Stereochemical Elucidation of Aldoses from the ^1H NMR Spectrum of Its Peracetylated Aldononitrile Derivatives with the Aid of MM2/3JHH Calculations

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The root mean square criterion is applied to compare the calculated and experimental H,H vicinal coupling constants of the peracetylated aldononitriles (PAAN) derived from threose, all the pentoses, all of the hexoses, and one heptose. The correlation is satisfactory in all the studied cases. This result supports the possibility of a complete stereochemical elucidation of an aldose from the NMR spectrum of its PAAN derivative.

Peracetylated aldononitriles (PAAN) and peracetylated ketooximes (PAKO)[1,2] (Figure 1) offer several advantages over other sugar derivatives. Each sugar, in spite of the variety of species present in solution (furanose, pyranose, and open forms; dimeric forms; etc.), gives rise to a single derivative (syn/anti mixtures in the case of PAKO) which preserves the full stereochemistry of the parent compound; they can be easily prepared in high yields in centigram quantities; and they are stable for months under normal laboratory conditions. PAAN and PAKO derivatives have been studied extensively in gas chromatography coupled with mass spectrometry[1-7] and have been used in several analyses of sugar mixtures.[8,9]

According to our own experience, no major problems are found in analyzing the 200-MHz NMR spectra of PAAN derivatives. We have determined the spectroscopy data of the PAAN derivatives of threose (4C-PAAN), the four pentoses (5C-PAAN), the eight hexoses (6C-PAAN), and one heptose.

Experimental NMR coupling constants of flexible molecules are considered to be population-weighted averages of the contributions of all the species present in the corresponding conformational equilibrium. Consequently, theoretical prediction of experimental J values implies the knowledge of conformer populations and of the expected J values in each conformer; in turn, H,H vicinal J values can be predicted from the optimized conformer geometry by applying a generalized Karplus equation.

A detailed conformational analysis of 4C-, 5C-, 6C-, and 7C-PAAN is reported elsewhere.[10] In that analysis, all significant conformers were subjected to complete geometry optimization by the MM2 method,[11] and their populations were calculated.

Table I. Experimental Proton Chemical Shifts of Peracetylated Aldonitriles

configuration	δ_2	δ_3	δ_4	$\delta_{4'}$
threo	5.6	5.4	4.5	4.3

configuration	δ_2	δ_3	δ_4	δ_5	$\delta_{5'}$
ribo	5.8	5.4	5.4	4.4	4.2
arabino	5.7	5.6	5.2	4.3	4.2
xylo	5.6	5.4	5.5	4.3	4.1
lyxo	5.6	5.6	5.4	4.3	4.1

configuration	δ_2	δ_3	δ_4	δ_5	δ_6	$\delta_{6'}$
allo	5.7	5.4	5.4	5.2	4.3	4.1
altro	5.7	5.5	5.4	5.3	4.3	4.2
gluco	5.5	5.4	5.6	5.2	4.3	4.1
manno	5.4	5.6	5.4	5.1	4.2	4.1
gulo	5.6	5.4	5.4	5.2	4.4	4.0
ido	5.6	5.4	5.5	5.3	4.4	4.3
galacto	5.6	5.6	5.5	5.3	4.3	3.9
talo	5.7	5.3	5.6	5.4	4.3	3.9

configuration	δ_2	δ_3	δ_4	δ_5	δ_6	δ_7	$\delta_{7'}$
D-*glycero*-D-*gulo*-heptose	5.6	5.5	5.5	5.4	5.0	4.3	4.1

In the present paper, after analyzing the experimental NMR spectra of PAAN derivatives, we apply Osawa's approach[12] using the MM2/3JHH tandem,[13] which includes the Altona equation, to predict the coupling constants between any given pair of vicinal protons in any one conformer and to calculate their population-weighted averages (J_{calc}); then, we correlate observed and calculated J values. The final aim of the study is to develop a simple procedure for complete stereochemistry elucidation of any aldose from the ^1H NMR spectrum of its PAAN derivative.

