CONFORMATION OF 5-AMINO-5-DEOXYPENTONOLACTAMS

Karel KEFURT[a1], Jaroslav HAVLICEK[b], Michaela HAMERNIKOVA[a2], Zdenka KEFURTOVA[a1] and Hana VOTAVOVA[c]

[a] *Department of Chemistry of Natural Compounds, Prague Institute of Chemical Technology, 166 28 Prague 6, Czech Republic; e-mail: [1] karel.kefurt@vscht.cz, [2] michaela.hamernikova@vscht.cz*

[b] *Department of Analytical Chemistry, Prague Institute of Chemical Technology, 166 28 Prague 6, Czech Republic; e-mail: jaroslav.havlicek@vscht.cz*

[c] *Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, 166 10 Prague 6, Czech Republic; e-mail: hanka@marilyn.uochb.cas.cz*

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Dedicated to the memory of Professor Rudolf Lukes (1897–1960).

Four configuration isomers of 5-amino-5-deoxy-D-pentonolactam **1a–4a** and their tri-*O*-acetyl derivatives **1b–4b** were studied using NMR and CD spectroscopy. For all compounds chemical shifts of the ^{1}H and ^{13}C nuclei as well as of vicinal coupling constants were obtained. Comparison of the observed ^{3}J(H,H) with those calculated for various conformations by a modified Karplus relationship led to the assignment of predominant conformation $^{3}H_{4}$(D) or $^{4}H_{3}$(D) to the lactams **1a–4a** and **1b–4b** in solution. The most important factor for determining the conformation seems to be the pseudo-equatorial position of the substituent on the carbon next to the carbonyl group. The results of the CD spectra of the lactams **1a–4a** in water, interpreted according to the currently used rules, agreed with the NMR results.

Key words: Carbohydrates; Azasugars; Lactams; Conformation analysis; NMR spectroscopy; Circular dichroism.

Recently six-membered lactams derived from 5-amino-5-deoxy-D-glucose (nojirimycin) and its diastereoisomers have been investigated, because of their significant activity as inhibitors of glycosidases (*cf.* refs[1–8]). Important structure–activity relationships could be supposed for these enzymatic processes and thus knowledge of prevailing conformation of the active molecules can be useful.

On the assumption of approximately planar arrangement of the "amide" (C_2–C_1(=O)–N–C_5) segment, two half-chair ($^{3}H_4$ or $^{4}H_3$) and two boat ($^{2,5}B$ or $B_{2,5}$) conformations could be considered as basic for the six-membered lactam ring (Fig. 1, p. 1924). According to the theory, possible interactions between the eclipsed substituents on C-3 and C-4, and also between the substituents bonded in the "flagpole" positions on C-2 and C-5 could make the boat conformations less advantageous for some diastereoisomers.

Structures of 5-amino-5-deoxy-D-gluconolactam[9] and some of its derivatives[4] were determined by X-ray diffraction, structures of further diastereoisomers can be deduced from their NMR spectra. Briefly: almost pure $^4H_3$(D) conformation was found for 5-amino-5-deoxy-D-gluconolactam in the solid state as well as in the solution[9]. The NMR data for 5-amino-5-deoxy-D-mannonolactam[7] and also for per-*O*-acetylated 5-amino-5-deoxy-D-mannonolactam oxime[4] correspond to the $^3H_4$ conformation. In the case of the 5-amino-2,3,4,6-tetra-*O*-benzyl-5-deoxyhexonolactams of D-*gluco*, D-*manno*, D-*galacto* and L-*gulo* configuration, the values of the coupling constants[6] indicate that the half-chair conformation prevails. On the other hand, the boat conformation was suggested[4] for the per-*O*-acetyl-5-amino-5-deoxy-D-gluconolactam oxime on the basis of its NMR spectra and for 5-amino-5-deoxy-L-idonolactam on the basis of circular dichroism[10].

In this paper, we present the results of structural study of the series homologous to the above mentioned hexonolactams which is derived from 5-amino-5-deoxypentoses, *i.e.* of 5-amino-5-deoxypentonolactams. The syntheses of the complete diastereoisomeric D-series of these compounds were described in the previous paper[11]. Other methods of preparation of some diastereoisomers of this series were also published[12–14]. Conformation of 5-amino-5-deoxypentonolactams could be more flexible than that of 5-amino-5-deoxyhexonolactams because of the absence of the bulky hydroxymethyl group on C-5. Only 5-amino-5-deoxy-D-ribonolactam and its 2,3-*O*-isopropylidene derivative has been studied so far from the point of view of conformation by the method of circular dichroism[10]. As in our former study of seven-membered lactams[15], the main methods in this work were NMR and CD spectroscopy.

