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Conformational analysis of 3-deoxy-3-nitroheptoseptanosides by molecular mechanics (MM2) and theoretical $^3J_{HH}$ calculation

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Abstract

Molecular mechanics (MM2) calculations were performed on conformers of a series of stereoisomeric methyl 5,7-*O*-benzylidene-3-deoxy-3-nitro-α-D-heptoseptanosides. The lowest-energy conformations are twist forms derived from the regular $^5C_{1,2}$ and $^OC_{3,4}$ chairs. The data obtained for the steric energies and the theoretically calculated $^3J_{H,H}$ coupling constants of the compounds are consistent with experimental observations on the synthetic products.

Keywords: 3-Deoxy-3-nitroheptoseptanosides; Molecular mechanics (MM2); Conformational analysis

1. Introduction

Recently the nitromethane cyclization of the dialdehyde [1] obtained by periodate oxidation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside was the subject of two independent investigations, performed and published almost simultaneously [2,3]. When the dialdehyde was treated for 32 h with nitromethane in acetonitrile solution at 45°C, under catalysis by potassium fluoride in the presence of a crown ether, methyl 5,7-*O*-benzylidene-3-deoxy-3-nitro-D-*glycero*-α-D-*ido*-heptoseptanoside (**1**) was obtained as the main product, in 68% yield [2]. Its configuration and conformation were deduced from ^{1}H NMR data including observed nOe differences. Molecular mechanics calculations using an implementation of the Allinger algorithm [4] were performed for the $^5C_{1,2}$ septanose chair (Fig. 1), which according to molecular models seemed the most probable conformation, and yielded a lowest-energy geometry [1] for which the generalized

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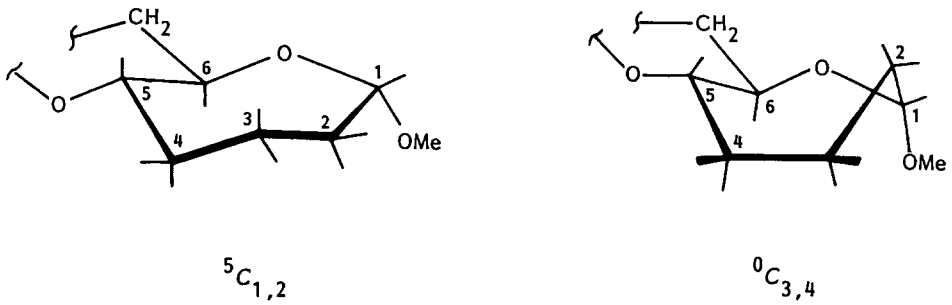


$^{5}C_{1,2}$ $^{O}C_{3,4}$

Fig. 1. Heptoseptanoside ring skeletons in basic flexible conformations from which the actual, lowest-energy twist forms are derived by pseudorotation.

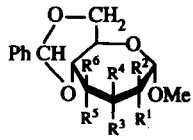
Karplus equation [5] predicted vicinal coupling constants in good agreement with those measured. On the other hand, cyclization of the dialdehyde promoted by sodium methoxide in methanol produced not only **1** but also its D-*glycero*-α-D-*gulo* (**2**), D-*glycero*-α-D-*altro* (**3**), D-*glycero*-α-D-*talo* (**4**), D-*glycero*-α-D-*galacto* (**5**), and D-*glycero*-α-D-*manno* (**6**) stereoisomers (some of them as a result of secondary epimerization) [3]. The configurations of all products were firmly established by chemical transformations into known sugar derivatives, as well as by ^{1}H NMR spectroscopy. Analysis of the $^{3}J_{H,H}$ values in conjunction with Dreiding models led to the suggestion [3] of certain twist forms as possible conformations, namely the form generated from the regular $^{5}C_{1,2}$ chair by a downward displacement of C-2 for **1**, **2**, and **3**, and forms derived from the regular $^{O}C_{3,4}$ chair (Fig. 1) by an upward displacement of C-3 (for **4** and **5**) or of C-4 (for **6**). Such twist chairs adjacent to regular chairs on the pseudorotational itinerary, herein labelled $^{5}C_{1,2}(T_2)$, $^{O}C_{3,4}(^{3}T)$, and $^{O}C_{3,4}(^{4}T)$, respectively, offered themselves for consideration in view of the general conformational behavior of cycloheptane [6] and the constraints imposed upon the seven-membered ring system by the 5,6-*trans* fusion of a six-membered 1,3-dioxane ring consequent on the benzylidene acetal structure.