Experimental NMR Spectra

A Varian XL-200 instrument was used throughout. The 200-MHz ^1H NMR spectra of threose, ribose, arabinose, xylose, altrose, glucose, mannose, and talose PAAN permitted first-order analyses, which were complemented,

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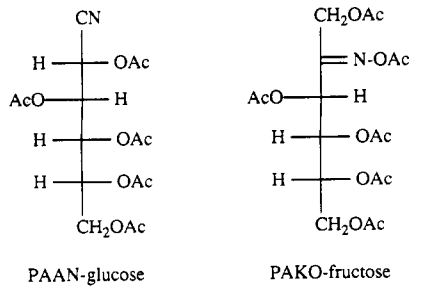

Figure 1.

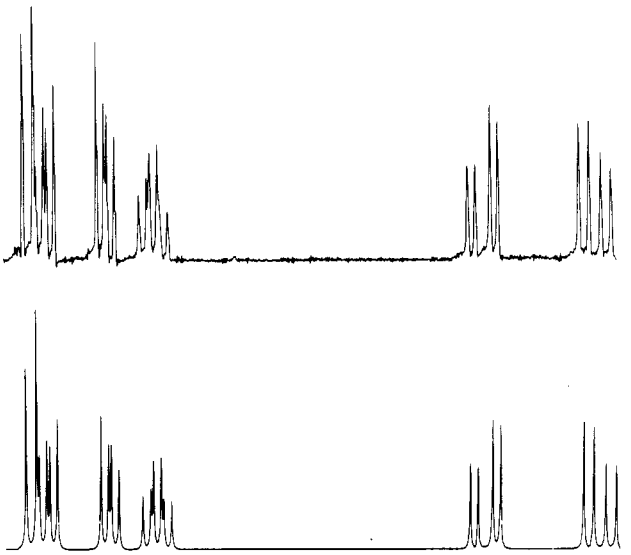

Figure 2. Experimental (up) and simulated (down) ^1H NMR spectra of idose PAAN.

when necessary, with double resonance experiments. Spectra of lyxose, allose, idose, gulose, galactose, and D-*glycero*-D-*gulo*-heptose PAAN were simulated by means of the LAOCOON-3 program;[14] experimental and simulated spectra of idose PAAN are shown by way of example in Figure 2. Due to the limitation of the LAOCOON-3 program to six nuclei, only the low-field region was simulated in the case of the heptose PAAN. Table I collects chemical shifts extracted from the spectra in $CDCl_3$ solution. Our values agree very satisfactorily with those published by Sweeting et al.[15] for arabinose, mannose, glucose, and galactose PAAN in pyridine-d_6 solution, which, incidentally, points to a small influence of solvent polarity in PAAN conformational equilibria. Agreement is not so good with the pentose PAAN values reported by Binkley et al.,[16] which were determined in dimethyl sulfoxide-d_6 using a 60-MHz spectrometer.

It is worth pointing out that vicinal coupling constants of epimers are very similar, which emphasizes the relationship between configuration and vicinal J values. The similar and intermediate values (between 4 and 6 Hz) of the coupling constants between the C_5-proton and the two methylene protons point to a practically free rotation at the hydroxylic end of the carbon chain.

It can be observed that all the spectra follow a similar pattern. Acetyl methyl groups give singlet peaks in the 2.0–2.2 ppm region; chain C-protons show up as multiplets in the 4–5 ppm region; and the two geminal protons (–C-H_2–O–) appear as the AM part of an AMX system at the high-field extreme of that region.

We have also registered the ^{13}C NMR spectra of the mentioned above 14 PAAN (Table II). Four different signal ranges can be observed: carbonyl carbons, at about 170 ppm; cyano carbons, at about 114 ppm; methyl carbons, at about 20 ppm; and other chain carbons, at about 62 ppm. Shift differences between diastereomers are not significant, which suggests that ^{13}C spectroscopy is a poor tool for stereochemical elucidation, and because of this we have centered our attention in the ^1H NMR spectra.

