_6 (11:4:1)	6.62q	5.99q	5.64q
7	*ribo*	C_5D_5N–C_6F_6 (4:1)	6.76q	6.37q	5.93q
		$CDCl_3$–Me_4Si (8:1)	6.07q[g,f]	5.89q[f]	5.48q[f]
8	*xylo*	C_5D_5N–Me_4Si (8:1)	6.49q[g]	6.29q	6.21q
		C_5D_5N–C_6F_6 (4:1)	6.45q	6.72q	6.15q
8-d_2[e]	*xylo*	C_5D_5N–D_2O–C_6F_6 (12:5:3)	6.79d	6.49q	6.11q
		$CDCl_3$–D_2O–Me_4Si (8:8:1)	5.86d[g]	6.33q	5.72q

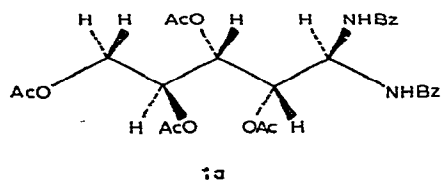
[a]First-order values (δ), in p.p.m., from internal tetramethylsilane, calculated from the shifts computed for individual peak maxima in the Fourier-transform spectra, unless indicated otherwise. [b]All solvent proportions are v/v. [c]H-5 and NH are to low field of H-5′ and NH′, respectively. [d]Signal multiplicities are indicated by d (doublet), m (multiplet), o (octet), q (quartet), s (sextet), and sp (septet). [e]*N,N′*-Dideuterated. [f]Incompletely resolved. [g]Measured manually from spectra recorded in the continuous-wave mode with field-frequency stabilization on the proton signal of internal tetramethylsilane.

H-4	*H-5*	*[c]H-5'[r]*	*NH*	*[c]NH'[r]*	*Ac*	*Ar*
5.48sp	4.41q	4.13q	10.12d	9.61d	2.06, 2.02 1.97, 1.88	8.07m 7.33m
5.59m[f]	4.49q	4.25q	—	—	2.35, 2.20 2.14, 2.05	8.14m 7.50m
5.62sp	4.78q	4.30q	10.17d	9.60d	2.07, 2.04 1.97	8.06m 7.36m
5.73m[f]	4.85q	4.44q	—	—	2.33, 2.15(×2)	8.11m 7.48m
6.21sp	5.08q	4.70q	10.65d	9.64d	—	8.00m 7.30m
5.96sp	4.84q	4.48q	10.02d	8.74d	—	7.99m, 7.67m 7.20m
5.91m[f]	4.84q	4.53q	~8.0——7.3[f]		—	8.0–7.3m
5.13[f]	4.25q	4.05q	7.06d	6.91d	2.17, 2.09, 2.07(×2), 1.99, 1.94	—
5.42sp	4.42q	4.15q	9.49d	9.31d	2.01(×3), 1.98 1.94(×2)	—
5.45m[f]	4.46q	4.21q	—	—	2.22, 2.20, 2.12, 2.10(×2), 2.08	—
5.43m[f]	4.34q	3.91q	8.25d	8.06d	2.16, 2.08 2.05, 1.94	7.84m 7.49m
5.76m[f]	4.56q	4.15q	9.58d	9.16d	2.03, 2.01 2.00, 1.91	8.00m 7.32m
~5.7[f]	4.54q	4.12q	—	—	2.24, 2.20 2.03, 1.95	8.08m 7.34m
~5.9m[f]	4.76q	4.52q	9.62d	9.23d	2.07, 2.05(×2)	8.04m 7.34m
5.80sp	4.56q	4.34q	—[f]	—[f]	1.98, 1.96 1.86	7.97m 7.20m
5.72s	4.61q	4.32q	9.70d	9.27d	2.12, 2.01 1.95, 1.91	8.06m 7.37m
5.36s[f]	4.39q	4.12q	8.11d	—[f]	2.11, 2.07 1.99(×2)	7.79m 7.39m
5.76sp	4.60q	4.23q	10.18d	9.61d	2.14, 2.01 2.08, 1.90	8.11m 7.38m
5.71o	4.58q	4.22q	10.08d	9.45d	2.04, 2.01(×2) 1.86	8.05m 7.33m
5.81o	4.68q	4.33q	—	—	2.28, 2.20 2.18, 2.03	8.12m 7.46m
5.27sp	4.41q	4.03q	—	—	2.05, 2.02(×2) 1.87	7.79m 7.33m

pyridine-d_5, than for solutions in chloroform-*d* (see Table I), thus indicating that hydrogen bonding between the NH and NH′ protons and the nitrogen atom of the pyridine-d_5 molecule is favored more than that between these protons and the π-electron cloud[25] of the pyridine-d_5 ring. The downfield shift of the anisochronous NH and NH′ signals in pyridine-d_5 solutions was a useful means for separation of these signals from those of the benzoyl protons.