EXPERIMENTAL

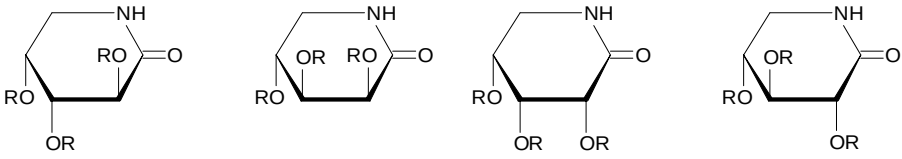
The studied compounds, 5-amino-5-deoxy-D-arabinonolactam (**1a**), 5-amino-5-deoxy-D-lyxonolactam (**2a**), 5-amino-5-deoxy-D-ribonolactam (**3a**) and 5-amino-5-deoxy-D-xylonolactam (**4a**) were prepared as previously[11]. The corresponding 2,3,4-tri-*O*-acetyl derivatives **1b–4b** were prepared as described below.

Most of the NMR spectra were measured on a Gemini 2000 (300HC Varian) instrument (^{1}H at 300 MHz, ^{13}C at 75 MHz), ^{1}H NMR of the lactam **1b** on a Bruker AM 400 instrument (^{1}H at 400 MHz), ^{1}H NMR of the lactams **3a**, **3b** on a Varian Unity-500 instrument (^{1}H NMR at 500 MHz). The samples were dissolved in deuterium oxide and CD_3SOCD_3 (**1a–4a**), and in CD_3Cl (**1b–4b**). 2,2-Dimethyl-2-silapentane-5-sulfonate (DSS) and tetramethylsilane (TMS) were used as internal standards. All measurements were performed at 24 °C. Assignment of ^{1}H and ^{13}C signals was verified using 2D homonuclear and heteronuclear correlated spectra (^{1}H-^{1}H COSY, ^{1}H-^{13}C HETCOR) and by help of simulated spectra conforming with programme VNMR Version 5.3b Software (Varian).

The CD spectra of the **1a–4a** lactams were obtained on a Jobin–Yvon Dichrographe Mark V instrument equipped with a data processor. The measurements were carried out at room temperature in a 0.1 cm cell in the range of 190–260 nm. Lactam concentration was about $1 . 10^{-3}$ mol l^{-1}, distilled water was used as a solvent. The data are given as the difference of molar absorption coefficients for the left and right polarized light $\Delta\varepsilon = \varepsilon_L - \varepsilon_R$ (cm^2 $mmol^{-1}$).

Preparation of 2,3,4-tri-*O*-acetyl derivatives **1b–4b**

Lactam **1a–4a** (180 mg, 1.2 mmol) was stirred in a mixture pyridine (1.5 ml) and acetanhydride (0.5 ml) at room temperature for 16 h. The reaction mixture was evaporated and the residue repeatedly evaporated with toluene (3 × 25 ml). Crude acetate was purified by liquid chromatography on silica gel (15 g, 40–100 μm) column using elution with chloroform–methanol (20 : 1). 2,3,4-Tri-*O*-acetyl-D-lyxonolactam (**2b**) was obtained as a solid, the other ones as syrups. Physical data and elemental analysis of the compounds **1b–4b** are collected in Table I.



In formulae **1-4** : **a,** R = H
b, R = Ac

RESULTS AND DISCUSSIONS

NMR Measurements of Lactams **1a–4a** *and Their O-Acetates* **1b–4b**

Chemical shifts of the ^{1}H and ^{13}C lactam ring atoms and the ^3J(H,H) coupling constants are summarized in Table II. 5-Amino-5-deoxy-D-arabinonolactam (**1a**) exhibited a simple spectrum in deuterium oxide and also in CD_3SOCD_3 while its tri-*O*-acetate **1b**

TABLE I
Physical constants and elemental analyses of the 2,3,4-tri-*O*-acetyl-5-amino-5-deoxy-D-pentonolactams **1b–4b**

Lactam configuration	$[\alpha]_D^{20}$ (c in $CHCl_3$)	Elemental analysis[a], found		
		% C	% H	% N
D-*arabino* **1b**	–146.1° (1.5)	48.43	5.81	4.89
D-*lyxo* **2b**[b]	–88.4° (1.3)	48.39	5.52	5.04
D-*ribo* **3b**	+39.1° (1.3)	48.44	5.70	4.86
D-*xylo* **4b**	–7.7° (1.5)	48.52	5.65	4.87

[a] Calculated for $C_{11}H_{15}NO_7$ (273.3): 48.35% C, 5.53% H, 5.13% N; [b] m.p. 126 °C (ethyl acetate–petrolether).