We have now extended molecular mechanics calculations to **2**–**6**, in order to buttress or modify the conformational proposals made earlier. Included in the study were also the two remaining, theoretically possible stereoisomers of this series, namely, the D-*glycero*-α-D-*allo* (**7**) and D-*glycero*-α-D-*gluco* (**8**) compounds, which did not appear to be formed (or were not detected) in the experimental work cited and are as yet unknown.

2. Methods and calculations

The Burkert and Allinger [7] method for molecular mechanics calculations was used by means of the program modified by Jaime and Osawa [8], which performs up to ten

[1] Designated as $^{O,3}C_{6}$ in ref. [2]; it is actually a twist form adjacent to the regular $^{5}C_{1,2}$ septanose chair on the pseudorotational itinerary, formed by a downward movement of C-2.



	Configuration	R^1	R^2	R^3	R^4	R^5	R^6
1	D-*glycero*-α-D-*ido*	H	OH	NO_2	H	H	OH
2	D-*glycero*-α-D-*gulo*	OH	H	NO_2	H	H	OH
3	D-*glycero*-α-D-*altro*	H	OH	NO_2	H	OH	H
4	D-*glycero*-α-D-*talo*	H	OH	H	NO_2	H	OH
5	D-*glycero*-α-D-*galacto*	OH	H	H	NO_2	H	OH
6	D-*glycero*-α-D-*manno*	H	OH	H	NO_2	OH	H
7	D-*glycero*-α-D-*allo*	OH	H	NO_2	H	OH	H
8	D-*glycero*-α-D-*gluco*	OH	H	H	NO_2	OH	H

bond rotations twice every 120°, so that the three staggered rotamers can be minimized. For each of the structures **1–8** the chair forms $^5C_{1,2}$ and $^OC_{3,4}$ of the septanoside ring were modeled. The input data were developed by use of the method described previously [9]. The conformations were optimized for lowest energy, and for each of them was executed conformational analysis of the rotameric orientations of the OH-groups at C-2 and C-4 and the NO_2-group at C-3, using the NTREE option of the MM2 program as modified by Jaime and Osawa [8]. The parameters for the NO_2 group were those used earlier [2] for calculating **1**. The glycosidic methoxyl group was assumed as fixed in the rotameric orientation demanded by the exo-anomeric effect [9,10]. The calculations were performed for room temperature (25°C). A collection of conformers of minimum energies and their corresponding Cartesian coordinates were obtained, and these conformations were then refined with respect to their geometries and energies by means of the MM2(91) program. In this program the nitro group was modeled in the standard way using one type 46 nitrogen and two type 7 oxygen atoms. From the new sets of optimized conformations so obtained the average proton–proton coupling constants and the relative conformer populations were calculated by the 3JHH2 program (QCPE program number 591), which is set up with the use of an extended multiparametric Karplus equation [11], mixing the minimum-energy Cartesian coordinates.

3. Results and discussion

Computer-generated representations of the lowest-energy conformations for **1–8** that resulted from the calculations are depicted in Fig. 2, and Table 1 shows the dihedral angles of the septanoside C–C and C–O ring bonds, which define the molecular shapes. Table 2 gives the steric energies and population percentages of these minimum-energy