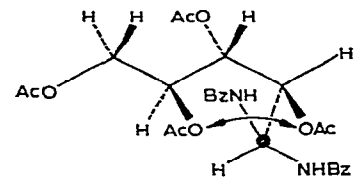
arabino *Derivatives* **1–4**. — The spectrum (see Fig. 1*a*) of a solution of the bis-(benzamido) derivative **1** in 4:1 (v/v) pyridine-d_5–hexafluorobenzene is typical of this series of derivatives. On deuterium exchange of the NH and NH- protons of **1** to give **1**-d_2, the quartet due to H-1 of **1** (see Fig. 1*a*) simplifies to a doublet in the spectrum of **1**-d_2, and simultaneously changes place with the H-2 quartet (see Fig. 1*b*). This interesting, chemical-shift effect caused by addition of deuterium oxide to solutions in pyridine-d_5–hexafluorobenzene is common to derivatives **1**, **2**, and **4**. [Compound **3** does not fall into this general pattern, because of the strong, deshielding effect (on H-2) of the benzoyloxy substituent at C-2. For solutions in a solvent mixture containing pyridine-d_5, this effect is sufficient to cause the H-2 signal to move downfield into the spectral region of the *meta* and *para* protons of the phenyl ring (see Table I)].

Solutions of derivatives **1–4** and their *N*,*N*′-dideuterated analogs in a variety of solvents display values of coupling constants (see Table II) in the ranges $J_{1,2}$ 7.9–10.4, $J_{2,3}$ ~0.6–2.6, $J_{3,4}$ 7.9–9.2, $J_{4,5}$ 2.4–3.4, $J_{4,5'}$ 4.9–6.1, $J_{5,5'}$ 12.2–12.5, $J_{1,NH}$ 7.3–8.5, and $J_{1,NH'}$ 6.7–8.5 Hz. On the basis that values of vicinal, proton–proton, coupling constants of <4 Hz correspond to protons having the *gauche* orientation, and that values of >7 Hz correspond principally to the *trans* orientation, the values for the *arabino* derivatives **1–4** are consistent with either the zigzag conformation or a sickle conformer in which atom 1 is exoplanar (for example, **1a** and **1b**, respectively), but not with other sickle conformations, each of which contains a 1,3-interaction, either between two oxygen atoms, or between an oxygen atom and a carbon atom. Conformer **1b** also contains a 1,3-interaction, between O-2 and O-4, and, therefore, this



1a
L-ARABINO

$J_{4,5}$ 3.1 $J_{3,4}$ 9.2 $J_{2,3}$ 1.8 $J_{1,2}$ 9.8
$J_{4,5'}$ 5.5 (Hz)

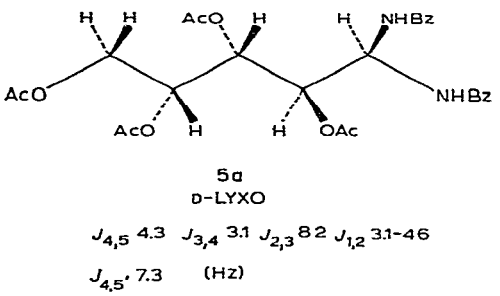


1b
L-ARABINO

conformer can, presumably, be regarded as unimportant. For compounds **1–4**, the intermediate magnitudes of the values of $J_{4,5'}$ indicate either that there is some distortion of the bonds about C-4 and C-5 away from a fully staggered arrangement,

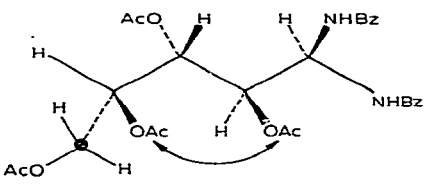
or that there is a contribution from one or more of the other two rotamers in which H-4 and H-5′ have the *gauche* orientation.

lyxo *Derivatives* **5** *and* **6**. — The D-*lyxo* derivatives **5** and **6** showed the coupling constants $J_{1,2}$ 3.1–4.6, $J_{2,3}$ 8.2–9.2, $J_{3,4}$ 1.8–3.1, $J_{4,5}$ 4.0–4.3, $J_{4,5'}$ 7.3, $J_{5,5'}$ 11.6–11.7, $J_{1,NH}$ 6.7–7.3, and $J_{1,NH'}$ 8.5–9.8 Hz (see Table II); these are consistent with either the zigzag conformation **5a** or the sickle conformation **5b**, but not with the three alternative sickle conformations in which either C-1 or C-5 is exoplanar. Each of these four sickle conformations contains a 1,3-interaction, and, presumably, they are disfavored in comparison with the zigzag conformation **5a**, which does not contain this interaction. As $J_{4,5'}$ is large, the contributions of rotamers about the C-4–C-5 bond (other than that present in the zigzag conformation **5a**) appear to be small.