Table II. Experimental Carbon Chemical Shifts of Four, Five, Six, and One Seven Carbon Atoms Sugars Peracetylated Aldononitriles

configuration	δ_{CO}	δ_{CN}	δ_{CH}	δ_{CH_2}	δ_{CH_3}
threo	170.798	114.545	168.951	61.221	21.164
	169.930		60.147		21.034
	169.001				20.627
arabino	170.321	113.940	67.891	61.130	20.549 (2)
	169.377		67.633		20.330
	168.789		59.425		20.000
	168.527				
ribo	170.230	113.700	68.909	61.246	20.642
	169.357		68.695		20.512
	169.113		60.253		20.446
	168.378				20.105
xylo	170.138	113.876	67.857	61.002	20.579
	169.588		67.510		20.478
	169.199		58.966		20.291
	168.197				20.049
lyxo	170.114	114.116	68.514	61.077	20.499 (2)
	169.832		67.611		20.347
	169.157		59.605		20.042
	168.265				
gluco	170.384	113.908	68.024	61.498	20.590 (2)
	169.550		67.051		20.273 (2)
	169.376 (2)		66.883		20.038
	168.104		58.691		
manno	170.423	114.112	67.484	61.332	20.668
	169.866		66.932		20.545
	169.647		63.873		20.476
	169.328		60.112		20.311
	168.385				20.056
allo	170.200	113.900	69.352 (2)	61.379	20.740
	169.774		68.785		20.570 (3)
	169.305		60.213		20.173
	169.188				
	168.543				
altro	170.503	113.825	69.341	61.218	20.773
	169.713		68.222		20.653
	169.122		68.089		20.523 (2)
	168.981		59.375		20.119
	168.570				
gulo	170.272	113.850	68.961	61.412	20.690
	169.668 (2)		68.395		20.599
	169.422		68.004		20.547
	168.338		60.313		20.428
					20.096
ido	170.262	113.818	69.153	61.664	20.700
	169.762		67.875		20.607 (2)
	169.507		67.497		20.493
	169.301		59.173		20.132
	168.183				
galacto	170.219	113.836	67.172	61.502	20.547
	169.988		67.042		20.495
	169.344		66.972		20.351
	168.780		59.202		20.264
	168.689				20.021
talo	170.317	113.634	68.556	61.501	20.612 (3)
	169.964		68.152		20.501
	169.537		68.020		20.174
	169.292		60.361		
	168.443				
D-glycero-D-gulo	170.374	113.749	68.713	61.115	20.670
	169.794		68.534		20.574
	169.708		68.401		20.514
	169.666		67.759		20.365
	169.619		60.428		20.076
	168.341				

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Table III. Experimental and Calculated H,H Vicinal J Values for 4C-, 5C-, and 6C-PAAN[a]

PAAN	$J_{2,3}$	$J_{3,4}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6}$
erythro							
	4.36	4.41	6.03				
	4.89	3.42	4.03				
threo	5.34	4.29	5.45				
	5.00	5.32	5.45				
	4.71	4.41	6.61				
ribo	2.98	7.00		3.00	3.80		
	3.07	6.56		4.51	6.31		
	2.72	7.03		3.51	4.84		
arabino	3.35	8.37		3.03	4.40		
	5.13	7.85		3.85	6.48		
	4.57	8.64		2.75	4.39		
xylo	5.90	3.60		5.50	6.00		
	4.83	5.91		5.79	5.87		
	5.20	5.32		5.08	5.59		
lyxo	6.32	2.94		5.58	6.50		
	5.09	4.06		6.37	6.39		
	5.03	2.39		5.62	7.06		
allo	3.20	5.10		5.34		3.90	5.70
	3.49	3.89		5.54		4.93	6.04
	3.17	3.87		5.74		3.93	4.95
altro	4.16	6.70		4.90		3.60	6.26
	4.62	4.97		4.67		5.07	6.55
	5.49	5.41		4.67		4.05	5.95
gluco	6.70	2.38		8.50		3.00	5.00
	5.75	4.43		7.56		3.85	6.34
	6.71	3.31		8.30		2.81	4.11
manno	6.30	2.00		9.54		2.70	4.00
	5.22	4.24		8.33		3.79	6.51
	5.16	2.71		9.24		2.73	4.36
gulo	5.40	3.10		6.30		3.95	5.45
	5.14	4.62		5.93		5.54	5.56
	5.06	3.53		5.43		4.72	4.74
ido	5.70	4.16		5.90		4.25	5.58
	5.01	4.97		5.63		5.02	6.19
	5.62	4.52		4.89		4.59	5.48
galacto	2.80	9.50		2.10		5.32	7.10
	4.79	7.97		3.69		6.00	6.57
	5.62	4.52		4.89		4.59	5.48
talo	2.46	8.25		2.52		5.40	7.04
	3.00	6.99		4.59		5.71	6.66
	2.65	8.00		3.08		5.96	6.30

