Research article

MRC

Received: 25 March 2014 Revised: 15 July 2014 Accepted: 16 July 2014 Published online in Wiley Online Library: 19 August 2014

(wileyonlinelibrary.com) DOI 10.1002/mrc.4123

Dynamic NMR study of cyclic derivatives of pyridoxine

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A series of pyridoxine derivatives was investigated by ^{1}H and 2D nuclear overhauser enhancement spectroscopy (NOESY) NMR. The free energies of activation for the pyridyl-oxygen rotation of the 2,4-dinitrophenyl ether of the seven-membered acetals of pyridoxine were measured by dynamic NMR. A conformational exchange between the *chair* and *twist* forms of the seven-membered acetal ring was confirmed by dynamic NMR and STO3G computations. Copyright © 2014 John Wiley & Sons, Ltd.

Keywords: dynamic ^{1}H NMR; energy barrier; pyridoxine

Introduction

NMR has been proven to be a powerful tool for conformational analysis and the investigation of stereodynamic processes.[1,2] Seven-membered heterocycles are interesting compounds for nuclear magnetic resonance studies because of the wide range of different structural types of these molecules.

Seven-membered cyclic acetals with planar fragments exist in solution in the dynamic equilibrium in the following two forms: the *chair* and the *twist*.[3–5] Previous studies have revealed certain correlations between the steric structure and the reactivity of these compounds.[6–9] In this study, we present the results of the investigation of the derivatives of pyridoxine **(I–IV)** by dynamic NMR spectroscopy.

The studied compounds have been reported as novel organic nonlinear optical (NLO) materials.[10,11] These materials exhibit physicochemical properties suitable for second harmonic generation. The possibility of creating efficient lasers based on the synthesized compounds directly depends on their physicochemical properties, which are closely related to the three-dimensional structure of the molecules. Therefore, the study of the spatial structure of these compounds and the dynamics of their molecular motion in solution is a real and is currently an interesting problem.

Compounds **(I–IV)** contain a seven-membered acetal ring with a 2,4-dinitrophenyloxy ortho-substituent (Fig. 1). This molecular configuration provides a good opportunity to study the influence of the rotation around the pyridine-oxygen bond on the conformation of the acetal ring, which is involved in the rapid conformational exchange between the different forms at an ambient temperature.[12]

Experimental section

Materials and NMR data acquisition

Compounds **(I–IV)** were synthesized as described in the patent.[10]

All of the NMR experiments were performed on a Bruker Avance II-500 NMR spectrometer equipped with a 5 mm probe using standard Bruker TOPSPIN software. The ^{1}H NMR data were collected with 32 k complex data points and were apodized with a Gaussian window function (lb = −0.5 and gb = 0.2) prior to Fourier transformation. ^{1}H NMR spectra were recorded using 90^0 pulses, a delay between pulses of 2 s, a spectrum width of 10 ppm and a minimum of ten scans. Signal-to-noise enhancement was achieved by multiplication of the FID with an exponential window function (lb = 3 Hz). The accuracy of the chemical shifts was at least 0.02 ppm, and the constant spin–spin interaction was at −0.5 Hz.

The assignments of the ^{1}H and ^{13}C NMR signals for the entire set of compounds were achieved from the signal multiplicities, the integral values and the characteristic chemical shifts from the through-bond correlations in the 2D correlated spectroscopy (COSY) spectra, the through-space correlations in the 2D nuclear overhauser enhancement spectroscopy (NOESY) spectra and from the ^{1}H–^{13}C heteronuclear correlations in the 2D heteronuclear single-quantum correlation (HSQC) and heteronuclear multiple bond correlation (HMBC) spectra.

All two-dimensional experiments were performed with 2 k × 512 data points; the number of transients (2–16 scans) and the sweep widths were optimized individually. In the homonuclear ^{1}H, ^{1}H COSY (Bruker pulse program *cosygpqf*) and NOESY (*noesygpph*) experiments, the relaxation delay was set to 1.5 s, and the 90° pulse length to 10.4 μs. The resulting FIDs were zero-filled to a 2 k × 1 k data matrix and apodized with a sine function for COSY and a shifted sine function for NOESY in both the ω1 and ω2 dimensions prior to Fourier transformation. 2D NOESY experiments were performed with pulsed filtered gradient techniques. The mixing time was 0.15 s. Heteronuclear spectra were recorded with 2 k × 512 data points, zero-filled in F1 to a 2 k × 512 data matrix, and apodized in both dimensions with a shifted sine function. HSQC experiments (*hsqcetgpsp*) were acquired using adiabatic pulses for inversion of ^{13}C and GARP-sequence for broadband ^{13}C-decoupling, optimized for ^{1}J (CH) = 145 Hz. The 90 ^{13}C pulse length was 7.5 μs. ^{1}H, ^{13}C long-range spectra HMBC (*hmbcgplpndqf*) were performed with ^{n}J(CH) set to 8 Hz.

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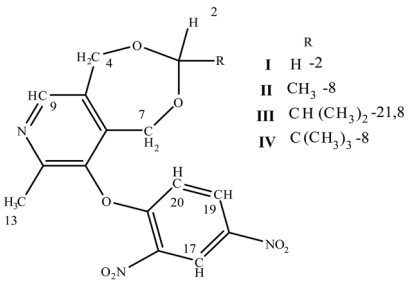

Figure 1. Molecular structures of compounds **I** R = H, **II** R = CH_3, **III** R = $CH(CH_3)_2$, **IV** R = $C(CH_3)_3$.

The dynamic ^{1}H NMR spectra were recorded at different temperatures over the range of 203–323 K every 5 K. Temperature control was achieved using a Bruker variable temperature unit (BVT-2000) in combination with a Bruker cooling unit (BCU-05) to provide chilled air. The experiments were performed without sample spinning.

The NMR samples were prepared by additional dissolving in an acetone-d_6 solvent. Chemical shifts are given in values of ppm, referenced to a residual solvent signals (2.07 for ^{1}H, 30.5 and 205.1 for ^{13}C). All of the samples were prepared in standard 5-mm ampoules. The working concentrations of the substances were 0.5% by weight, the solution volume was 0.6 mL, and the stabilizing magnetic field was carried by the deuterium signals of the solvent.