5a
D-LYXO

$J_{4,5}$ 4.3 $J_{3,4}$ 3.1 $J_{2,3}$ 8.2 $J_{1,2}$ 3.1-4.6
$J_{4,5'}$ 7.3 (Hz)



5b
D-LYXO

The H-1 signals of **5** and **6** in solution in pyridine-d_5–hexafluorobenzene are ~0.6 p.p.m. to low field of their H-2 signals (see, for example, the spectrum of **5** in Fig. 2), in contrast to the reversal of the positions of these signals mentioned already for the *arabino* derivatives **1**, **2**, and **4** (see Fig. 1*a*). For derivatives having the same substituents at C-1, C-2, and C-3, this difference between the *arabino* and *lyxo* derivatives in solution in pyridine-d_5–hexafluorobenzene may be due to deshielding of H-1 of the *lyxo* derivatives by the *trans*-coplanar oxygen-atom at C-2 of the zigzag conformation (for example, **5a**), and to the fact that H-2 is *trans*-coplanar to an oxygen atom (O-3) in the *arabino* zigzag conformation (**1a**) but *trans*-coplanar to a less electronegative nitrogen atom in the *lyxo* zigzag conformation (**5a**), with the result that there is less deshielding of the H-2 nuclei of the *lyxo* derivatives[26]. However, from the results shown in Table I, it is apparent that the effects of configuration on the chemical shifts of the 1,1-bis(acylamido) derivatives are readily dominated by the influence of the solvent. For example, in pyridine-d_5–tetramethylsilane solution, the *xylo* derivative **8** displays its H-1 signal at lower field than that of H-2, but at higher field in pyridine-d_5–hexafluorobenzene solution (see Table I).

ribo *Derivative* **7**. — Compound **7** displays the coupling constants $J_{1,2}$ 7.0–7.8, $J_{2,3}$ 3.4–4.6, $J_{3,4}$ 5.3–6.1, $J_{4,5}$ 2.6–3.1, $J_{4,5'}$ 5.5–5.6, $J_{5,5'}$ 12.1–12.3, $J_{1,NH}$ 7.3–7.9, and $J_{1,NH'}$ 7.9–8.5 Hz (see Table II); these values are consistent with a preponderance of either the conformation **7a** or **7b**, but not with the zigzag conformation, or with the

TABLE II

COUPLING CONSTANTS[a] (HZ) OF ACYLATED 1,1-BIS(ACYLAMIDO)-1-DEOXYPENTITOLS

Compound	*Configuration*	*Solvent*[b]	$J_{1,2}$	$J_{2,3}$
1	*arabino*	C_5D_5N–C_6F_6 (4:1)	9.8	1.8
1-d_2[d]	*arabino*	C_5D_5N–D_2O–C_6F_6 (12:5:3)	9.4	2.1
2	*arabino*	C_5D_5N–C_6F_6 (4:1)	9.5	1.7
2-d_2[d]	*arabino*	C_5D_5N–D_2O–C_6F_6 (12:4:3)	9.2	1.8
3	*arabino*	C_5D_5N–C_6F_6 (4:1)	~8.5	1.5
		$CDCl_3$–C_6D_6–C_5D_5N–C_6F_6 (4:4:2:1)	9.8	1.5
		$CDCl_3$–C_6F_6 (4:1)	10.4	~0.6
4	*arabino*	$CDCl_3$–C_6F_6 (9:1)	9.2	1.8
		C_5D_5N–C_6F_6 (4:1)	7.9	2.4
4-d_2[d]	*arabino*	C_5D_5N–C_6F_6–D_2O (20:5:3)	8.3	2.6
5	*lyxo*	CD_3COCD_3–C_6F_6 (4:1)	3.1	8.5
		C_5D_5N–C_6F_6 (4:1)	4.6	8.2
5-d_2[d]	*lyxo*	C_5D_5N–D_2O–C_6F_6 (4:1:1)	3.7	9.2
6	*lyxo*	C_5D_5N–C_6F_6 (4:1)	4.3	8.5
		C_6D_6–CD_3COCD_3–C_6F_6 (11:4:1)	3.7	8.7
7	*ribo*	C_5D_5N–C_6F_6 (4:1)	7.0	4.6
		$CDCl_3$–Me_4Si (8:1)	7.8[f]	3.4
8	*xylo*	C_5D_5N–Me_4Si (8:1)	8.9[f]	2.2
		C_5D_5N–C_6F_6 (4:1)	9.2	2.4
8-d_2[d]	*xylo*	C_5D_5N–D_2O–C_6F_6 (12:5:3)	8.3	2.9
		$CDCl_3$–D_2O–Me_4Si (8:8:1)	8.3[f]	1.7

[a]First-order values calculated from the frequencies computed for individual peak maxima in the Fourier-transform spectra, unless indicated otherwise. [b]All solvent proportions are v/v. [c]H-5 and NH are to low field of H-5′ and NH′, respectively. [d]*N*,*N*′-Dideuterated. [e]Incompletely resolved. [f]Measured manually from spectra recorded in the continuous-wave mode with field-frequency stabilization on the proton signal of internal tetramethylsilane.