TABLE II
^{1}H and ^{13}C NMR chemical shifts (δ-scale, ppm) and ^3J(H,H) coupling constants (Hz) of lactams **1a–4a** in deuterium oxide (*A*) and CD_3SOCD_3 (*B*) and their tri-*O*-acetyl derivatives **1b–4b** in $CDCl_3$ (*C*)

Parameter	**1a**[a]		**1b**[b]	**2a**[a]		**2b**[a]	**3a**[c]		**3b**[c]	**4a**[a]		**4b**[a]
	A	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*
						Chemical shifts						
H-2	4.07 (d)	3.74 (dd)	5.37 (d)	4.38 (d)	4.02 (d)	5.66 (d)	4.18[d]	3.81 (dd)	5.53 (d)	3.96 (d)	3.57 (dd)	5.16 (d)
H-3	3.79 (dd)	3.58 (ddd)	5.30 (ddd)	4.17[d]	3.85 (dd)	5.48 (ddd)	4.19[d]	3.89 (ddd)	5.71 (dd)	3.64 (dd)	3.32 (ddd)	5.39 (dd)
H-4	4.10 (ddd)	3.90 (m)	5.46 (m)	4.15[d]	3.80 (m)	5.17 (m)	4.16 (ddd)	3.86 (m)	5.31 (m)	3.89 (ddd)	3.56 (m)	5.12 (ddd)
H-5	3.37 (dd)	3.15 (ddd)	3.57 (dd)	3.64 (dd)	3.41 (ddd)	3.76 (ddd)	3.38 (dd)	3.11 (dd)	3.52[d]	3.44 (dd)	3.17 (ddd)	3.61 (ddd)
H-5′	3.17 (dd)	3.03 (ddd)	3.37 (m)	3.22 (dd)	2.92 (ddd)	3.40 (m)	3.26 (dd)	3.01 (ddd)	3.49[d]	3.07 (dd)	2.85 (ddd)	3.34 (ddd)
H–N	–	7.36	7.51	–	7.27	7.04	–	7.31[e]	6.48	–	7.51	6.92
HO-2	–	5.25[f]	–	–	4.66[g]	–	–	4.65[e,f]	–	–	4.94[f,h]	–
HO-3	–	5.03[f]	–	–	5.10[g]	–	–	5.00[e,f]	–	–	5.20[f]	–
HO-4	–	4.93[f]	–	–	5.25[g]	–	–	4.95[e,f]	–	–	5.12[f,h]	–

TABLE II
(*Continued*)

Parameter	**1a**[a]		**1b**[b]	**2a**[a]		**2b**[a]	**3a**[c]		**3b**[c]	**4a**[a]		**4b**[a]
	A	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*
						Chemical shifts						
C-1	175.8	175.2	168.1	181.6	172.8	167.9	175.8	172.8	167.5	174.8	171.9	167.7
C-2	71.8	70.5	69.3	74.8	67.7	66.9	70.6	69.3	67.1	72.7	72.0	71.3
C-3	74.1	72.0	70.1	78.5	71.6	68.8	73.4	71.8	69.1	76.1	75.8	72.3
C-4	69.3	65.6	67.3	74.4	67.6	67.1	67.2	65.9	65.8	69.0	68.4	69.1
C-5	47.3	44.1	43.5	52.1	45.3	43.5	44.9	44.0	41.7	45.3	44.2	42.3
						Coupling constants (H,H)						
J(2,3)	9.6	7.8	10.1	3.0	3.1	3.6	2.8[d]	2.9	3.3	9.3	8.5	8.5
J(3,4)	2.5	2.1	2.4	4.4[d]	4.4	4.4	2.7	2.0	2.1	8.9	7.8	7.1
J(4,5)	3.0	3.2	2.5	3.6	3.9	4.2	6.4	10.0	7.1	5.7	4.9	4.5
J(4,5′)	2.8	2.4	2.6	3.0	2.6	2.5	9.6	6.1	9.3	9.0	7.8	7.0
J(HN,5)	–	1.5	0.8	–	1.9	1.6	–	≈3	3.1[d]	–	3.3	3.4
J(HN,5′)	–	5.0	2.6	–	2.6	2.6	–	2.9	2.3[d]	–	2.1	2.9
J(HO,2)	–	4.9	–	–	[g]	–	–	4.2[e]	–	–	4.5[h]	–
J(HO,3)	–	4.5	–	–	[g]	–	–	3.4[e]	–	–	4.5	–
J(HO,4)	–	4.3	–	–	[g]	–	–	6.1[e]	–	–	4.4[h]	–