[a] In each entry: first row, experimental values; second row, calculated values with Altona's parameters; third row, calculates values with proposed new parameters.

Predicted J Values and Correlation Studies

Calculated H,H vicinal J values using the geometries and populations reported in ref 10, and the P_i parameters published by Altona et al. and incorporated in the 3JHH program, present a relative good concordance with observed values (Table III and Figure 3), with a standard deviation of 1.20 Hz. However, differences between observed and calculated J values are too high to allow one-to-one comparison to be used for structural elucidation. We have applied to this purpose the root mean square correlation test (Table IV). The smallest root mean square value had to be in the diagonal line of the table if the comparison was to bring us to a correct prediction. It can be observed that for the set of four 5C-PAAN plus eight 6C-PAAN, use of Altona's parameters leads to 10 correct predictions.

Several attempts were made to improve the above correlation: use of a recently published alternative set of parameters;[12] use of Altona's parameters in three separate sets as proposed by himself;[17] study of the NC-$CH_{(a)}$R-$CH_{(b)}$R′ J_{calc} dependence as a function of the electronegativity assigned to the sp C and to the NC group as a whole; and "intuitive" changes of some of the P_i values more closely related to electronegativity factors (as reported elsewhere,[10] we have also studied the possible effect of the medium polarity on conformer populations).

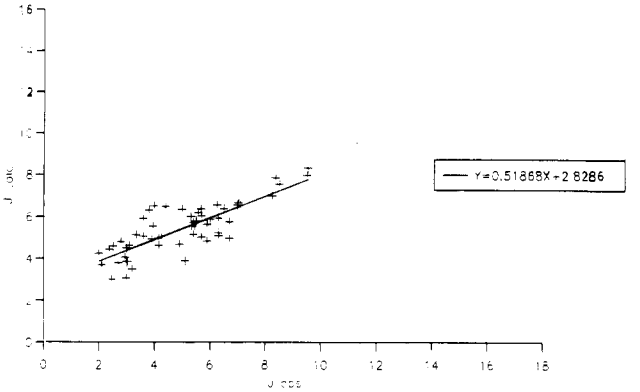

Figure 3. Representation of J_{obs} versus J_{calc}. Calculated coupling constants using Altona's parameters.

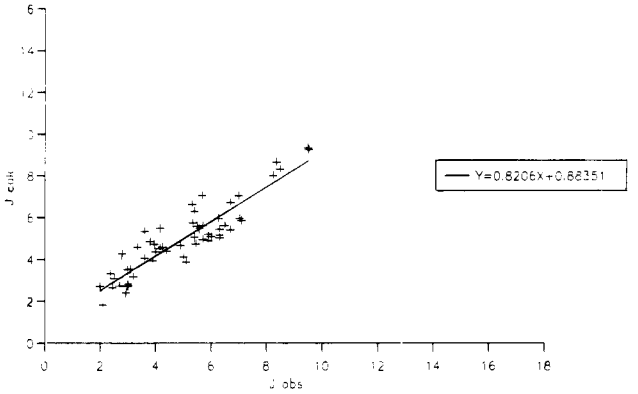

Figure 4. Representation of J_{obs} versus J_{calc}. Calculated coupling constants using the new parameter set.