$J_{3,4}$	$J_{4,5}$	$^{c}J_{4,5'}$	$J_{5,5'}$	$J_{1,NH}$	$^{c}J_{1,NH'}$
9.2	3.1	5.5	12.2	7.9	7.3
8.9	2.7	6.1	12.4	—	—
9.2	2.4	5.8	12.4	8.5	7.3
9.2	2.4	5.2	12.4	—	—
8.2	3.1	5.2	12.4	7.3	8.5
8.2	3.4	5.2	12.5	7.3	8.5
7.9	3.1	4.9	12.5	—[e]	—[e]
9.2	3.1	4.9	12.5	7.9	7.9
8.5	3.1	5.8	12.4	7.9	6.7
8.2	3.1	5.5	12.2	—	—
~1.8	4.3	7.3	11.6	6.7	9.8
3.1	4.3	7.3	11.6	7.3	9.2
~1.8	4.0	7.3	11.7	—	—
—[e]	4.3	7.3	11.6	7.3	8.5
2.1	4.3	7.3	11.6	—[e]	—[e]
6.1	3.1	5.5	12.1	7.3	8.5
5.3	2.6	5.6	12.3	7.9	7.9
7.3	3.1	6.1	12.4	7.5	7.8
7.9	3.1	5.8	12.4	7.9	7.9
7.0	3.4	6.1	12.4	—	—
9.0	2.7	5.1	12.7	—	—

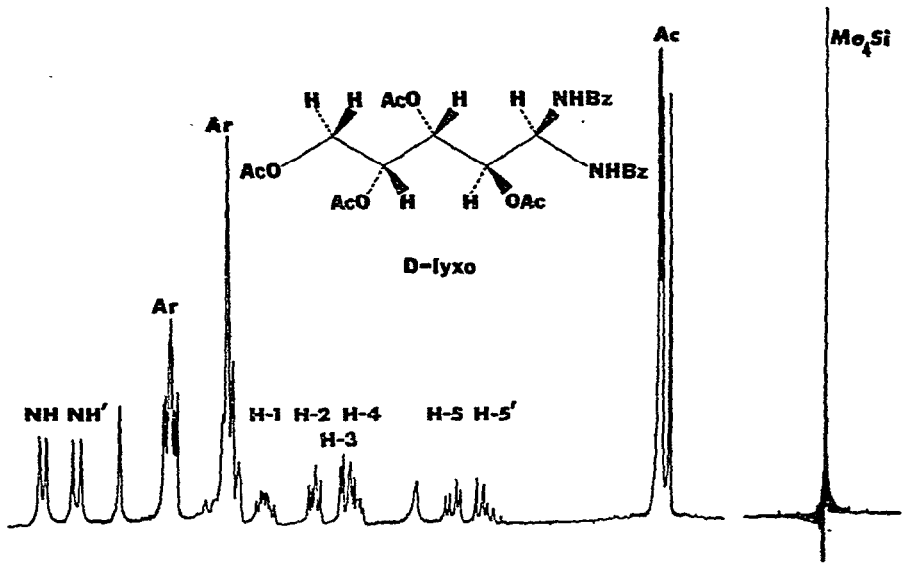
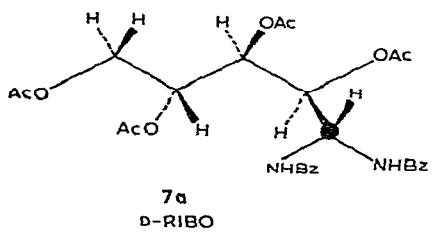


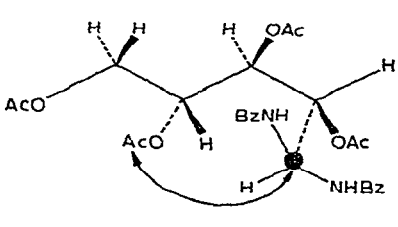
Fig. 2. Fourier-transform, p.m.r. spectrum of tetra-*O*-acetyl-1,1-bis(benzamido)-1-deoxy-D-lyxitol (5) in 4:1 (v/v) pyridine-d_5–hexafluorobenzene at 90 MHz.

alternative sickle conformations that have C-5 exoplanar and contain a 1,3-interaction. Conformation **7b** also contains a 1,3-interaction, between C-1 and O-4, and hence, conformation **7a** is favored. The diminished magnitude of $J_{3,4}$ and $J_{4,5'}$ (see Table II) suggests (*a*) contributions from rotamers in which H-3 and H-4, and H-4 and H-5', have *gauche* orientations, or (*b*) the presence of distortions of the relevant proton–proton dihedral angles away from 180°.