[a] Measured on 300 MHz instrument; [b] measured on 400 MHz instrument; [c] measured on 500 MHz instrument; [d] overlapped signals: chemical shifts and ^3J(H,H) values were obtained from the simulated spectra; [e] conforming with the data in ref.[30]; [f] dublet; [g] broad singlet; [h] may be interchanged.

required measuring on 400 MHz instrument to show separated signals of H-2 and H-3. ^{1}H NMR spectra of lactam **1a** as well as of its tri-*O*-acetate **1b** exhibited some characteristic indications: signal of H-4 shifted downfield relative to the signals of the other ring H-atoms, rather high (7–10 Hz) value of J(2,3) and low (≈3 Hz) values of J(3,4), J(4,5) and J(4,5′). All these symptoms indicate the prevailing $^3H_4$(D) conformation (see Fig. 1) of lactams **1a** and **1b** in measured solutions. The observed values of ^3J(H,H) as well as of ^{1}H and ^{13}C chemical shifts in the spectra of **1a** are close to the values which were described[14] for this lactam in CD_3OD solution.

The spectrum of lactam **4a** recorded in deuterium oxide was intelligible due to a complete separation of all the signals. The values of the vicinal coupling constants J(2,3), J(3,4), J(4,5′) were high (9.3–8.9 Hz). In CD_3SOCD_3 solution, these constants were slightly lower (8.5–7.8 Hz). Because of partially coinciding signals of H-2 and H-4, assignment of the doublets C(2)–OH and C(4)–OH using of the ^{1}H-^{1}H COSY experiment is uncertain and could be reversed. In the spectrum of acetate **4b** measured in $CDCl_3$ solution, the ^3J values were close to the corresponding constants in the spectrum of **4a** measured in CD_3SOCD_3 (and also close to the values published[13] for tri-*O*-benzoate of lactam **4a**). The mentioned values of the coupling constants J(2,3), J(3,4) and J(4,5′) found both in spectra of **4a** and in spectrum of **4b**, confirm prevailing axial or pseudoaxial positions of atoms H-2, H-3, H-4 and H-5′ as it can be realized in $^4H_3$(D) conformation. This conclusion also agrees with the finding[9] concerning the conformation of 5-amino-5-deoxy-D-gluconolactam having an identical relative configuration of the substituents on C-2, C-3 and C-4 as the lactam **4a**.

5-Amino-5-deoxy-D-lyxonolactam (**2a**) in deuterium oxide solution exhibited the most downfield shifted H-2 signal and unseparated signals of H-3 and H-4. All signals were split by small vicinal coupling constants. In the spectrum of **2a** measured in

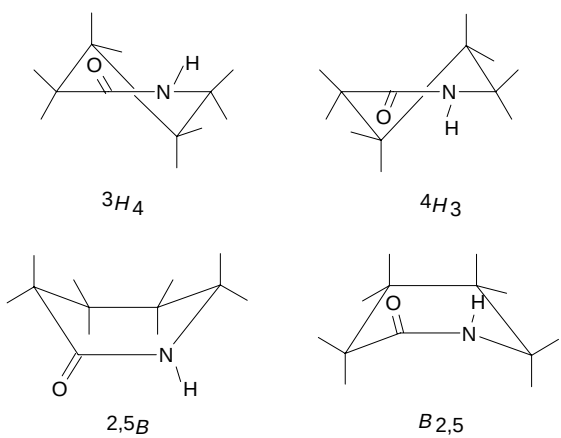


FIG. 1
Possible half-chair and boat conformations of the six-membered lactam ring

CD_3SOCD_3, the coupling constants $J(2,3)$, $J(3,4)$, $J(4,5)$ and $J(4,5')$ were found to be very similar varying in the range of 2.6–4.4 Hz. The corresponding acetate **2b** measured in $CDCl_3$ solution showed sharply separated signals. In addition to the small vicinal coupling constants (^3J ≈2.5–4.4 Hz), the long-range coupling ($J(3,5)$, $J(4,NH)$ ≈ 0.8–1.1 Hz) was also observed. These results confirm that the $^3H_4$(D) conformation prevails in the solutions of lactams **2a**, **2b** in the measured solvents.