For the full line shape analysis, the WinDNMR-Pro 7.1.14 program designed by Hans J. Reich at the University of Wisconsin was used.[13] As an input to the program, the chemical shifts, the transverse relaxation times T_2^* and the constants of the spin–spin interaction were used. Calculation of a rate constant (k) was performed by full line shape analysis using the following expressions:

$$P_1(k_{ab}) = P_2(k_{ba}); P_1 + P_2 = 1$$

where P_1 and P_2 represent the populations of the relevant conformers A and B in the resulting NMR signal.

The activation parameters were calculated using the Eyring equation. The errors in the determination of the $\Delta H^{\neq}$ and $\Delta G^{\neq}$ activation parameters were less than 4 and 1 kJ/mol, respectively.[14,15]

The free energy of activation of first-order monomolecular reversible reactions, which include intramolecular rotation processes and interconversions of cyclic systems, can be found using the following equations:[16–18]

$$A \underset{k_{ab}}{\overset{k_{ab}}{\rightleftharpoons}} B$$

$$\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq}$$

$$\ln(k/T) = -\Delta H^{\neq}/RT + \Delta S^{\neq}/R + 23.76$$

where $\Delta H^{\neq}$ and $\Delta S^{\neq}$ correspond to the activation enthalpy and entropy, respectively, T is the temperature in K and R is the universal gas constant.

Results and discussion

Dynamic NMR study of 9-(2,4-dinitrophenyloxy)-8-methyl-1,5-dihydro-[1,3]dioxepino[5,6-c]pyridine (I)

The chemical structure of compound **I** was confirmed by the results of the 1D ^{1}H, ^{13}C and 2D NMR experiments. The signals in the ^{1}H NMR spectrum (Fig. 2) were assigned using the 2D ^{1}H–^{1}H COSY, 2D ^{1}H–^{13}C HSQC, 2D ^{1}H–^{13}C HMBC and 2D NOESY NMR spectra at room temperature and at a temperature of 203 K. The ^{1}H NMR chemical shifts are presented in Table 1.

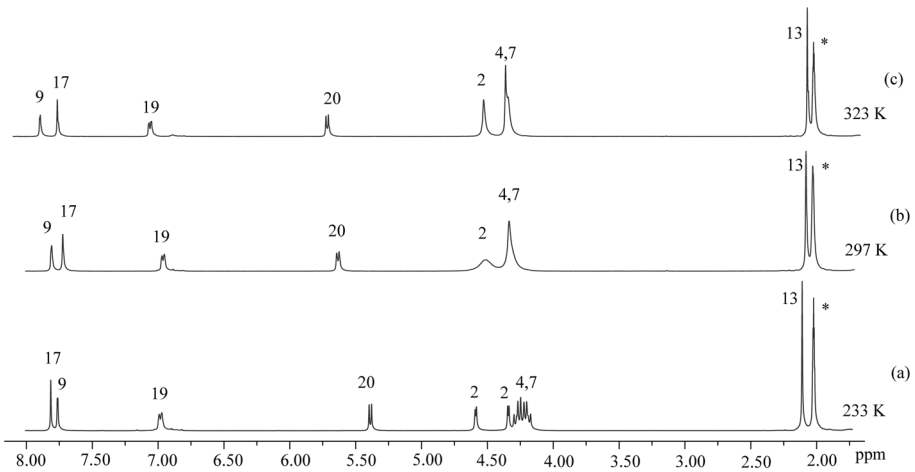

Figure 2. The ^{1}H NMR spectra of compound **I** dissolved in acetone-d_6 at a temperature of 233 K (a), 297 K (b) and 323 K (c). The solvent signal is marked by «*».

Table 1. ^{1}H NMR spectra parameters (δ, ppm) and spin–spin interaction constants (J, Hz) of compound **I** in acetone-d_6 at different temperatures*

T, K	CH-9	CH-17	CH-19	CH-20	CH_3-13	CH_2-2	CH_2-4	CH_2-7
323	8.08	7.95	7.26 d (9.2)	5.72 d (9.1)	2.12	4.55	4.38	4.36 b
297	8.03	7.95	7.20 d (9.2)	5.64 d (9.1)	2.12	4.53 b	4.53 b	4.35 b
233	7.89	7.94	7.05 d (9.2)	5.41 d (9.1)	2.17	4.37, 4.62 m (5.1)	4.27 q (26.8, 15.3)	4.27 q (49.8, 14.4)

*d, douplet; Q, quadruplet; m, multiplet b, broadened signal.

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In the ^{1}H NMR spectra of compound **I**, the signals of the aromatic protons CH-17, CH-19 and CH-20, the methyl protons CH_3-13 of the substituent at the pyridoxine base and the CH-9 proton are observed. The line shape of the signals of the CH_2-2, CH_2-4 and CH_2-7 methylene protons of the heterocyclic pyridoxine portion of the molecule strongly depends on the temperature. With a decreasing temperature, the signals are broadened. At a low temperature (233 K), the CH_2-2 methylene signals are divided into two doublets with equal intensity (J = 5.1 Hz). The splitting is explained by the spin–spin interaction between the geminal protons. However, each of the CH_2-4,7 methylene protons are displayed in the form of AB-quadruplets.

To define the type of exchange process that is observed for compound **I**, an analysis of the line shape of the NMR signals was performed (Fig. 3). The temperature dependence of the chemical exchange rate constant *k* for the CH_2-2 signal is shown in Fig. 4. The results of the energy parameters calculation are presented in Table 1.

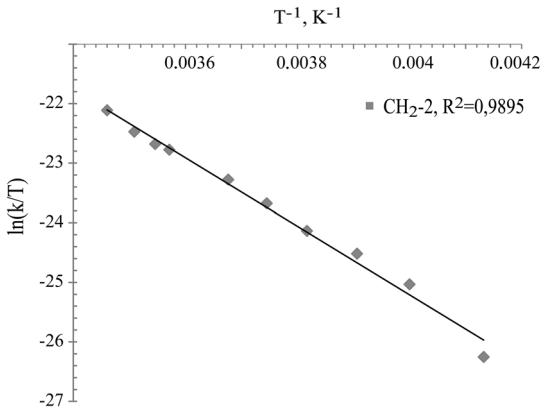

Figure 4. Temperature dependence of the exchange rate constant of the CH_2-2 signal for the compound **I**.

Dynamic NMR study of 9-(2,4-dinitrophenyloxy)-3,8-dimethyl-1,5-dihydro-[1,3]dioxepino[5,6-c]pyridine (II)

To confirm the chemical structure of compound **II**, ^{1}H and ^{13}C NMR experiments were performed. The assignment of the signals in the ^{1}H NMR spectrum (Fig. 5) was performed similarly to compound **I**. The ^{1}H NMR chemical shifts are presented in Table 2.