7a
D-RIBO

$J_{4,5}$ 3.1 $J_{3,4}$ 6.1 $J_{2,3}$ 4.6 $J_{1,2}$ 7.0
$J_{4,5'}$ 5.5 (Hz)



7b
D-RIBO

Although H-1 of **7** resonates at lower field than H-2 by 0.2–0.4 p.p.m. (see Table I and Fig. 3*a*), in the favored conformation **7a**, H-1 is not in a *trans*-coplanar relationship to an electronegative substituent, as is H-2. The position of the H-1 signal at lower field may possibly be due to the proximity of H-1 to the three atoms H-4, C-4, and O-3 in conformation **7a**.

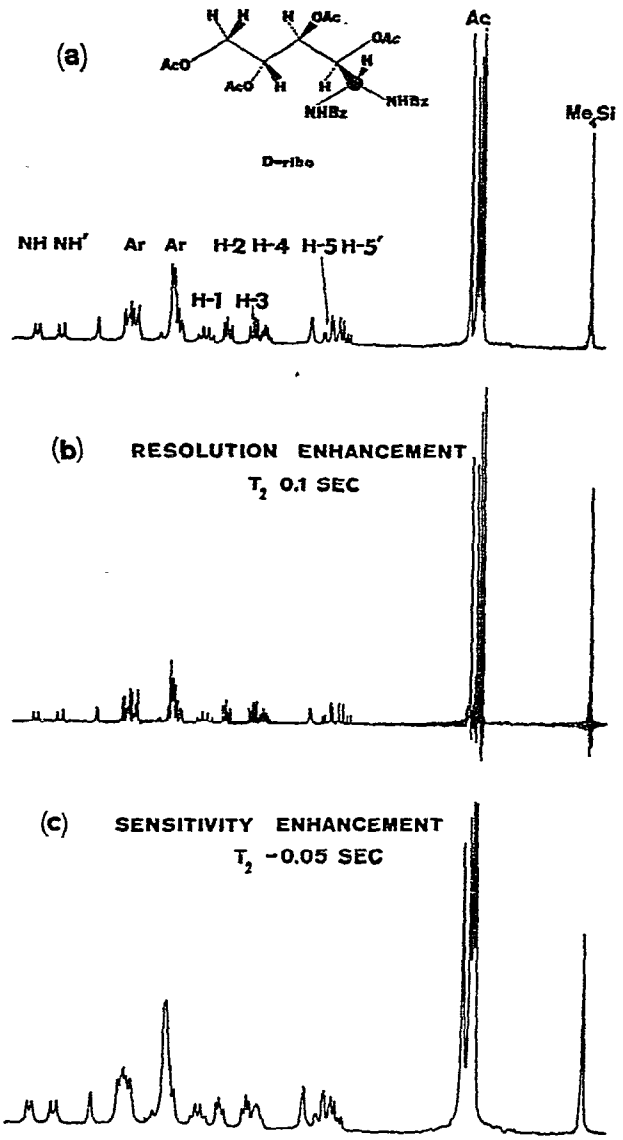


Fig. 3. Fourier-transform, p.m.r. spectra (256 scans) of tetra-*O*-acetyl-1,1-bis(benzamido)-1-deoxy-D-ribitol (7) in 4:1 (v/v) pyridine-d_5–hexafluorobenzene at 90 MHz: (*a*) direct transform of free-induction decay (f.i.d.) signal, (*b*) enhancement of resolution by exponential filtering of the f.i.d. signal by using a time-constant T_2 0.1 sec, and (*c*) enhancement of sensitivity by exponential filtering by using T_2 −0.05 sec.

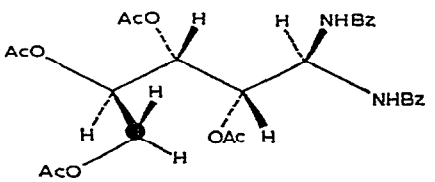
One advantage of the pulse Fourier-transform method and its associated equipment is that mathematical, convolution techniques may be applied to improve the quality of the spectra, by enhancement either of resolution or sensitivity[27,28]. Such enhancement is particularly easy to achieve, because the Fourier transform of the

frequency spectrum is already available in the form of the free-induction decay (f.i.d.) signal that is observed following the termination of the pulse. Thus, the convolution is performed by first multiplying the f.i.d. point-by-point with a suitable filtering function, and then taking the Fourier transform of the product in order to obtain the improved frequency-spectrum. The result of convolution with an increasing, exponential function is enhancement of resolution at the expense of sensitivity, so that most of the multiplets are now split to the baseline, but the signal:noise ratio of the spectrum is degraded (see Fig. 3*b*). Convolution with a decreasing, exponential function affords enhancement of sensitivity at the expense of resolution (see Fig. 3*c*).

xylo *Derivative* **8**. — Derivatives **8** and **8**-d_2 showed the coupling constants $J_{1,2}$ 8.3–9.2, $J_{2,3}$ 1.7–2.9, $J_{3,4}$ 7.0–9.0, $J_{4,5}$ 2.7–3.4, $J_{4,5'}$ 5.1–6.1, $J_{5,5'}$ 12.4–12.7, $J_{1,NH}$ 7.5–7.9, and $J_{1,NH'}$ 7.8–7.9 (see Table II); these values are consistent only with the sickle conformation **8a**, in which H-1 and H-2, H-3 and H-4, and H-4 and H-5′ have the *trans* orientation, and H-2 and H-3, and H-4 and H-5, the *gauche* orientation. Again, the diminished magnitude of $J_{4,5'}$ indicates that the rotameric state about the C-4–C-5 bond (depicted in formula **8a**) is either distorted, or is in equilibrium with one or more other rotamers in which H-4 and H-5′ have the *gauche* orientation.