Deuterium oxide solution of 5-amino-5-deoxy-D-ribonolactam (**3a**) exhibited the 300 MHz ^{1}H NMR spectrum with an unresoluted, complex signal of higher order of protons H-2, H-3 and H-4. Using a 500 MHz NMR spectrometer, separation of the H-4 signal from this complex was achieved. For this reason, the further discussion of spectral values of **3a** and **3b** takes into account only values from the 500 MHz ^{1}H NMR spectra. In deuterium oxide solution, lactam **3a** exhibited $J(5',4)$ ≈ 9.6 Hz, $J(5,4)$ ≈ 6.4 Hz and $J(4,3)$ ≈ 2.7 Hz. In CD_3SOCD_3 solution, the signals of all ring H-atoms were well separated. From this spectrum, low values for $J(2,3)$ and $J(3,4)$, intermediate (≈6.1 Hz) for $J(4,5')$ and high (≈10 Hz) for $J(4,5)$ were obtained. The spectrum of acetate **3b** gives values of the vicinal spin–spin constants similar those of lactam **3a**. Good separation of the signals of H-2, H-3, H-4 was accompanied by overlapped signals of two H-5 atoms in this spectrum. All data indicate that the lactams **3a** and **3b** are very probably in the $^4H_3$(D) conformation.

In agreement with the general experience, signals of the equatorial protons H-3 or H-4 and pseudoequatorial protons on C-5 are located more downfield than those of axial protons in the spectra of compounds **1a–3a** and **1b–3b**. The exception from this rule can be observed in C-5 methylene group of the lactam **3a** measured in CD_3SOCD_3: here the position of the signals is reversed, *i.e.*, H-5a signal appears downfield relative

TABLE III
Calculated values of vicinal coupling constants ^3J(H,H) (Hz) for the corresponding torsion angles Φ (H,H) (°) in the $^3H_4$(D) and $^4H_3$(D) conformations of 5-amino-5-deoxy-D-pentonolactams[a]

Lactam	$J(2,3)/\Phi(2,3)$		$J(3,4)/\Phi(3,4)$		$J(4,5D)/\Phi(4,5D)$[b]		$J(4,5L)\Phi/(4,5L)$[b]	
	$^3H_4$	$^4H_3$	$^3H_4$	$^4H_3$	$^3H_4$	$^4H_3$	$^3H_4$	$^4H_3$
1a	8.1/164	1.9/76	2.2/–61	2.1/61	2.6/–68	10.5/–170	2.5/51	4.7/–51
2a	4.1/46	4.7/–41	4.9/53	9.2/177	2.8/–66	10.1/–170	2.3/53	4.7/–51
3a	4.6/42	3.0/–54	2.2/–61	2.0/62	2.8/–66	9.4/–164	2.3/53	5.4/–46
4a	1.8/–77	8.3/–165	4.5/56	9.1/176	2.8/–66	9.6/–166	2.4/52	5.1/–48

[a] The coupling constants were calculated using a modified[16] Karplus relationship for torsion angles found in optimized conformations (*cf.* Table VI); [b] hydrogen termed as "5D" is pseudoequatorial or pseudoaxial in the $^3H_4$(D) or $^4H_3$(D) conformations, respectively, hydrogen "5L" is situated reversely.

to the H-5e one. This relation of chemical shifts was observed and commented[15] also in the spectra of the set of 6-amino-6-deoxyhexonolactams.

Theoretical values of the coupling constants for both $^3H_4$(D) and $^4H_3$(D) conformations of lactams **1a–4a** were calculated according to the modified Karplus equation[16] (Table III). Considering the experimental ^3J(H,H) as a sum of quotients of the two theoretical values of ^3J(H,H) calculated for $^3H_4$(D) and $^4H_3$(D) conformations, we can determine the equilibrium $^3H_4(D) \rightleftharpoons {}^4H_3(D)$ quantitatively. The following data result from these relations for certain lactams measured in certain solvents: **1a**: 94% (D_2O), 93% (CD_3SOCD_3) of $^3H_4$(D); **1b**: 95% ($CDCl_3$) of $^3H_4$(D); **2a**: 80% (D_2O), 87% (CD_3SOCD_3) of $^3H_4$(D); **2b**: 89% ($CDCl_3$) of $^3H_4$(D); **3a**: 100% (D_2O, CD_3SOCD_3) of $^4H_3$(D); **3b**: 95% ($CDCl_3$) of $^4H_3$(D); **4a**: 94% (D_2O), 79% (CD_3SOCD_3) of $^4H_3$(D); **4b**: 65% ($CDCl_3$) of $^4H_3$(D). Surprisingly low values found for lactams **4a** in CD_3SOCD_3 and **4b** in $CDCl_3$ especially are only with difficulties explainable. However, some comments should be pronounced to the above mentioned data: (i) Only half-chair conformations were considered in our calculations. (ii) Content of the prevailing conformation is from each triplet (one experimental and two theoretical) values of ^3J(H,H) for certain torsion angle obtainable, if the relation $^3J(H,H)_{theor}$ for the first half-chair conformation $\leq {}^3J(H,H)_{exp} \geq {}^3J(H,H)_{theor}$ for the second half-chair conformation has been realized. The numbers mentioned above resulted as an arithmetical average from 2–3 such calculations carried out for various torsion angles of each lactam. In some cases (*e.g.*, just for **4a**/CD_3SOCD_3 and **4b**/$CDCl_3$), the contents resulting from the values of J(3,4), J(4,5) and J(4,5′) differed from the average significantly (±7–8%). (iii) The experimental ^3J(H,H) values unconforming to the condition given in the comment (ii) (mostly of J(2,3)) were not used for the calculations. All consequences following from the facts in the notes (i)–(iii) could effect accuracy of the calculations.