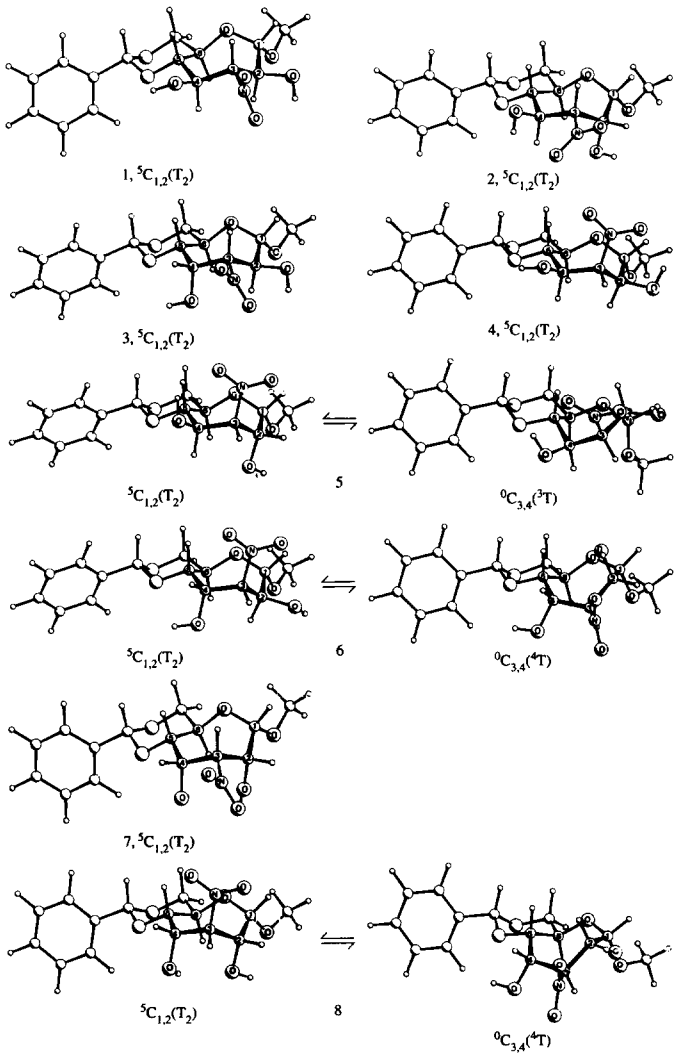


Fig. 2. Computer-generated representations of the preferred conformations of **1–8**.

conformers. In Table 3 are listed the H–C–C–H dihedral angles ($\Phi_{H,H}$) and theoretical coupling constants ($^3J_{H,H}$) for the above, most stable conformers (identified by their population percentages; compare Table 2) and, additionally for each, the same sets of data for the most important rotameric variants, together with their relative energies and populations. The variants constitute forms having essentially the same geometry of the carbon skeleton but differ in rotameric orientations of their nitro and hydroxy groups. A number of further rotamers (higher in energy) were computed for each stereoisomer but omitted from the table; jointly they account for the difference to 100% in population. For the listed rotamers and for those of the unlisted ones which contribute at least 1%,

Table 1
Calculated dihedral angles (°) of ring bonds [a] in the lowest-energy conformers of **1–8** (shown in Fig. 2)

Compound	Conformer	$\Phi_{1,2}$	$\Phi_{2,3}$	$\Phi_{3,4}$	$\Phi_{4,5}$	$\Phi_{5,6}$	$\Phi_{6,O}$	$\Phi_{O,1}$
1	$^5C_{1,2}(T_2)$	−35.9	84.2	−70.4	55.1	−74.0	97.7	−48.4
2	$^5C_{1,2}(T_2)$	−31.6	79.8	−67.2	51.5	−71.3	97.4	−50.8
3	$^5C_{1,2}(T_2)$	−34.7	80.2	−64.6	50.7	−73.9	99.4	−48.7
4	$^5C_{1,2}(T_2)$	−30.8	79.1	−69.1	55.5	−73.4	99.3	−52.7
5	$^OC_{3,4}(^3T)$	86.4	−39.2	−36.4	85.1	−74.0	60.1	−74.8
	$^5C_{1,2}(T_2)$	−30.8	77.5	−64.9	50.6	−71.6	99.2	−52.1
6	$^OC_{3,4}(^4T)$	66.9	−78.9	38.6	32.4	−84.6	81.3	−60.4
	$^5C_{1,2}(T_2)$	−40.5	82.7	−62.4	49.4	−73.2	96.8	−44.6
7	$^5C_{1,2}(T_2)$	−35.3	81.0	−62.7	46.6	−70.3	98.3	−49.3
8	$^5C_{1,2}(T_2)$	−33.3	78.6	−61.3	46.3	−69.8	98.7	−50.7
	$^OC_{3,4}(^4T)$	73.2	−82.5	34.9	37.9	−86.3	78.2	−60.7
	$^OC_{3,4}(^3T)$	86.5	−51.4	−17.6	71.6	−75.9	64.7	−73.9

[a] For example, $\Phi_{1,2}$ is the dihedral angle for the C-1.2 bond, defined by the ring atom sequence O–C-1–C-2–C-3.

the deviations in skeletal dihedral angles from those of the main conformer, caused by functional-group rotation, generally amount to less than 4° (typically, 0.5°–1.5°). The weighted averages of the $^3J_{H,H}$ values of all rotamers (including the minor, unlisted ones just referred to) are highlighted in Table 3 by italics, and juxtaposed to the experimentally observed [3] couplings.