$J_{4,5}$ 3.1 $J_{3,4}$ 7.9 $J_{2,3}$ 2.4 $J_{1,2}$ 9.2

$J_{4,5'}$ 5.8 (Hz)



8a
D-XYLO

In conformation **8a**, H-1 is *trans*-coplanar to H-2 (and, hence, not to an electronegative substituent), but H-2 is *trans*-coplanar to O-3 and also has a 1,3-*gauche* orientation to C-5 and its attached hydrogen atoms. These deshielding contributions evidently cause the quartet due to H-2 to appear downfield of that due to H-1 in the spectrum (see Fig. 4*a*) of **8** in pyridine-d_5–hexafluorobenzene solution. However, the addition of deuterium oxide to this solution was sufficient to reverse the order of chemical shifts for H-1 and H-2 (see Fig. 4*b*), as had also been found for the *arabino* derivatives **1**, **2**, and **4** (see, for example, Fig. 1). The presence of the H-1 signal of the *xylo* derivative **8** at higher field than that of the H-2 signal (for the solution in chloroform-*d*–deuterium oxide–tetramethylsilane) suggests that the opposite order of these shifts that was observed for solutions in pyridine-d_5–hexafluorobenzene, and the reversal on addition of deuterium oxide (see Table I) does not depend merely on the direct solvent-effect of the deuterium oxide. The effect may be due to displacement of the hexafluorobenzene from a collision complex or hydrogen-bonding site that

causes shielding of H-1 by virtue of a particular, favored orientation of the hexafluorobenzene molecule. It seems sterically feasible for adjacent fluorine atoms of a hexafluorobenzene molecule to form hydrogen bonds simultaneously with the NH and NH′ protons of **1–8**, and this interaction (which would be expected to be weak) would probably be broken down by addition of a stronger hydrogen-bonding molecule, such as deuterium oxide. However, the effects of solvent on the chemical shifts shown in Table I are complex, and at present it is difficult to provide a unified rationalization of these effects for the different configurations of the pentitol derivatives.

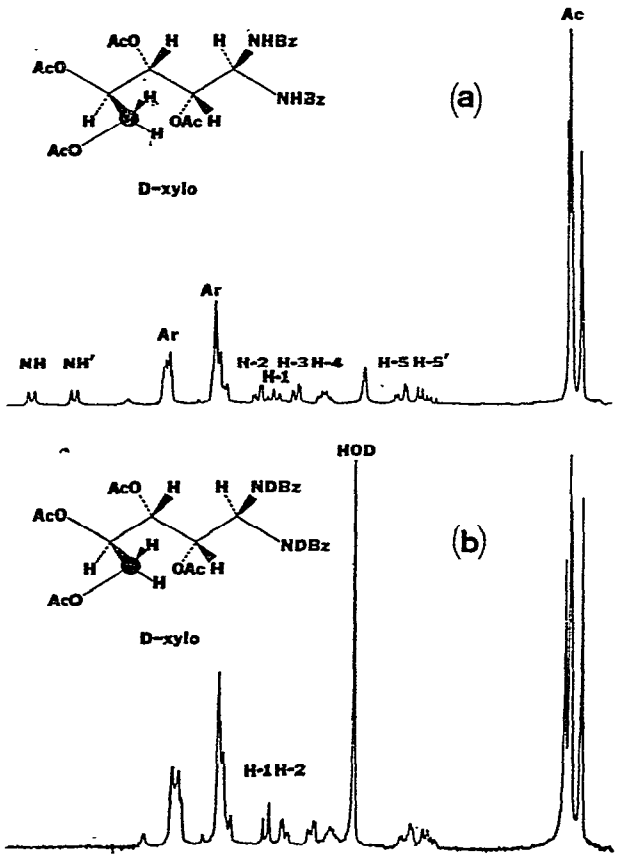


Fig. 4. Fourier-transform, p.m.r. spectra at 90 MHz: (*a*) tetra-*O*-acetyl-1,1-bis(benzamido)-1-deoxy-D-xylitol (**8**) in 4:1 (v/v) pyridine-d_5–hexafluorobenzene, and (*b*) the *N,N′*-dideuterated derivative (**8**-d_2) in 12:5:3 (v/v) pyridine-d_5–deuterium oxide–hexafluorobenzene.