Data of the simultaneously measured ^{13}C NMR spectra of lactams **1a–4a** and **1b–4b** are summarized in Table II. As in our previous study[15], no correlation between the set of ^{13}C chemical shift values of lactams and their conformation was observed.

CD Measurements of Lactams **1a–4a**

CD measurements of lactams **1a–4a** were limited by the low solubility of the compounds in all solvents except water. On the other hand, similar conditions of the NMR and CD measurements allow to compare the results obtained for lactams **1a–4a** by both methods.

Two bands located in the wavelength regions of about 195 and 220 nm were observed in the CD spectrum of each studied lactam. The long-wavelength band may be assigned to the $n \rightarrow \pi$ transition of the amide chromophore[15,17], the short-wavelength band is most probably due to the $\pi \rightarrow \pi^*$ transition of the same chromophore. The results of CD measurements of lactams are presented in Table IV.

The configuration at C-2 carbon atoms seems to be crucial for the sign of both bands. In the *R* series the long-wavelength band is negative and the short-wavelength one is positive whereas in the *S* series the situation is reversed. This finding is in agreement with our former results obtained for the set of 6-amino-6-deoxyhexonolactams[15] and also with the results of the Japanese authors[10,18] obtained for the set of various five- or six-membered lactams.

For interpretation of the CD spectra, it is possible to use the rules relating the CD parameters to the spatial arrangement of the studied compound[15,17]. According to the so-called lactam rule which has been formulated by Ogura's group[19–21], the sign of the CD band is determined exclusively by the chirality of the lactam ring. However, the authors admitted[9] that some difficulties occurred when this rule was applied to conformation analysis of six-membered lactams. A similar rule, also taking into account only the chirality of the ring, was suggested by Wolf[22,23] mainly for six-membered lactones (or lactams). According to the rule, the above mentioned lactones or lactams exhibit a positive Cotton effect in the $^3H_4$ or $B_{2,5}$ conformations and negative one in the $^4H_3$ or $B^{2,5}$ conformations. On the basis of the same type of data, Legrand and Bucourt[24] proposed the rule of the reverse relation between the signs of the CD band and the torsion angle C_1–C_2–C_3–C_4 in the corresponding conformation. The Japanese authors[10,18] observed a relation between the CD sign and the configuration of some non-carbon (–OR, $–NR_2$, –X) substituent at C-2 in a set of the five- and six-membered lactams. They assumed that the C-2 configuration is crucial for the sign of CD band, independently of the ring conformation. Another rule that may be used is the so-called amide quadrant rule[25–27]. Similarly to other sector rules, this approach evaluates the contribution of individual atoms on the lactam ring projected by certain way into the quadrants, to the resulting Cotton effect of the studied compound.

All the above mentioned rules evaluate only the bands of $n\rightarrow\pi^*$ transition of the amide chromophore. For this reason, we shall further discuss only the CD bands of lactams **1a–4a** located at about $\lambda \approx 220$ nm.

TABLE IV
CD bands of the 5-amino-5-deoxy-D-pentonolactams **1a–4a** in the region 190–260 nm (water, 25 °C)

Lactam, configuration	λ, nm (Δε, $cm^2\ mmol^{-1}$	
	1st band	2nd band[a]
1a, D-*arabino*	221 (+4.8)	195 (–12.8)
2a, D-*lyxo*	219 (+4.1)	195 (–11.5)
3a, D-*ribo*	219 (–8.5)[b]	196 (+19.7)
4a, D-*xylo*	220 (–6.3)	196 (+10.3)

[a] Position and magnitude of the 2nd band could not been determined accurately; [b] ref.[10]: 219 (–6.7).