It is seen from Table 3 that good agreement between calculation and observation exists for the **1**, **2**, and **3** isomers. Inspection of Fig. 2 and evaluation of the ring-bond

Table 2
Steric energies and populations of conformers [a] of **1–8** as obtained by molecular mechanics calculations

Compound	Conformer	E (kcal/mol)	Population (%)
1	$^5C_{1,2}(T_2)$	32.548	96.29 (99.9995)
	$^OC_{3,4}(^3T)$	39.811	0.0004
2	$^5C_{1,2}(T_2)$	33.303	32.206 (99.903)
	$^OC_{3,4}(^3T)$	36.740	0.097
3	$^5C_{1,2}(T_2)$	32.463	57.619 (99.9999)
4	$^5C_{1,2}(T_2)$	35.158	55.406 (99.692)
	$^OC_{3,4}(^3T)$	38.232	0.308
5	$^5C_{1,2}(T_2)$	34.663	42.051 (47.650)
	$^OC_{3,4}(^3T)$	34.672	42.768 (46.438)
	$^OC_{3,4}(^4T)$	35.834	5.912 (5.912)
6	$^5C_{1,2}(T_2)$	36.311	13.535 (53.838)
	$^OC_{3,4}(^4T)$	35.980	23.492 (46.162)
7	$^5C_{1,2}(T_2)$	33.377	54.812 (99.9785)
	$^OC_{3,4}(^3T)$	38.021	0.0215
8	$^5C_{1,2}(T_2)$	36.017	25.383 (58.637)
	$^OC_{3,4}(^4T)$	36.223	17.923 (39.927)
	$^OC_{3,4}(^3T)$	37.812	1.224 (1.436)

[a] The data refer to the minimum-energy rotamer of each conformer listed. The Population column additionally shows (in parentheses) the total contribution from all rotamers of the conformer.