In the ^{1}H NMR spectrum of compound **II** dissolved in acetone at a temperature of 298 K, the signal of the methyl CH_3-13 protons at $\delta = 2.36$ ppm is a singlet. A doublet at 1.31 ppm was assigned to the CH_3-8 protons. The CH-17, 19, 9, 20 and 2 protons resonate at 8.95, 8.50, 8.40, 7.03, 5.17 ppm, respectively. The diastereotopic protons of the CH_2-4 and CH_2-7 methylene group signals have chemical shifts over the range of $\delta = 4.50$–5.10 ppm. A well-resolved AB-quadruplet is observed for the CH_2-4 group. The CH_2-7 signal is broadened at room temperature.

The CH_2-7, CH-19 and CH-20 signals are broadened at room temperature as a result of the participation of the compound in the partially decelerated process of a conformational exchange. To accelerate this process and to obtain a well-resolved spectrum, experiments with increasing temperatures were performed. With an increasing temperature, the CH_2-7 lines are narrowed and at a temperature of 323 K, the CH_2-7 signals appear in the spectrum as an AB-quadruplet from the diastereotopic protons of the methylene groups (Fig. 5(d)).

The experiments with increasing temperatures showed that the investigated compound participates in a conformational exchange process. To obtain the energetic parameters and to define the type of the observed conformational exchange, process experiments with decreasing temperatures were performed.

With a decreasing temperature, the line shape of the signals in the ^{1}H NMR spectrum of compound **II** changed (Fig. 5(a)). The CH_2-7 proton signals initially broadened; then, a coalescence of the signals was observed, and finally, at a temperature of 203 K, these protons appeared in the spectrum as two AB-quadruplets. For the CH_2-4 signals, a similar evolution of the line shape was observed, but the difference between the chemical shifts of the geminal proton signals was less than that observed for one of the CH_2-7 protons as a result of the greater distance from the rotating

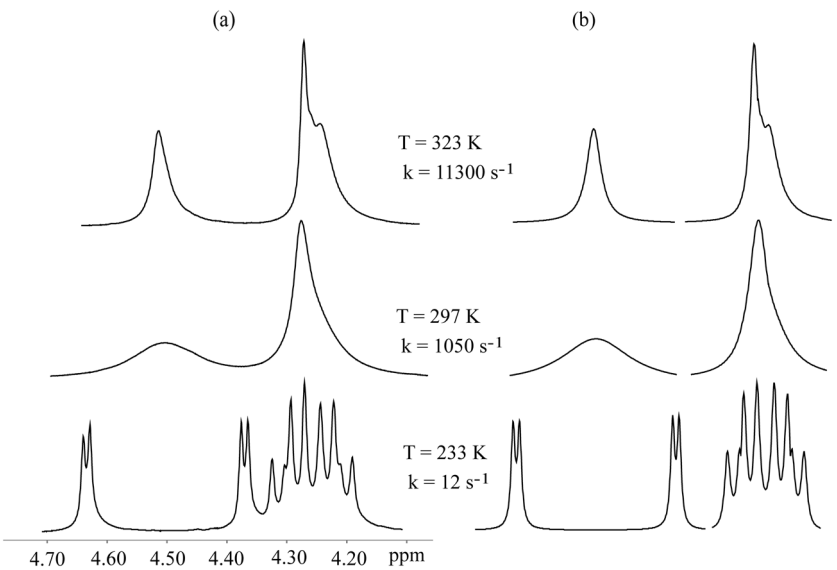

Figure 3. Line shape analysis of the CH_2-2 signal of compound **I** and the exchange rate constants at different temperatures: (a) experimental ^{1}H NMR spectrum; (b) calculated ^{1}H NMR spectrum.

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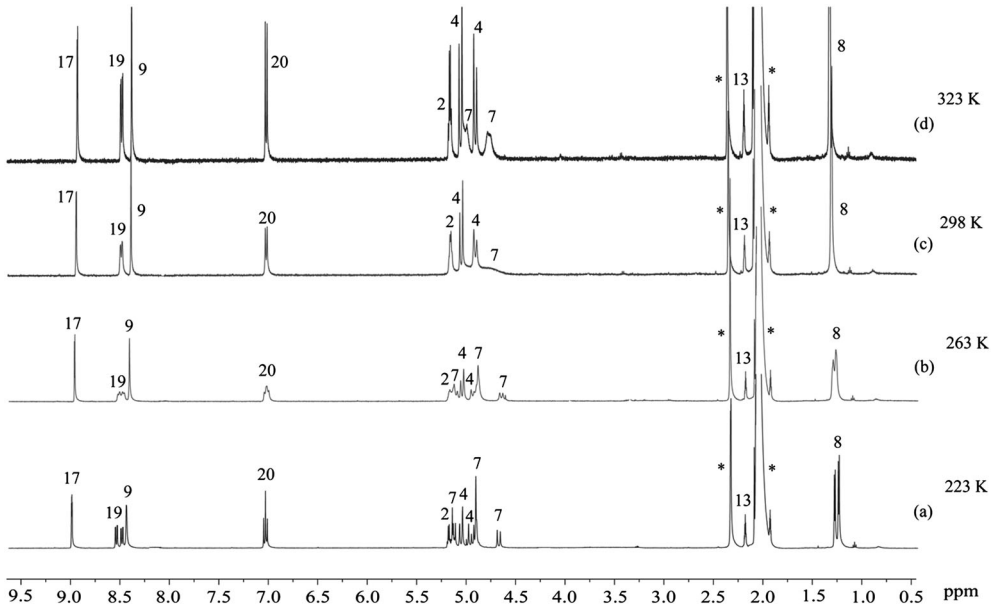

Figure 5. The ^{1}H NMR spectra of compound **II** dissolved in acetone-d_6 at a temperature of 203 K (a), 263 K (b), 298 K (c) и 323 K (d). The solvent signal is marked by «*».