As all the above attempts were unsuccessful, we decided to reoptimize the generalized Karplus equation for the specific series of compounds under study. To this end, we applied the KEONE program,[18] in the Newton–Raphson method option, to the Altona equation, using a set of 59 experimental coupling constants extracted from the PAAN spectra. The optimization process gave the following set of values (Altona's parameters in parentheses; P_3 = 0, as usual):

P_1 = 17.41 (13.70), P_2 = −2.78 (−0.73), P_3 = 0 (0), P_4 = 1.69 (0.56), P_5 = −7.30 (−2.47), P_6 = 16.17 (16.9), P_7 = 0.38(0.14)

Calculated 4C-, 5C-, and 6C-PAAN J values using the new set of parameters show an improved concordance with experimental values (Table III and Figure 4), with a global standard deviation of 0.77 Hz. Moreover, the root mean square identification test (Table V) now gives satisfactory results in all cases. Predicted J values in the 16 7C-PAAN have been calculated using both the new set of parameters and Altona's. The results are shown in Table VI.

The validity of the two sets of predicted J values was tested for the commercially available D-heptose,[19] D-*glycero*-D-gulo-heptose. The observed J values of its PAAN derivative are given in Table VI, as well as the root mean square deviations for both sets of 16 possibilities.

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(18) Personal communication from E. Ōsawa and T. Fujiyoshi.

(19) The authors offer themselves to register and analyze NMR spectra of any aldose PAAN derivatives; they would also appreciate being informed of results from the use of the reported sets of calculated J values.

Table IV. Root Mean Square Deviation between Experimental and Calculated (Altona's Parameters) H,H Vicinal Coupling Constants for 4C-, 5C-, and 6C-PAAN

	erythro	threo	ribo	arabino	xylo	lyxo	allo	altro	gluco	manno	gulo	ido	galacto	talo	result
threo	0.66	1.11													(-)
ribo			1.48	1.82	2.04	2.79									(+)
arabino			1.52	1.45	2.12	3.03									(+)
xylo			2.11	2.32	1.28	0.67									(-)
lyxo			2.56	2.69	1.69	1.50									(+)
allo							0.74	1.07	1.57	1.70	1.19	0.99	1.94	1.29	(+)
altro							1.45	1.05	1.72	1.95	1.46	1.12	1.37	1.11	(+)
gluco							2.29	2.55	1.30	1.31	2.04	2.16	3.73	3.47	(+)
manno							2.71	3.08	1.84	1.74	2.52	2.68	4.23	3.91	(+)
gulo							1.11	1.36	0.93	1.15	1.10	1.08	2.70	2.38	(-)
ido							1.07	1.00	0.85	1.20	0.66	0.65	2.20	2.02	(+)
galacto							2.96	2.48	3.66	3.87	3.05	2.71	1.41	1.64	(+)
talo							2.47	2.02	3.28	3.47	2.62	2.36	1.22	1.13	(+)

Table V. Root Mean Square Deviation between Experimental and Calculated (New Parameters) H,H Vicinal Coupling Constants for 4C-, 5C-, and 6C-PAAN