Table 3
Proton–proton dihedral angles (Φ) and coupling constants J for **1–8**

Compound	Conformer	Rotameric form [a] Population (%)	E_{rel} [c]	Φ values (°) and J values [b]													
				$\Phi_{1,2}$	$J_{1,2}$	$\Phi_{2,3}$	$J_{2,3}$	$\Phi_{3,4}$	$J_{3,4}$	$\Phi_{4,5}$	$J_{4,5}$	$\Phi_{5,6}$	$J_{5,6}$	$\Phi_{6eq,7}$	$J_{6eq,7}$	$\Phi_{6ax,7}$	$J_{6ax,7}$
1	$^5C_{1,2}(T_2)$	96.3	0.00	−152.0	6.39	−163.0	10.56	175.1	11.70	168.6	9.03	171.7	9.09	−49.4	6.12	−169.5	8.74
		2.4	2.19	−8.5	7.15	−158.1	9.77	175.2	11.71	165.5	8.74	73.2	9.06	49.7	6.16	−169.7	8.82
		1.1	2.63	−8.3	7.18	−162.6	10.55	178.1	11.90	167.3	8.97	70.9	8.96	48.3	6.21	−168.3	8.68
					6.42		*10.54*		*11.70*		*9.02*		*9.08*		*6.12*		*8.74*
					(6.5)		(10.2)		(10.2)		(8.1)		(10.0)		(5.8)		(10.0)
2	$^5C_{1,2}(T_2)$	32.2	0.00	−35.6	3.93	78.7	0.48	178.4	12.04	164.2	8.57	174.3	9.18	−50.0	6.16	−169.9	8.86
		27.2	0.10	−36.0	3.89	78.65	0.49	178.6	12.05	164.3	8.58	174.0	9.17	−49.7	6.20	−169.6	8.85
		19.0	0.31	−35.7	3.92	78.7	0.48	178.4	12.04	164.4	8.59	174.2	9.18	−49.8	6.19	−169.7	8.86
		5.3	1.07	−36.3	3.77	77.3	0.58	178.9	12.05	166.4	8.86	171.4	9.03	−48.2	6.26	−168.1	8.72
		4.8	1.13	−36.5	3.74	77.3	0.58	179.1	12.06	166.3	8.84	171.5	9.03	−48.2	6.26	−168.2	8.73
		4.5	1.16	−36.2	3.77	77.3	0.58	178.9	12.06	166.2	8.83	171.7	9.05	−48.5	6.24	−168.5	8.73
		4.2	1.20	−36.2	3.78	77.4	0.58	178.9	12.06	166.1	8.82	171.8	9.05	−48.6	6.23	−168.6	8.74
					3.88		*0.51*		*12.05*		*8.63*		*9.15*		*6.20*		*8.83*
					(4.2)		(0)		(10.5)		(8.3)		(9.8)		(5.6)		(10.0)
3	$^5C_{1,2}(T_2)$	57.6	0.00	−150.2	6.14	167.5	11.42	−65.4	0.44	51.3	3.25	171.2	9.24	−48.3	6.22	−168.3	8.71
		42.1	0.19	−149.8	6.09	167.5	10.41	−65.5	0.43	51.0	3.27	171.8	9.28	−48.9	6.18	−168.9	8.73
		0.2	3.31	−155.4	6.94	162.3	10.69	−67.4	0.49	52.8	3.04	169.7	9.13	−46.5	6.35	−166.2	8.58
					6.12		*11.41*		*0.43*		*3.26*		*9.26*		*6.21*		*8.72*
					(5.7)		(10.5)		(1.2)		(3.0)		(10.0)		(6.0)		(10.0)
4	$^5C_{1,2}(T_2)$	55.4	0.00	−148.7	6.02	70.4	3.13	−63.8	4.12	170.5	9.40	172.7	9.19	−49.1	6.12	−169.1	8.72
		33.0	0.31	−149.9	6.17	71.0	3.02	−62.9	4.30	69.0	9.23	173.5	9.21	−50.0	6.07	−170.1	8.76
		7.4	1.19	−158.4	7.30	76.0	2.40	−57.6	5.01	64.2	8.56	174.8	9.25	−50.0	6.14	−170.0	8.83
					6.22		3.05		*4.33*		*9.27*		*9.20*		*6.11*		*8.74*
					(5.9)		(1.8)		(4.5)		(7.5)		(10.7)		(5.5)		(10.0)