Table 2. ^{1}H NMR spectra parameters (δ, ppm) and spin–spin interaction constants (J, Hz) of compound **II** in acetone-d_6 at different temperatures*

T, K	CH-9	CH-17	CH-19	CH-20	CH_3-13	CH_3-8	CH-2	CH_2-4	CH_2-7
323	8.38	8.93 d (2.8)	8.47, 8.49 m (2.8)	7.01, 7.03 d (9.2)	2.36	1.31d (5.2)	5.17 m	4.98 q (73.9, 14.7)	4.89 q (120.1, 15.5)
298	8.40	8.95 d (2.8)	8.48 b, 8.50 b	7.02 b, 7.04 b	2.36	1.31d (5.2)	5.17 m	4.98 q (73.9, 14.7)	4.89 b
263	8.42	8.98 d (2.8)	8.47 b, 8.49 b, 8.52 b, 8.54 b	7.02 b, 7.04 b, 7.06 b	2.35	1.28 b, 1.31 b	5.14b, 5.18 b	4.90b, 4.98b	4.92b, 5.04b
203	8.45	9.00, 9.01 m (2.8)	8.49, 8.51 m, 8.55, 8.57 m (2.8)	7.04, 7.06, m (9.2)	2.34, 2.35 d	1.25, 1.29 m (5.2)	5.15, 5.20 m (5.2)	4.92b, 5.02 q (46,4, 14.7)	4.92 q (227.2,15.5), 5.07 q (73.2, 15.5)

*d, douplet; q, quadruplet; m, multiplet b, broadened signal.
Notation: chemical shifts of dominant form signals is underlined.

portion of the molecule. The line shape of the other signals also changed with the temperature variation. A number of signals in the ^{1}H NMR spectrum of compound **II** at a temperature of 203 K doubled compared with the spectrum at room temperature. An analysis of the integral intensities of the signals assigned to the different conformations showed that they are presented in a solution in the ratio of 1:1.06. The difference between the Gibbs free energy, ΔG_0, of the two conformations was calculated using the following formula:[19]

$$\Delta G_0 = -RT \ln(P_1/P_2)$$

To determine the energy parameters of the conformational transitions, a line shape analysis of the NMR signals at different temperatures was performed. The change in the ratio of the different conformations with the temperature variation was controlled based on certain values of ΔG_0 under the assumption that $\Delta S = 0$.

A comparison of the theoretical and experimental fragments of the spectra containing the CH-19 signal at different temperatures is shown in Fig. 6. The temperature dependence of the chemical exchange rate constant *k* is shown in Fig. 7. All of the obtained activation parameters are presented in Table 5.

Dynamic NMR study of 9-(2,4-dinitrophenyloxy)-3-(isopropyl)-8-methyl-1,5-dihydro-[1,3]dioxepino[5,6-c]pyridine (III)

The signals in the ^{1}H NMR spectrum of compound **III** (Fig. 8) were assigned similarly to compound **I**. The ^{1}H NMR chemical shifts are presented in Table 3.

The signals of the CH_2-7 protons of the seven-membered ring are broadened in the spectrum at room temperature (Fig. 8(c)). Therefore, this compound participates in a partially decelerated conformational exchange process. To investigate this process, NMR experiments with decreasing temperatures were performed.

With a decreasing temperature, the line shape of the diastereotopic protons of the CH_2-4 and CH_2-7 methylene groups changed. Finally, the line shapes were observed as four AB-quadruplets at a temperature of 203 K (Fig. 8(a)). Two AB-quadruplets of the CH_2-4 protons and one AB-quadruplet of the CH_2-7 protons were well resolved in the spectrum. The second AB-quadruplet of the CH_2-7 protons appeared in the

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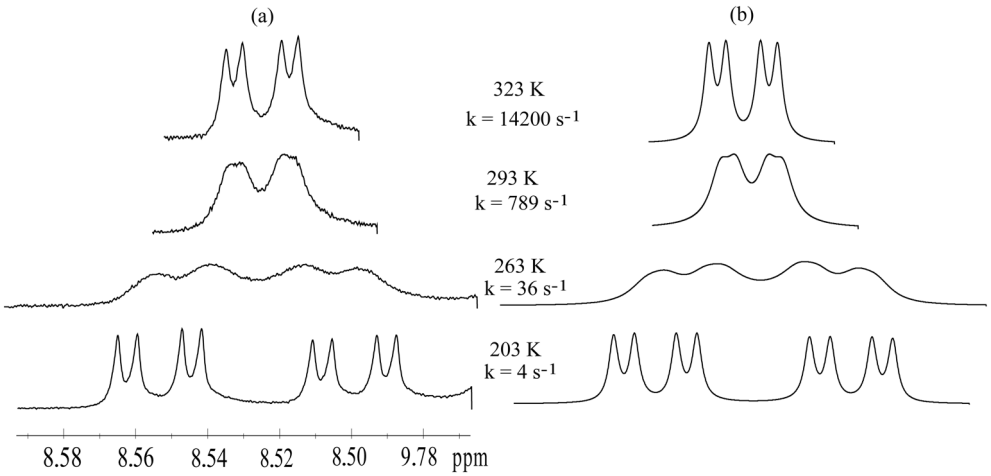

Figure 6. Line shape analysis of the CH-19 signal of compound **II** and the exchange rate constants at different temperatures: (a) experimental ^{1}H NMR spectrum; (b) calculated ^{1}H NMR spectrum.

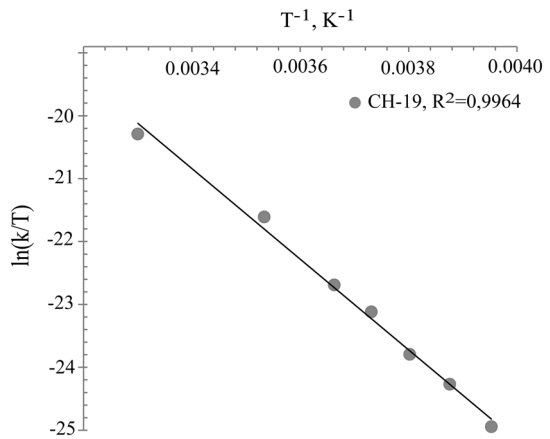

Figure 7. Temperature dependence of the exchange rate constant of the CH-19 signal for the compound **II**.

spectrum as a broadened signal with a chemical shift of 4.92 ppm. A number of signals assigned to the protons at the C-17, C-19, C-20, C-13, C-2, C-21 and C-8 carbons doubled compared with the spectrum at room temperature. The integral intensities of the signals belonging to the different conformations allowed a comparison of their ratios in the solution, which was determined as 1:1.14.