	erythro	threo	ribo	arabino	xylo	lyxo	allo	altro	gluco	manno	gulo	ido	galacto	talo	result
threo	1.00	0.75													(+)
ribo			0.60	1.19	1.95	3.97									(+)
arabino			0.81	0.64	2.14	3.62									(+)
xylo			2.67	3.12	1.04	1.09									(+)
lyxo			3.13	3.58	1.50	1.08									(+)
allo							0.67	1.09	2.37	2.36	1.23	1.42	2.69	1.92	(+)
altro							1.52	0.87	2.64	2.83	1.71	1.63	2.08	1.60	(+)
gluco							2.15	2.34	0.59	0.84	1.82	2.24	4.48	4.19	(+)
manno							2.45	2.89	0.83	0.64	2.25	2.70	5.19	4.63	(+)
gulo							1.11	1.29	1.33	1.52	0.66	1.19	3.61	3.06	(+)
ido							1.40	1.29	1.74	2.08	0.63	0.50	3.20	2.70	(+)
galacto							3.35	2.86	4.76	4.98	3.42	2.98	1.05	1.07	(+)
talo							2.83	2.50	4.37	4.53	2.94	2.56	1.26	0.69	(+)

Table VI. Calculated H,H *J* Values for 7C-PAAN

	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7}$	$J_{6,7}$	NC[a]	rms[b]
D-*glycero*-D-*allo*-heptose	3.73	4.96	3.67	6.03	4.60	5.90	65	1.134
	3.47	5.31	3.48	6.33	3.62	5.17		1.390
D-*glycero*-D-*altro*-heptose	4.93	5.45	3.28	7.16	4.41	5.92	65	1.281
	5.58	6.12	2.94	7.80	3.47	5.20		1.627
D-*glycero*-D-*gluco*-heptose	4.18	7.67	3.70	6.84	4.26	5.16	55	1.740
	4.89	8.51	3.76	7.50	3.39	4.26		2.114
D-glycero-D-*manno*-heptose	4.96	5.06	6.18	3.95	5.51	6.22	55	1.089
	4.94	4.10	7.17	4.06	4.59	5.68		0.097
D-*glycero*-D-*gulo*-heptose	5.72	5.06	4.21	6.56	4.64	6.10	51	0.880
	5.68	3.98	5.56	6.71	4.14	4.79		0.448
D-*glycero*-D-*ido*-heptose	3.79	5.95	5.02	7.48	4.16	5.31	55	1.215
	2.88	6.18	4.19	8.21	3.17	4.53		1.802
D-*glycero*-D-*galacto*-heptose	4.11	7.71	3.31	7.60	4.84	5.66	42	1.959
	4.52	8.08	3.51	0.19	2.15	4.57		2.738
D-*glycero*-D-*talo*-heptose	3.80	6.18	5.45	8.17	3.67	5.80	44	1.483
	3.60	7.06	4.32	9.10	2.70	4.92		2.116
D-*glycero*-L-*galacto*-heptose	4.08	7.31	4.06	6.36	4.69	5.98	51	1.578
	3.86	8.44	2.67	5.78	3.50	5.63		2.232
D-*glycero*-L-*talo*-heptose	2.85	7.19	4.50	6.09	5.37	5.50	56	1.711
	2.54	8.32	3.21	5.48	4.36	4.80		2.259
D-*glycero*-L-*gulo*-heptose	6.09	3.92	5.59	3.79	4.61	7.10	66	1.213
	6.14	3.90	6.45	3.56	4.14	6.93		1.288
D-*glycero*-L-*ido*-heptose	3.45	6.30	4.48	6.27	4.17	6.48	66	1.390
	2.99	7.02	3.87	6.02	3.16	6.33		1.812
D-*glycero*-L-*gluco*-heptose	4.69	4.38	6.07	3.17	5.43	7.14	45	1.463
	6.14	3.90	6.45	3.56	4.14	6.93		1.288
D-*glycero*-L-*manno*-heptose	5.78	1.62	9.12	2.30	6.30	6.68	53	2.501
	5.96	1.47	0.75	0.06	4.66	6.77		3.971
D-*glycero*-L-*allo*-heptose	3.95	3.21	6.31	5.71	5.53	6.32	55	1.025
	3.69	3.16	6.99	4.96	5.11	5.63		1.095
D-*glycero*-L-*altro*-heptose	4.33	6.39	3.39	7.73	4.90	6.86	55	1.738
	3.98	7.36	3.31	7.93	4.59	6.58		2.007

[a] Number of significative conformations. [b] Standard deviation between experimental *J* values of D-*glycero*-D-*gulo*-heptose PAAN and calculated ones: first row, calculated using new parameters; second row, calculated using Altona's parameters. [c] Experimental values, in the same order: 5.33, 4.20, 5.60, 5.76, 4.40, 5.04.