5	$^{O}C_{3,4}(^{3}T)$	42.8	0.00	77.4	2.04	−155.7	10.40	−34.8	7.99	−162.8	9.78	174.2	9.17	−50.5	6.35	−170.5	9.15
		1.9	1.85	77.7	2.10	−158.7	10.85	−31.7	8.46	−167.7	10.15	175.8	9.14	−51.8	6.28	−171.8	9.23
		1.8	1.88	77.6	2.10	−158.6	10.85	−31.6	8.48	−168.1	10.16	176.1	9.14	−52.2	6.25	−172.2	9.25
	$^{O}C_{3,4}(^{4}T)$	5.9	1.17	66.1	2.37	169.9	11.69	31.8	5.02	154.2	6.97	164.7	8.85	−44.1	6.62	−163.4	8.52
	$^{5}C_{1,2}(T_2)$	42.1	0.01	−35.0	3.83	−44.3	4.52	−58.8	4.76	165.4	8.72	174.7	9.28	−49.7	6.19	−169.7	8.85
		5.6	1.20	−35.7	3.78	−45.1	4.35	−60.6	4.56	167.2	9.08	175.0	9.24	−49.9	6.16	−170.0	8.84
					2.91		*7.68*		*6.28*		*9.14*		*9.20*		*6.29*		*8.97*
					(2.0)		(9.0)		(6.5)		(9.0)		(9.0)		(d)		(d)
6	$^{O}C_{3,4}(^{4}T)$	23.5	0.00	−55.0	3.64	−75.4	1.02	153.7	10.02	35.7	4.95	162.4	8.78	−42.1	6.77	−161.4	8.30
		22.7	0.02	−54.7	3.66	−75.4	1.02	153.6	10.01	35.6	4.96	162.8	8.82	−42.6	6.74	−161.9	8.31
	$^{5}C_{1,2}(T_2)$	13.5	0.33	−56.4	7.14	74.5	2.52	56.8	2.84	50.9	3.12	173.6	9.34	−49.2	6.20	−169.3	8.68
		12.1	0.39	−156.6	7.17	74.4	2.53	56.9	2.83	51.3	3.09	173.2	9.32	−48.8	6.24	−168.8	8.65
		11.75	0.41	−156.4	7.13	74.5	2.52	56.8	2.84	51.0	3.12	173.6	9.34	−49.2	6.20	−169.3	8.68
		10.7	0.47	−156.5	7.14	74.7	2.50	56.9	2.83	50.5	3.16	174.0	9.35	−49.6	6.18	−169.7	8.83
		5.8	0.83	−157.1	7.21	74.7	2.48	57.2	2.80	50.4	3.17	173.9	9.37	−49.5	6.19	−169.6	8.80
					5.54		*1.83*		*6.15*		*3.97*		*9.09*		*6.46*		*8.60*
					(5.9)		(1.8)		(6.2)		(3.5)		(9.6)		(5.8)		(9.7)
7	$^{5}C_{1,2}(T_2)$	54.8	0.00	−38.5	3.61	77.7	0.85	−62.3	0.93	46.2	3.81	175.4	9.42	−49.7	6.30	−169.8	8.96
		29.8	0.36	−35.6	3.92	74.3	0.98	−61.7	1.00	48.6	3.60	172.6	9.32	−48.5	6.32	−168.5	8.82
		13.4	0.83	−21.8	5.38	71.5	0.78	−71.4	0.65	57.7	2.60	172.6	9.37	−49.3	6.21	−169.3	8.83
		1.8	2.01	−33.0	4.19	76.8	0.85	−65.9	0.97	51.7	3.19	171.0	9.23	−47.8	6.31	−167.6	8.72
					3.95		*0.88*		*0.92*		*3.57*		*9.38*		*6.29*		*8.90*
8	$^{5}C_{1,2}(T_2)$	25.4	0.00	−36.9	3.59	−43.1	4.63	58.7	2.75	46.9	3.66	176.4	9.52	−50.2	6.24	−170.2	8.96
		18.5	0.19	−25.4	4.94	−49.7	3.85	52.1	3.36	55.0	2.69	173.6	9.38	−50.1	6.15	−170.3	8.86
		11.9	0.45	−34.5	3.95	−46.7	4.18	58.3	2.73	50.1	3.30	173.0	9.35	−48.9	6.27	−168.9	8.81
		2.3	1.43	−35.2	3.82	−45.8	4.37	58.4	2.73	49.0	3.43	174.1	9.43	−49.3	6.25	−169.4	8.86
	$^{O}C_{3,4}(^{4}T)$	17.9	0.21	65.3	2.46	164.3	1.04	150.8	9.33	40.2	4.44	160.6	8.58	−41.4	6.85	−160.7	8.32
		16.7	0.25	67.7	2.32	167.4	1.44	144.1	8.17	45.1	3.89	161.2	8.63	−42.0	6.82	−161.3	8.37
		3.0	1.26	64.7	2.47	166.6	1.34	151.7	9.52	38.7	4.71	161.8	8.79	−41.4	6.80	−160.5	8.28
		2.3	1.43	63.3	2.49	159.6	0.30	157.0	10.39	38.2	4.74	160.6	8.55	−40.8	6.89	−160.0	8.25
	$^{O}C_{3,4}(^{3}T)$	1.2	1.79	77.0	2.00	−165.0	11.74	96.6	1.60	68.8	1.77	174.2	9.25	−50.2	6.46	−170.1	9.20
		0.2	2.83	77.5	1.99	−160.3	11.22	90.6	1.44	73.4	1.58	174.7	9.41	−50.1	6.44	−170.0	9.17
					3.40		*7.14*		*5.31*		*3.63*		*9.11*		*6.47*		*8.67*

[a] Differing in rotameric orientations of the NO_2 and OH groups; the orientation of the glycosidic OMe group was in every case assumed to be that demanded by the exoanomeric effect. In addition to the data listed the computations produced data for numerous rotamers of higher energy and, for **1**, **2**, **4**, and **7**, the corresponding high-energy $^{O}C_{3,4}$ conformers, all of which contributed very small population percentages only (jointly, 0.2 % for **1**, 2.7 % for **2**, 0.05 % for **3**, 4.2 % for **4**, and 0.15 % for **7**). These data were omitted from the table but included in the computation of the weighted averages of the J values. [b] The weighted averages are given in italics, and the experimentally observed values (ref. [3]) are shown in parentheses. [c] Energy content relative to that of the most abundant rotamer. [d] Not determined.