Similar to the previous case, the energy parameters of the conformational exchange were defined using a line shape analysis of the NMR signals using the WINDNMR-Pro software. The parameters of the energy barrier of the rotation of the dinitrophenyl fragment around the C–O bond in compound **III** are presented in Table 5.

Dynamic NMR study of 9-(2,4-dinitrophenyloxy)-3-(tert-butyl)-8-methyl-1,5-dihydro-[1,3]dioxepino[5,6-c]pyridine (IV)

Similar NMR studies were performed for compound **IV** (Fig. 9). The ^{1}H NMR chemical shifts are presented in Table 4.

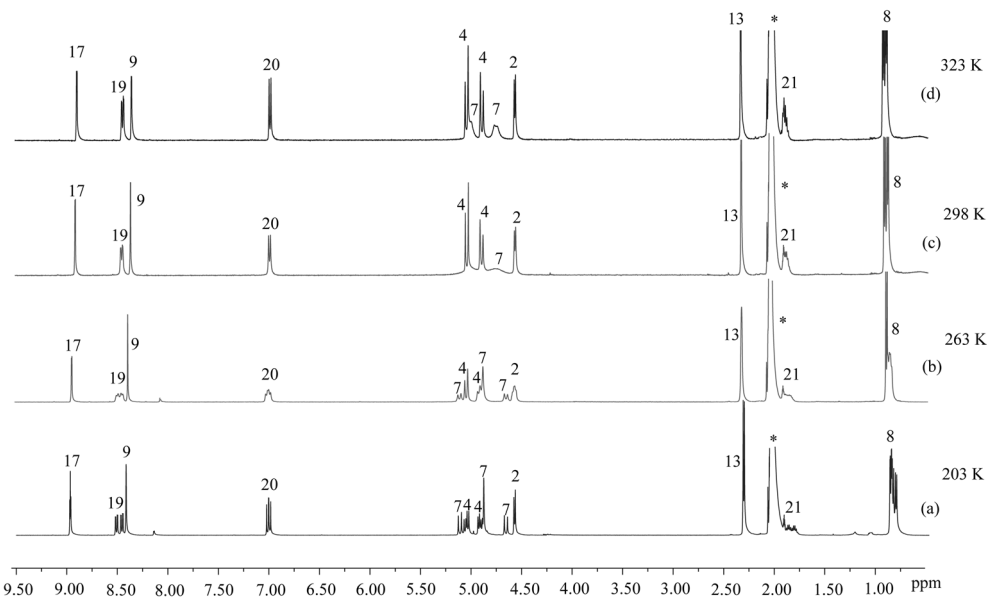

Figure 8. The ^{1}H NMR spectra of compound **III** dissolved in acetone-d_6 at a temperature of 203 K (a), 263 K (b), 298 K (c) and 323 K (d). The solvent signal is marked by «*».

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Table 3. ^{1}H NMR spectra parameters (δ, ppm) and spin–spin interaction constants (J, Hz) of compound **III** in acetone-d_6 at different temperatures*

T, K	CH-9	CH-17	CH-19	CH-20	CH_3-13	CH-21	$(CH_3)_2$-8	CH-2	CH_2-4	CH_2-7
323	8.39	8.93 d (2.8)	8.47, 8.49 m (2.8)	7.01, 7.03 d (9.3)	2.36	1.93 m	0.92, 0.95 m (6.7)	4.59, 4.61d	5.06 b, 5.00 q (75.2, 14.5)	4.91 b
298	8.40	8.95 d (2.8)	8.48 b, 8.50 b	7.02 b, 7.04 b	2.36	1.92 m	0.91, 0.94 m (6.7)	4.59, 4.61 d	5.06 b, 5.00 q (75.2, 14.5)	4.91 b
263	8.43	8.98 b	8.47 b, 8.49 b, 8.52 b, 8.54 b	7.01 b, 7.03 b, 7.04 b, 7.06 b	2.35	1.89 b	0.88 b, 0.92 m (6.7)	4.60 b	4.91 b, 5.00 q (77.5, 14.5)	4.91q (230.7, 15.5)
203	8.46	9.00, 9.01 m (2.8)	8.49, 8.51 m, 8.54, 8.56 m (2.8)	7.03, 7.04, 7.05, 7.07 m (9.3)	2.34, 2.35 d	1.84, 1.90 m	0.89 b, 0.85 m (6.7)	4.61, 4.62 m	5.02 q (76.3, 14.5), 5.02 q (60.5, 14.5)	4.92 b, 4.93 q (227.9, 15.5)

*d, douplet; q, quadruplet; m, multiplet; b, broadened signal.
Notation: chemical shifts of dominant form signals are underlined.

The signals of the CH_2-4 group are observed as a well-resolved AB-quadruplet in the spectrum at room temperature, but the signal of the CH_2-7 group is broadened (Fig. 9(b)).

The signals of CH_2-7, CH-19, CH-20 and CH-2 are broadened in the ^{1}H NMR spectrum at room temperature because of the participation of compound **IV** in the partially decelerated conformational exchange process. To accelerate this process, experiments with increasing temperatures were performed.

With an increasing temperature, the CH_2-7 signals narrowed, and at a temperature of 323 K, they were observed as a well-resolved AB-quadruplet (Fig. 9(c)). Moreover, the narrowing of the line shape led to a splitting of the CH-19, CH-20 and CH-2 signals.

As shown in the dynamic NMR experiments, the investigated compound is involved in a conformational exchange process. The NMR experiments with a decreasing temperature showed that the line shape of the NMR signals changed with the temperature variation (Fig. 9(a)). The CH_2-4 and CH_2-7 signals initially broadened; then, a coalescence of the signals was observed, and finally, at a temperature of 203 K, these signals resonated as four AB-quadruplets. The other signals showed the same line shape evolution.

An analysis of the integral intensities of the signals related to different conformations showed that they are present in solution in a proportion of 1:1.66 (Fig. 9(a)). The nonequivalence of the CH_2-4 AB-system protons is negligible, and the J-coupling constants are nearly the same for the signals of the two conformations, indicating that the observed conformations have a C_s plane of symmetry. Therefore, based on the results of previous studies,[20,21] we concluded that the seven-membered cycle of compound **IV** is present in the *chair* conformation in solution. The results of the conformational exchange energy parameter calculations are shown in Table 5.

Analysis of the activation parameters of the conformational process

The studied compounds contain a seven-membered acetal ring with a 2,4-dinitrophenyloxy ortho-substituent. Therefore, there are two conformational processes that can be determined by DNMR (Fig. 10). The first process is the rotation around the pyridine–oxygen bond. The second process is the dynamic equilibrium between the *chair* and *twist* conformations of the seven-membered acetal ring.