The conformational results for the 1,1-bis(acylamido) derivatives **1–8** are in general agreement with those for other types of acyclic pentose derivatives[1–15]. Thus, derivatives having the *arabino* and *lyxo* configurations tend to favor the zigzag conformation (which contains no 1,3-interactions), whereas derivatives having the

ribo and *xylo* configurations adopt a sickle conformation that affords relief of the 1,3-interactions that are present in the zigzag conformers having these configurations. However, the particular sickle form adopted depends on the substituents that are present in the alditol derivative. For example, the vicinal, proton–proton, coupling constants of tetra-*O*-acetyl-D-ribose diethyl[7] and diphenyl[8] dithioacetals have been interpreted in favor of a sickle form in which C-5 is exoplanar, whereas tetra-*O*-acetyl-D-ribose dimethyl acetal[9] and tetra-*O*-acetyl-1,1-bis(benzamido)-1-deoxy-D-ribitol (7) favor conformer **7a**, in which C-1 is exoplanar. A semi-quantitative treatment of these differences in conformation that is based on additivity of 1,2-*gauche* interactions and of 1,3-interactions that could be approximated as conformational free-energies (*A*-values) of the substituents does not appear to be justified at the present time, as the methoxyl and phenylthio groups, for example, possess very similar *A*-values[29].

It may be seen that, for compounds **1–8**, the method of p.m.r. spectroscopy provides a unique, conformational solution only for the derivative that has the *xylo* configuration. For derivatives having the *arabino*, *lyxo*, and *ribo* configurations, there are alternative conformations (**1b**, **5b**, and **7b**, respectively) that are also consistent with the coupling constants. The possibility exists that the coupling constants observed might be averaged values resulting from an equilibrium between the two conformations that are consistent with these coupling constants. However, few conformational equilibria of carbohydrate derivatives have been documented thus far[14c], and only a relatively small difference in the free energies of two conformations (for example, due to the presence of a 1,3-interaction) would be sufficient to cause one of these conformations to preponderate. These limitations also apply to previous investigations on acyclic-sugar conformations, although they have not always been given sufficient emphasis. In order that a definite conformational assignment may be made, it is necessary to make the slightly speculative assertion that, because the 1,3-interaction is important in determining the relative stabilities of *some* conformers (as judged by the incompatibility of the coupling constants of some derivatives with those for the zigzag conformer), this interaction must be important in controlling the relative stabilities of all of the conformers that may be considered.

Although the pulse, Fourier-transform technique is extremely useful, and perhaps even mandatory, for recording the n.m.r. spectra of small samples, the use of a signal-averaging computer of small memory-size (4,096 words in the present work) limits the accuracy of the results. In order to obtain *complete* p.m.r. spectra of derivatives **1–8**, it was necessary to sample a frequency range of at least 960 Hz [which corresponds to the maximum chemical shift observed, namely, that of the NH proton of **3** (see Table I)]. However, the frequency ranges available in the pulse, Fourier-transform mode are restricted by the sampling rates (possibly fixed) that are available in the digitizer. A sampling rate of 2.5 kHz was used, giving a frequency range of 1.25 kHz, as at least two points per cycle are required in order to define the frequency of a sine wave. For signal averaging in the continuous-wave mode, all of the memory of the signal-averaging computer is available for storage of the frequency

spectrum. However, in the digital Fourier-transform mode, the frequency resolution available is smaller, by a factor of 0.5, than that in the continuous-wave mode, because digital, Fourier transformation of N (= 4,096) points in the time domain yields only $N/2$ (= 2,048) points in the frequency domain[27]. Hence, the resolution of the Fourier-transform, p.m.r. spectra of **1–8** was restricted to 1,250/2,048 = 0.6 Hz, and so the values of the line frequencies are quantized at multiples of 0.6 Hz.

The precision (readability) of the line frequencies measured is ±0.3 Hz if this precision is assumed to be limited only by the size of the computer memory used to store the transformed spectra. From a pessimistic point of view, the precision of chemical shifts and coupling constants, calculated as differences in the frequencies measured for two lines, is ±0.6 Hz; but the precision is likely to be better than this, because these line frequencies are not totally independent (in the sense that drifts in the frequencies of the oscillators in the spectrometer will probably cause the errors in the frequencies of each pair of lines to have the same sign; that is, the line frequencies will drift in the same direction). A precision of ±0.6 Hz is entirely adequate for most measurements of chemical shifts, because ±0.6 Hz is equivalent to only 0.007 p.p.m. at 90 MHz. However, for coupling constants, a precision of ±0.6 Hz, or even of ±0.3 Hz, is appreciably poorer than can be achieved by means of the continuous-wave method with use of a single, analog can (the use of digital signal-averaging in the continuous-wave mode tends to suffer from the same defect, albeit it is less by a factor of 0.5).