angles in Table 1 reveals that the computed minimum-energy conformation of these isomers is indeed the $^{5}C_{1,2}(T_2)$ twist chair as anticipated (and as already computed earlier for **1**). The twisting in question is most readily recognizable by the opening of the ring-bond dihedral angle $\Phi_{1,2}$ to approximately $-31°$ to $-36°$ (see Table 1) from its theoretical value of 0° for the parent, regular chair conformation, as well as by the concomitant changes in dihedral angles between hydrogen atoms appended to C-1 and C-2 (see Table 3 for $\Phi_{H\text{-}1,H\text{-}2}$ values). Whereas in the regular $^{5}C_{1,2}$ form pairs 1,2-*cis* and 1,2-*trans* hydrogens subtend dihedral angles of 0° and $-120°$, respectively, in the T_2 variant these angles are widened to approximately $-36°$ for a *gauche* relationship (as in **2**), and to $-150°$ to $-160°$ for *trans* relationships (in **1** and **3**). Relief of bond eclipsing is thereby achieved. Minimum-energy rotamers of twist forms derived from the $^{O}C_{3,4}$ chair were found to exceed those of the $^{5}C_{1,2}$ chair by 7.3 (for **1**) and 3.4 (for **2**) kcal/mol; their populations in conformational equilibrium are therefore negligible (Table 2).

For the D-*glycero*-α-D-*talo* isomer **4**, manipulation of a Dreiding model had not appeared to yield a twist conformation adjacent to the $^{5}C_{1,2}$ chair which would satisfactorily accommodate the experimental $^{3}J_{H,H}$ data, and an alternative twist form (^{3}T), related to the $^{O}C_{3,4}$ chair, was proposed instead [3]. In it, compound **4** would avoid an axial orientation of the nitro group, a circumstance which had been considered advantageous [12]. However, the present calculations determined for **4** also a lowest-energy, $^{5}C_{1,2}(T_2)$ geometry (Fig. 2 and Table 1), very close to that of the foregoing isomers. Minimization of the $^{O}C_{3,4}$ form gave its ^{3}T twist conformer which was higher in energy by more than 3 kcal/mol and, therefore, similarly insignificant in population as in **1–3**. The calculated $^{3}J_{H,H}$ data for **4** agree reasonably with the observed values (Table 3). Evidently, a nitro group in axial disposition on a septanose ring presents less of a steric encumbrance than one on a pyranose ring.

Dreiding models of the D-*glycero*-D-*galacto* (**5**) and D-*glycero*-D-*manno* (**6**) isomers had suggested that the $^{O}C_{3,4}(^{3}T)$ and $^{O}C_{3,4}(^{4}T)$ geometries, respectively, were compatible with the ^{1}H NMR data [3]. These twist forms arise from the parent, regular $^{O}C_{3,4}$ chair ($\Phi_{3,4} = 0°$) by a counterclockwise torsion of the C-3,4 bond about its midpoint, effecting an upward displacement of C-3 and concomitant change of $\Phi_{3,4}$ to $-36°$ (^{3}T form); or by a clockwise rotation, with an upward displacement of C-4, to give the ^{4}T form with $\Phi_{3,4} = +39°$ (Table 1). The present calculations indicate that these conformations do indeed play an important role in these compounds. However, the energy differences between them and the $^{5}C_{1,2}(T_2)$ form are not large and a substantial proportion of the latter must therefore occur in conformational equilibrium (Fig. 2 and Table 1). Thus, in **5** the minimum-energy rotamer of the $^{O}C_{3,4}(^{3}T)$ form (42.8% of population) and its two rotamers next-lowest in energy (1.9 and 1.8%) together constitute 46.4% of the equilibrium mixture which additionally contains 5.9% of the closely related $^{O}C_{3,4}(^{4}T)$ variant, whereas the almost equally stable minimum-energy rotamer of the $^{5}C_{1,2}(T_2)$ form (42.0%) and its next-abundant rotamer (5.6%) make up 47.7% (Table 3). The equilibrium ratio of $^{O}C_{3,4}$ to $^{5}C_{1,2}$ conformers is, therefore, 1.1:1.