Therefore, there are eight possible conformations for compound **I** (the R_a/S_a orientations of the ether moiety, the P/M twist conformations and the P/M chair conformations), resulting in four pairs of enantiomers (the R_a,P-twist/S_aM-twist, the S_a,P–twist/R_a,M-twist, the R_a,P-chair/S_a,M-chair and the S_a,P–chair/R_a,M-chair). The appearance of a chiral atom in compounds **II–IV** leads to the following six pairs of enantiomers (in this case, only one chair conformation is allowed, which depends on the configuration of the chiral atom): the R,R_a,P-twist/S,S_a,M-twist, the R,S_a,P–twist/S,R_a,M-twist, the S,R_a,P-twist/R,S_a,M-twist, the S,S_a,P–twist/R,R_a,M-twist, the R,R_a,chair/S,S_a,chair and the R,S_a,chair/S,R_a,chair (Fig. 10).

The *chair–twist* conformational equilibrium depends on the volume of the substituents at the acetal carbon atom,[3,4] and compounds with a 'bulky' substituent, such as tert-butyl, contain the *chair* form of the ring. However, in the case of a relatively small substituent, such as methyl or isopropyl, the ratio of the *twist* conformation increases.[22,23]

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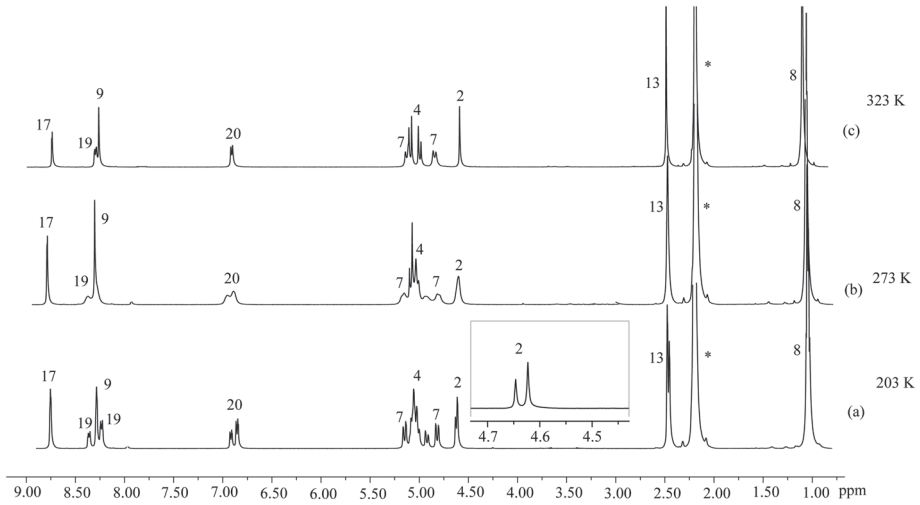

Figure 9. The ^{1}H NMR spectra of compound **IV** dissolved in acetone-d_6 at a temperature of 203 K (a), 273 K (b), 323 K (c). The solvent and impurities signals are marked by «*».

Table 4. ^{1}H NMR spectra parameters (δ, ppm) and spin-spin interaction constants (J, Hz) of compound **IV** in acetone-d_6 at different temperatures*

T, K	CH-9	CH-17	CH-19	CH-20	CH_3-13	$(CH_3)_2$-8	CH-2	CH_2-4	CH_2-7
323	8.45	8.95 d (2.8)	8.48 b	7.02 b	2.37	0.91	4.59	5.06 q (42.1, 14.3)	5.00 q (190.2, 14.5), 5.01b
273	8.48	8.98 d (2.8)	8.45 b, 8.56 b	6.99 b, 7.07 b	2.37	0.89	4.59 b, 4.62 b	5.07 q (35.2, 14.3)	5.00 b
203	8.51, 8.52 d	9.01, 9.02 m (2.8)	8.46, 8.48, 8.59, 8.61 m (2.8)	6.99, 7.01, 7.06, 7.08 m (9.3)	2.34, 2.37 d	0.86, 0.85 d	4.62, 4.65 d	5.09 q (36.3, 14.3), 5.09 q (19.8, 14.3)	5.02 q (176.0, 14.5), 5.03 q (73.5, 14.9)

*d, douplet; q, quadruplet; m, multiplet; b, broadened signal.
Notation: chemical shifts of dominant form signals are underlined.

Table 5. Activation parameters of the rotation of dinitrophenyl fragment around the C–O bond for the compounds **I**, **II**, **III**, **IV**. All values are obtained for acetone-d_6 solvent

No. of the compound	**I** R: H		**II** R: CH_3		**III** R: $CH(CH_3)_2$		**IV** R: $C(CH_3)_3$
Analyzed signal	CH_2-2,4,7	CH-19	CH_3-8	CH_2-4,7	CH-20	CH-19	CH-19
$\Delta G^{\neq}_{203k}$, kJ/mol	52.8	51.0	51.1	51.0	50.9	50.9	50.1
P_1 /P_2	—		1/1.06		1/1.14		1/1.66
ΔG_0 kJ/mol	-		0.1		0.2		0.9

* Error in $\Delta G^{\neq}$ calculation is less than 1 kJ/mol

As observed in Table 5, the energy barriers of exchange for the studied compounds are close to each other and to the value of the rotational barriers of the dinitrophenyl fragment around the C–O bond.[24]

This fact and the ratio of the resulting conformers indicates that an observed process is the rotation around the pyridine–oxygen bond, whereas the *chair* and *twist* conformations are in a rapid exchange.

The effect of the second process on the NMR spectrum can be observed with a further temperature decrease from 257 to 203 K. There are no significant NMR line shape evolutions. However, this temperature change leads to a change in the NMR spectral parameters, such as the chemical shifts δ and the nonequivalence Δν of the geminal CH_2-4 protons of the corresponding AB-system signals (Fig. 11).