Increased accuracy of the line frequencies may be achieved by sampling (*a*) the f.i.d. signal for a longer time by use of a larger signal-averaging computer, or (*b*) a smaller frequency-range by means of a lower sampling-rate. In the latter method, the absence of an analog frequency-filter prior to the digitizer causes resonances lying outside the diminished frequency-range to be "folded back" into this range, and, in a complex spectrum, this can result in unacceptable confusion. However, the use of analog filters to restrict the frequency range digitized is somewhat inconvenient (as compared with the rapid switching of sweep widths in the continuous-wave mode) if the phase shifts produced by the filter can only be corrected relatively slowly by the computer system at hand. Analog filters also have the disadvantage of a nonlinear frequency-response.

For conformational analysis of **1–8** according to the criteria already discussed, a precision of ±0.3 Hz, or even ±0.6 Hz, for the values of the coupling constants is quite adequate, but it is less so, if quantitative analysis of the coupling constants in terms of populations of conformers[12] is to be attempted; this approach has recently[3,9] been criticized.

The coupling constants of the 1,1-bis(acylamido) derivatives (see Table II) are not greatly affected by changing the solvent, and it is concluded that, despite the obvious involvement of pyridine-d_5 in hydrogen bonding with the NH and NH′ protons, the conformational populations of these derivatives show little dependence on the solvent present.

EXPERIMENTAL

General. — Derivatives **1–8** were prepared as previously described[19–22]. Fourier-transform, p.m.r. spectra were recorded at 90 MHz and 31° with a Bruker Scientific n.m.r. spectrometer* model HFX-11 that was equipped with a pulse amplifier (model B-SV-2P) and internal, heteronuclear, field frequency stabilization[17] on the ^{19}F signal of hexafluorobenzene at 84.7 MHz.

Solutions of the pentitol derivatives (9–116 mg) in a solvent mixture (0.35–1.2 ml) that contained hexafluorobenzene (see Tables I and II) were excited in the crossed-coil mode with 16 to 16,384 pulses of 40-μsec width.

The free-induction decay (f.i.d.) signal was averaged in 2,048 channels of a Fabritek instrument computer, model 1074, having a nine-bit digitizer. The averaged f.i.d. signal plus 2,048 zero data-points (zero-filling[23,30]) was then transformed (100 sec) in a Digital Equipment Corporation computer, model PDP8E (equipped with wired multiplication and division), that was also programmed to type the frequencies (Hz from the pulse frequency) and chemical shifts (p.p.m. from internal tetramethylsilane) of peak maxima within the spectral width of 1,250 Hz defined by the f.i.d. sampling rate of 2.5 kHz.

Enhancement of sensitivity or resolution. — Enhancement of signal:noise ratio additional to that provided by the pulse, Fourier-transform method was obtained by computerized, digital filtering of the f.i.d. signal before transformation. For compound **7**, this was achieved by point-by-point multiplication of its f.i.d. signal $[A(n\delta t)]$ by the decreasing function, $\exp(-n\delta t/T_2)$, where δt was the time interval between datum points, n was the data-stepping index which took values from 0 to 2,047, and the time-constant, T_2 was adjusted to 0.05 sec by trial-and-error application of the exponential filtering. Conversely, enhancement of resolution at the expense of sensitivity was achieved, for **7**, by multiplication of its f.i.d. signal by the increasing function, $\exp(n\delta t/T_2)$, by using $T_2 = 0.1$ sec.

Spectral assignments. — The addition of deuterium oxide (0.12–0.16 ml) and pyridine-d_5 (0.04 ml, if not already present in the solvent mixture used) to the solutions of the pentitol derivatives caused the disappearance of two doublets at low field; these, therefore, were assigned to the (nonequivalent) NH and NH′. The use of smaller volumes of deuterium oxide resulted in incomplete exchange of these protons. Dilution of solutions in pyridine-d_5–hexafluorobenzene with deuterium oxide sometimes caused the separation of an underlayer of hexafluorobenzene; this was usually removed from the n.m.r. sample tube, as the under-layer generated a fluorine signal having a chemical shift different from that of the hexafluorobenzene in the pyridine-d_5–deuterium oxide layer, on which the spectrometer was stabilized. Once the assignment of the H-1 signal as the multiplet that undergoes simplification on exchange of the NH protons had been made, the assignments of H-2–H-5′ were

*Mention of commercial instrumentation in this article does not imply recommendation or endorsement by the National Bureau of Standards.

obvious, and confirmation thereof by double-resonance techniques was unnecessary. The spectra were analyzed by first-order methods, and the coupling constants were obtained from the differences of the frequencies of peak maxima listed in the automatic printout. In order to confirm the accuracy of the printout, a limited number of spectra were recorded in the continuous-wave mode at 90 MHz.

ACKNOWLEDGMENTS

Thanks are due Dr. R. Schaffer for his support, and Drs. R. B. Johannesen and C. H. Lochmuller for computer programs.

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