The observed and theoretical (*i.e.*, obtained according to the above mentioned rules) signs of the long wavelength CD extremes of the 5-amino-5-deoxy-D-pentonolactams and their prevailing conformations determined using the ^{1}H NMR spectroscopy are shown in Table V. The results show that the lactams assumed to be in $^3H_4$ or $^4H_3$ half-chair conformations exhibit different signs of CD bands and that the observed and "theoretical" signs of CD bands agree. The Wolf–Legrand–Bucourt rule[22–24] seems to be the most reliable for determination of conformation of the six-membered lactams. However, according to this rule, the sign of the CD band does not allow to distinguish between one half-chair and one boat conformation possible for every lactam. Wolf observed[22,23] a blue shift of CD maxima or minima for six-membered lactones in boat conformations in comparison with lactones in half-chair conformation. We obtained similar results for the set of diastereoisomeric 4,6-dideoxyhexono-1,5-lactones[28] exhibiting a difference in wavelength of about 6–9 nm for CD maxima or minima corresponding to the conformations of the *H* or *B* type. However, in the present set of lactams we have found almost identical wavelength of the $n\rightarrow\pi^*$ CD maxima or minima for all samples investigated. Therefore, we may suppose that lactams **1a–4a** exist preferentially in only one type (*i.e.* half-chair) conformation, which is in agreement with the NMR results.

In the series of 6-amino-6-deoxyhexonolactams, different intensity of the CD maxima or minima was observed[15] which seemed to be dependent on the axial or equatorial positions of the substituents on C-3 and C-4 of the seven-membered lactam rings and on their distance from the carbonyl group. The relative intensities of the bands changed with the substituents position order *aa*, *ae*, *ea* and *ee*. The present 5-amino-5-

TABLE V
Correlation of the ^{1}H NMR and CD experimental and theoretical (various chiroptical rules) results[a] for 5-amino-5-deoxy-D-pentonolactams

Lactam, configuration	C-2 configuration	Predominant conformation by ^{1}H NMR	Sign of CD extreme[a]			
			observed[b]	theoretical according to rule		
			λ, 219–221 nm	Wolf–Legrand–Bucourt[c]	amide[d]	Meguro[e]
1a, D-*arabino*	*S*	$^3H_4$	+	+	[f]	+
2a, D-*lyxo*	*S*	$^3H_4$	+	+	+	+
3a, D-*ribo*	*R*	$^4H_3$	–	–	–	–
4a, D-*xylo*	*R*	$^4H_3$	–	–	[f]	–

[a] Only bands at 219 and 220 nm are considered; [b] see Table IV; [c] refs[22–24]; [d] refs[25–27]; [e] refs[10,18]; [f] uncertain assignment.

deoxy-D-pentonolactams exhibit also bands with different intensities, but no above mentioned dependence has been found.

The conformational studies of lactams **1a–4a** based on the interpretation of NMR and CD data were compared with the molecular mechanics calculations using MM^+ force field[29]. The values of potential energies (kJ mol^{-1}) having no intrinsic physical meaning were used for comparison of the molecules. For 5-amino-5-deoxy-D-ribonolactam (**3a**) and 5-amino-5-deoxy-D-xylonolactam (**4a**), the $^4H_3$(D) conformation seems to be more favourable while 5-amino-5-deoxy-D-arabinonolactam (**1a**) and 5-amino-5-deoxy-D-lyxonolactam (**2a**) were found to prefer conformation $^3H_4$(D). These results are in agreement with conclusions based on the interpretation of the NMR and CD data. Table VI shows the computed values of the potential energies (kJ mol^{-1}) for the lactams **1a–4a** optimized for both $^3H_4$(D) and $^4H_3$(D) conformations. In the series **1a–4a**, a comparison of the lactam molecules in the preferred conformations shows the dependence of the computed potential energies on the number of equatorial or pseudoequatorial hydroxy groups. Thus lactam **4a** with two equatorial and one pseudoequatorial hydroxy groups in its preferred $^4H_3$(D) conformation exhibited the lowest computed energy in the compared series, the difference between energies of two conformations taken into account being highest among the discussed diastereoisomers. On the other hand, the computed energy of 5-amino-5-deoxy-D-lyxonolactam (**2a**) possessing one pseudoequatorial and two axial hydroxy groups in its preferred $^3H_4$(D) conformation was a highest one. Lactams **1a** and **3a** have one pseudoequatorial, one equatorial and one axial hydroxy groups in their preferred conformations. The molecule of lactam **3a** has a lower computed energy than lactam **1a**. Lactam **1a** exhibits the smallest difference between the energies of molecules in the $^3H_4$(D) or $^4H_3$(D) conformations.