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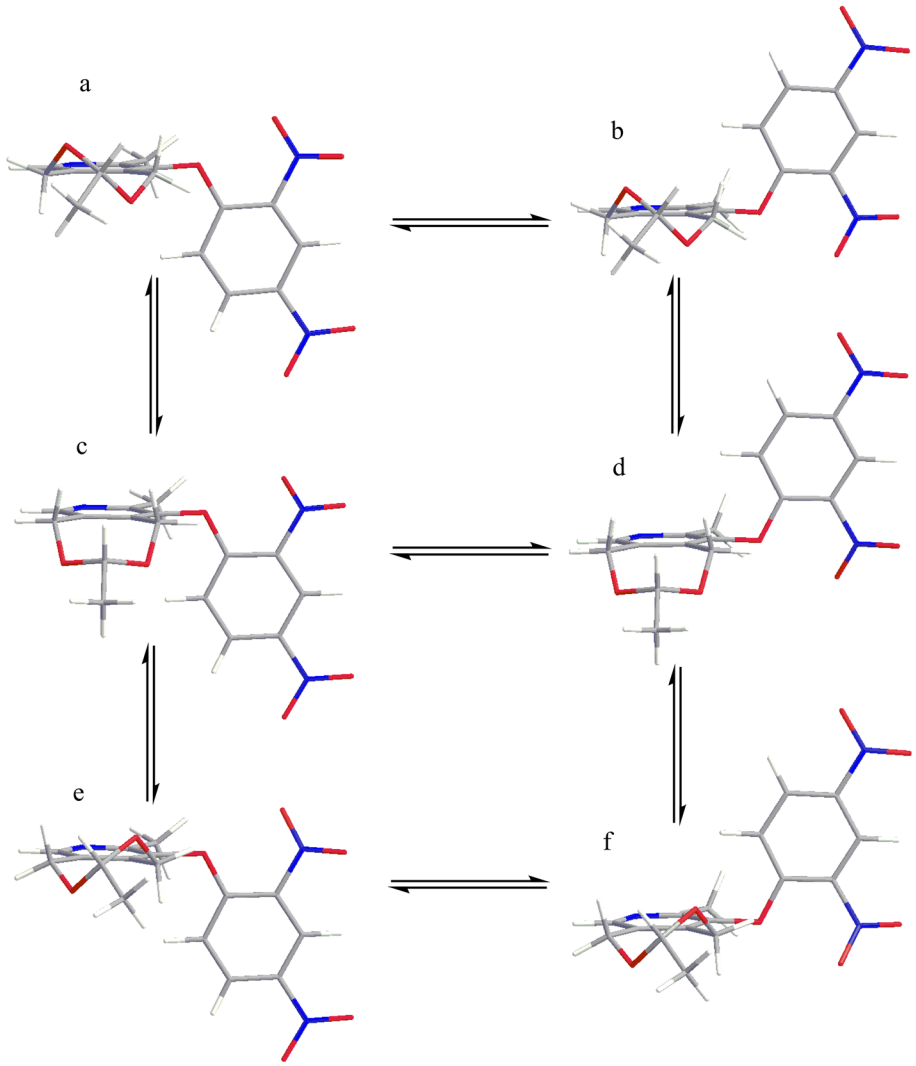

Figure 10. Conformational transformations of 9-(2,4-dinitrophenyloxy)-3,8-dimethyl-1,5-dihydro-[1,3]dioxepino[5,6-c]pyridine (**II**). Conformations: a) RR_aM-twist; b) RS_aM-twist; c) R,R_a,chair; d) R,S_a,chair; e) RR_aP-twist; f) RS_aP-twist.

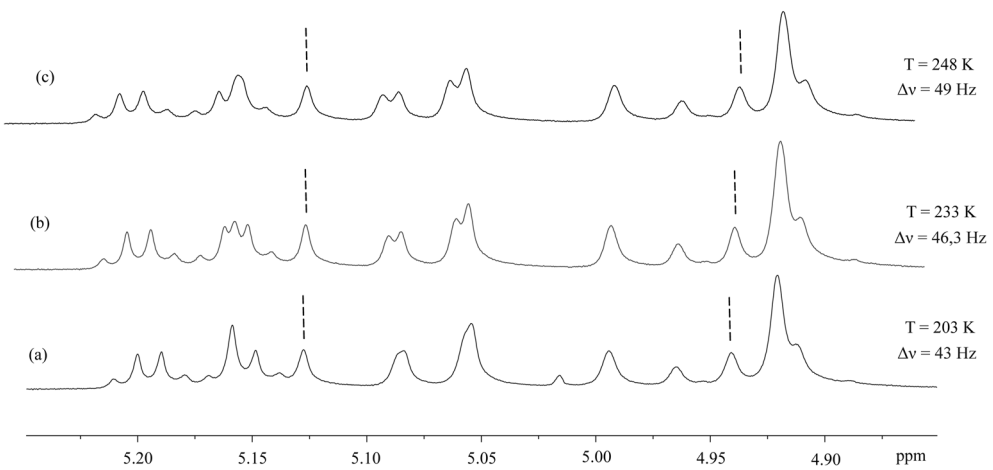

Figure 11. The fragments of ^{1}H NMR spectra of the compound **II** dissolved in acetone-d_6 at a temperature 203 K (a), 233 K (b), 248 K (c) and corresponding nonequivalences ($\Delta\nu$) of the geminal CH_2-4 protons signals. Dashed lines are shown for tracking of small changes of nonequivalences.

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Presumably, this phenomenon is explained by the existence in solution of a certain fraction of compounds (**II** and **III**) in a *twist* conformation, as has been described in the literature[22,23].

The NMR spectra of the rapidly exchanging conformations of one compound contain information about the spectral characteristics of each conformer and its abundance in a solution. At a certain temperature, it is possible to measure the statistically averaged parameter *y* (where *y* can represent the chemical shift δ, the nonequivalency Δν or the J-coupling constant). The relationship between the averaged parameter *y* and the spectral characteristics of each individual conformer is described by the following equation[23]:

$$< y >= \sum_{i}^{n} P_i * y_i$$

where P_i is the content of each conformation in solution. The summation is performed on the possible equilibrium states.

For the case of the bilateral exchange, the following equation applies: $P_1 + P_2 = 1$. The seven-membered cyclic portion of the considered compounds can be present in solution in the following two equilibrium states: the *chair* and the *twist* with P_c and P_t content respectively. The nonequivalence Δν of the geminal CH_2-4 proton signals is considered as the *y* parameter. The dependence of Δν on the temperature for compounds **II**, **III** and **IV** is shown in Fig. 12.