In compound **6**, the most stable species is the minimum-energy rotamer of the $^{O}C_{3,4}(^{4}T)$ twist form (23.5%), which is distinctly more stable (by 0.33 kcal/mol) than its $^{5}C_{1,2}(T_2)$ counterpart (13.5%). However, with inclusion of the higher-energy rotamers

of each, the populations are 46.2 and 53.8%, respectively, representing a ratio of 0.86:1 (see Table 3).

4. Conclusion

In summary, molecular mechanics calculations have led to geometries of the favored conformations for the synthetic deoxynitroheptoseptanoside stereoisomers **1–6** and their as yet unknow stereoisomers **7** and **8**, together with their steric energies and populations (Fig. 2 and Tables 1–3). The sequence of their thermodynamic stabilities appears to be **1** $\approx$ **3** > **2** > **7** > **5** > **4** > **6** $\approx$ **8** (Table 2). The isomers **1–6** arose in nitromethane cyclizations of a dialdehyde as mentioned in the Introduction, and **1** was indeed isolated as the main product (68% yield) when the reaction was performed under conditions of thermodynamic control [2], although **3**, which appears equally stable according to the present calculations, was not obtained under those conditions. On the other hand, methoxide-promoted nitromethane cyclizations in methanolic solution are known to be generally controlled kinetically, with partial thermodynamically conditioned epimerizations occurring as the reactions progress [13]. Product ratios therefore do not reflect stabilities. Thus, in the present series the kinetic product **6** was the most abundant species isolated (42%) under these conditions, but **1** ranked second (36%) and **5** ranked third (12%) [3]. Base-catalyzed epimerizations can take place at C-2 and C-4 (by way of retrocyclization), but most facile is mutual interconversion in pairs of 3-epimers by epimerization at the nitromethine position. No efforts were made in the preparative work to determine epimeric equilibria in an accurate way, but semiquantitative experiments suggested a 10:1 equilibrium ratio for the pair **1** and **4**, which accords well with the data now calculated. Compound **5** in pyridine solution underwent partial C-3 epimerization to give an ~3:2 equilibrium of **2** and **5**, also qualitatively in line with the calculated sequence of stabilities. Similarly, **6** was partially converted, in pyridine, into its 3-epimer **3** [2]. Consideration of the energy data in Table 2 reveals that **1–4** must exist in practically homogeneous form as $^{5}C_{1,2}(T_2)$ twist chairs, whereas **5** and **6** partially adopt alternative conformations and exist as mixtures of conformers. Epimerization at C-3, to place the nitro group in an axial position, is associated with a considerable increase in energy (as anticipated [3,12]), but for **4** this is evidently not enough to enforce conformational change to a significant extent such as we had speculated, with the alternative $^{O}C_{3,4}(^{3}T)$ form being surprisingly strongly disfavored. On the other hand, in **5** and **6** the energy differences between both respective conformers are small, and the resulting conformational inhomogeneity endows these compounds with an entropic advantage that diminishes the conformational free-energy difference between them and their epimers.

[2] It was stated [3] that in the equilibrium **3** $\rightleftharpoons$ **6** (from which **3** was isolated in 30% yield), **6** predominated moderately. This is in contradiction with the calculated sequence; equilibration was very slow in this case and a true equilibrium had, perhaps, not been reached.

Finally it is interesting to consider the molecular mechanics predictions for the D-*glycero*-α-D-*allo* (**7**) and D-*glycero*-α-D-*gluco* (**8**) structures that were not encountered in the chemical reactions. In **7** the vastly predominant conformer should be the $^{5}C_{1,2}(T_2)$ chair as in **1–4**, and its energy position in the middle of the sequence affords no thermodynamic reason for its apparent lack among the reaction products. However, because of its 1,2-*cis* constitution its formation is kinetically disfavored (see the detailed discussion of this point in ref. [3]), and the short reaction time of the cyclization (2 h at 0–5°C) may not have allowed it to arise in detectable quantity through a secondary epimerization. Calculation for **8** indicated that it should be capable of existence as a mixture of conformers, mainly the $^{5}C_{1,2}(T_2)$ and $^{O}C_{3,4}(^{4}T)$ forms, resembling in that regard the D-*glycero*-α-D-*manno* isomer **6** with which it also shares the position at the high end of the energy scale. Unlike **6**, however, it is kinetically disfavored for the same reason as **7** and it is therefore understandable that it was not found among the products.

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