TABLE VI
Potential energy (kJ mol^{-1}) computed using molecular mechanics[29] for $^3H_4$(D) and $^4H_3$(D) conformations of lactams **1a–4a**

Conformation	**1a**	**2a**	**3a**	**4a**
$^3H_4$(D)	0.75	5.53	7.29	13.57
$^4H_3$(D)	3.64	10.0	–0.50	–2.09

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REFERENCES

1. Fleet G. W. J., Ramsden N. G., Witty D. R.: Tetrahedron Lett. *29*, 2871 (1988).
2. Fleet G. W. J., Petursson S., Campbell A. L., Mueller R. A., Behling J. R., Babiak K. A., Ng J. S., Scaros M. G.: J. Chem. Soc., Perkin Trans. 1 *1989*, 665.
3. Hoos R., Naughton A. B., Vasella A.: Helv. Chim. Acta *75*, 1802 (1992).
4. Hoos R., Naughton A. B., Thiel W., Vasella A., Weber W.: Helv. Chim. Acta *76*, 2666 (1993).
5. Hoos R., Vasella A., Rupitz K., Withers S. G.: Carbohydr. Res. *298*, 291 (1997).
6. Overkleeft H. S., van Wiltenburg J., Pandit U. K.: Tetrahedron *50*, 4215 (1994).
7. Cook G. R., Beholz L. G., Stille J. R.: J. Org. Chem. *59*, 3575 (1994).
8. Gibson W. T. (Unilever PLC): Eur. Pat. Appl. 0334586 (1989); Chem. Abstr. *113*, 11926 (1990).
9. Ogura H., Furuhata K., Takayanagi H., Tsuzuno N., Iitaka Y.: Bull. Chem. Soc. Jpn. *57*, 2687 (1984).
10. Meguro H., Konno T., Tuzimura K.: Tetrahedron Lett. *1975*, 1309.
11. Kefurt K., Kefurtova Z., Markova V., Slivova K.: Collect. Czech. Chem. Commun. *61*, 1027 (l996).
12. Hanessian S., Haskell T. H.: J. Heterocycl. Chem. *1*, 55 (1964).
13. Norris P., Horton D., Levine B. R.: Tetrahedron Lett. *36*, 7811 (1995).
14. Tschamber T., Rodriguez-Perez E.-M., Wolf P., Streith J.: Heterocycles *42*, 669 (1996).
15. Kefurt K., Kefurtova Z., Trska P., Blaha K., Fric I., Jary J.: Collect. Czech. Chem. Commun. *54*, 2156 (1989).
16. Haasnoot C. A. G., de Leeuw F. A. A. M., Altona C.: Tetrahedron *36*, 2783 (1980).
17. Legrand M., Rougier M. J. in: *Stereochemistry, Fundamentals and Methods* (H. B. Kagan, Ed.), Vol. 2, p. 142. Thieme, Stuttgart 1977.
18. Konno T., Meguro H., Tuzimura K.: Tetrahedron Lett. *1975*, 1305.
19. Ogura H., Takayanagi H., Furuhata K.: Chem. Lett. 1973, 387.
20. Ogura H., Takayanagi H., Kerbo K., Furuhata K.: J. Am. Chem. Soc. *95*, 8056 (1973).
21. Ogura H., Takayanagi H., Furuhata K.: J. Chem Soc., Perkin Trans. 1 *1976*, 665.
22. Wolf H.: Tetrahedron Lett. *1965*, 1075.
23. Wolf H.: Tetrahedron Lett. *1966*, 5151.
24. Legrand M., Bucourt R.: Bull. Soc. Chim. Fr. *1967*, 2241.
25. Schellman J. A., Oriel P.: Chem. Phys. *37*, 2114 (1962).
26. Litman J., Schellman J. A.: J. Phys. Chem. *67*, 978 (1965).
27. Schellman J. A.: Acc. Chem. Res. *1*, 144 (1968).
28. Kefurt K., Snatzke G., Snatzke F., Trska P., Jary J.: Collect. Czech. Chem. Commun. *41*, 3324 (1976).
29. *HyperChem for Windows, Rel. 2, 1992*, Autodesk, Inc.
30. Herdeis C., Waibel C.: Arch. Pharm. *324*, 269 (1991).