Figure 10 shows that the temperature changes do not affect the value of the nonequivalence Δν of the geminal CH_2-4 AB-system protons of compound **IV**. Therefore, this result confirms the rigid *chair* conformation of the seven-membered cycle. In contrast to compound **IV**, the Δν value of the same signals of compounds **II** and **III** strongly depends on the temperature, thus showing the changes in the conformational equilibrium between chair and twist forms.

To confirm this reasoning, *ab initio* STO3G calculations of the relative energy of the stable conformations for compounds **I–IV** were performed (Table 6) using the HyperChem 8 software. The computations were performed in vacuo as a result of the slight influence of the solvent on the equilibrium of the chair and twist forms. The differences in the ratios of the chair conformation of the 2-R-1,3-dioxacyclohept-5-enes (R = H, CH_3, $CH(CH_3)_2$, $C(CH_3)_3$) dissolved in dioxane and in acetone are 1% or less [6]. The ratio of each conformer (Table 6) was calculated using the following equation:

$$P_i = \frac{\omega_i}{\sum_{i=0}^{n} \omega_i}$$

where P_i is the ratio of each conformer and ω_i is a frequency distribution derived from the Boltzmann distribution, as follows:

$$\omega_i = \frac{\exp\left(-\frac{\Delta G_i}{RT}\right)}{\exp\left(\sum_{i=0}^{n}\left(-\frac{\Delta G_i}{RT}\right)\right)}$$

where ΔG_i is the relative free energy of each conformer and T is the temperature in K.

The calculated data are in good agreement with the results of the DNMR study, confirming the dynamic equilibrium between the *chair* and *twist* conformations for compounds (**II** and **III**), whereas compound **IV** exists only in the rigid chair conformation. The ratio of the S_a and R_a conformers strongly depends on the solvent (for compound **IV**, the ratio is 1:1.66 in acetone-d_6 and 1:3.67 in CS_2 + $CDCl_3$) and cannot be measured with the calculated data. However, certain correlations remain; the ratio is nearly equal for compounds (**II** and **III**), and it rises significantly for compound **IV**.

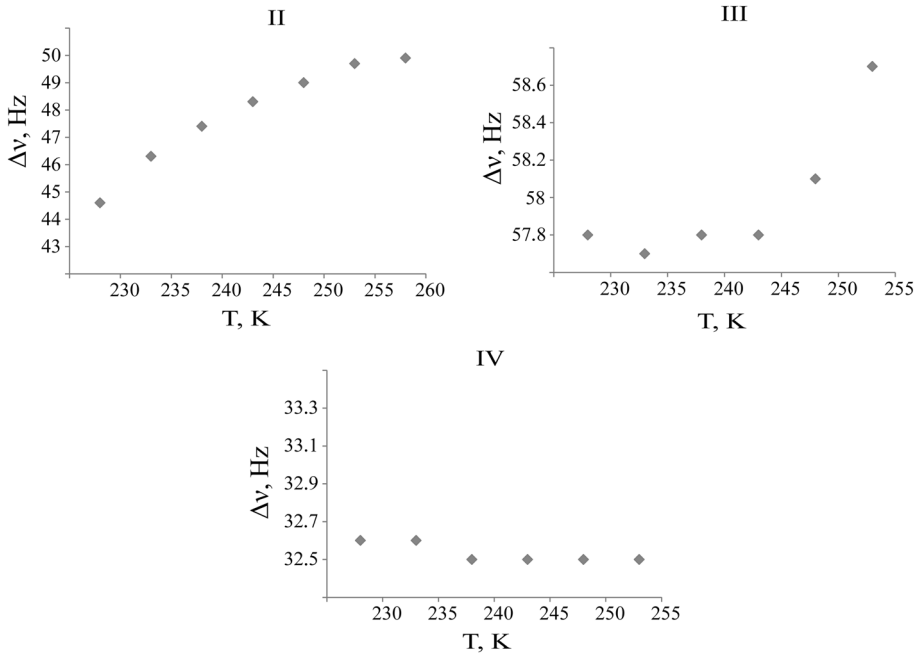

Figure 12. The dependences of nonequivalence Δν of geminal CH_2-4 protons signals from a temperature. Plots signed by the numbers of the compounds (according to Fig. 1).

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Table 6. Relative free energies (G) and ratio of conformers (P)* for compounds **I–IV**

Conformation	Compound **I**		Compound **II**		Compound **III**		Compound **IV**	
	G (kcal)	P	G (kcal)	P	G (kcal)	P	G (kcal)	P
R,S_a,chair (S_a,M-chair)[b]	0	0.002	0	0.016	0[c] −0.25[c] −0.27[c]	0.018	−1.48	0.065
R,R_a,chair (R_a,M-chair)[b]	−1,39	0.068	−1.24	0.355	−1.39[c] −1.44[c] −1.81[c]	0.593	−2.56	0.926
R,S_a,M-twist (S_a,M-twist)[b]	−2,23	0,542	−1.01	0.199	−1.33	0.102	−0.06	0.002
R,R_a,M-twist (R_a,M-twist)[b]	−2,09	0,388	−0.89	0.148	−1.11	0.059	−0.30	0.003
R,S_a,P-twist	—	—	−0.90	0.152	−1.14	0.065	−0.14	0.002
R,R_a,P-twist	—	—	−0.84	0.130	−1.52	0.163	0	0.002
ratio of chair conformation	0.07		0.37		0.61		0.991	
ratio of S_a:R_a conformations	1:0.84		1:1.73		1:4.42		1:13.49	

[a]Ratio of conformers (P) were calculated for T = 203 K.

[b]For compound **I.**

[c]Irregular substituent (*iso*-propyl) at acetal carbon atom leads to three stable conformations for chair form and one for twist form.

Conclusions

The conformational properties and dynamics of a number of pyridoxine derivatives were investigated by dynamic NMR experiments. The line shape analysis of the NMR signals showed that all of the studied compounds participate in a conformational exchange. The NMR experiments with decreasing temperatures allowed deceleration of the rate of the conformational exchange caused by the rotation of the dinitrophenyl fragment around the pyridine–O bond. The energy barriers of the rotation were calculated for all of the compounds. It was found that the seven-membered cycles of compounds **II** and **III** are present in solution in a dynamic equilibrium between the chair and twist conformations of the acetal ring, and the same cycle of compound **IV** exists in solution only in the rigid *chair* conformation.

Acknowledgements

This work was funded by the subsidy allocated to Kazan Federal University for the state assignment in the sphere of scientific activities. The work was also performed according to the Russian Government Program of Competitive Growth of Kazan Federal University.

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