The smallest root mean square value corresponds in either case to the correct assignation, which supports the correctness of the structural identification method here presented.

Finally, it should be observed that using the new set of parameters the root mean square for the correct assignation is smaller (0.448 vs 0.880 Hz) and the range of root mean square values wider (0.448–3.971 vs 0.880–2.501 Hz),

which means a better discriminating power between diastereomers.

Conclusion

In our view, the results reported indicate the possibility of a complete stereochemical elucidation of any aldose from the NMR spectrum of its PAAN derivative. Fulfilment of this possibility depends on two factors: (i) complete and correct analysis of experimental NMR spectra; (ii) correct predictive sets of calculated J values. Increasing accessibility to higher field spectrometers and to a wide range of complementary programs and pulse sequences (LAOCOON-3, homonuclear correlation proton-proton, heteronuclear correlation carbon-proton, ...) makes us feel optimistic on the subject of point i; and, in relation to point ii, the self-improving capabilities of the procedure should be emphasized: in fact, each new correct structural assignation affords a new set of experimental J values that could be used for further sharpening of the P_i parameters set used in the 3JHH program.

Computational Methods

All MM2 calculations were carried out with a local IBM/CMS version of MM2(77).[11] KEONE program was run on a VAX-8800 computer.

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Conformational Study of Peracetylated Aldononitriles

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A conformational study of the tetrose, pentose, hexose, and heptose diastereomeric peracetylated aldononitrile derivatives (PAAN) based on force-field calculations is described.

The study of the structure of flexible organic molecules is a challenging problem of current interest. In the present paper, a detailed molecular mechanics[1] conformational study of the tetrose, pentose, hexose, and heptose (D series) diastereomeric peracetylated aldononitrile derivatives (PAAN) (Figure 1) is presented. This study is closely related to that which led to the setting up of a direct and simple procedure for the stereochemical elucidation of aldoses.[2]

We will use the conformational symbolism proposed by J. A. Mills[3] throughout, but differentiating O//C from C//C interactions by using primed letters for the former (Figure 2).

Selection of Starting Geometries. The importance of a correct selection of starting geometries cannot be overemphasized because in all the computational methods available to date[4] only local energy minima are identified.

Using a very large number of correctly selected starting geometries and (energetically) minimizing them to the nearest local minimum, practically all parts of the conformational space are sampled and the lowest local minimum can be taken as the "global minimum", i.e. the lowest energy state overall. Staggered bond conformations (180: G, G', A. 60: U, U', P. -60: K, K', M; Figure 3) have been taken as starting points in the MM2 energy optimization processes. Combination of these conformations leads to nine possible conformers for each two tetrose PAAN, 27 for each four pentose PAAN, 81 for each eight hexose PAAN, and 243 for each 16 heptose PAAN.

Several approximations have been carried out to reduce the number of conformers to be considered, thus shortening the required computational time.

(a) Conformational considerations concerning C-C-C-C-C, O-C-C-C-C, and O-C-C-C-O fragments. As a rule, in the absence of hydrogen bonding and/or other modifying factors, heavy atom//heavy atom 1,3 interactions (the symbol // will be used to denote 1,3 interactions) destabilize conformers in which they are present.[5] The point to discuss here is the relative extent of destabilizing effect of the three types of 1,3 interactions possible in PAAN derivatives: C//C, C//O, and O//O.

Until recently, the accepted view[6-11] was that C//O interactions were stronger than O//O interactions: typical accepted values in aqueous solution are 2.5-2.6 kcal/mol and 1.9 kcal/mol, respectively.[12-14] Many authors[3,5,15-21]

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