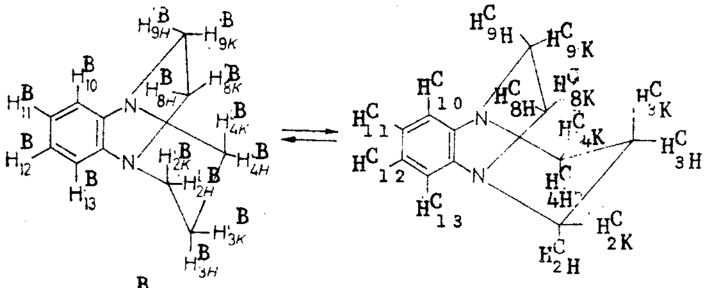
DIAZOBICYCLOALKANES WITH BRIDGEHEAD NITROGEN ATOMS IN NODAL POSITIONS. 22.* CONFORMATIONAL ANALYSIS OF BENZODIAZABICYCLOALKENES. ITERATIVE EVALUATION OF SPECTRAL AND THERMODYNAMIC PARAMETERS

G. E. Sal'nikov, A. A. Gall', G. V. Shishkin, and V. I. Mamatyuk

UDC 547.863.13'896/897.07:
543.422.25

^{1}H and ^{13}C NMR were used to investigate the conformational equilibrium of benzo[f]-1,5-diazabicyclo[3,2.2]nonene and benzo[g]-1,6-diazabicyclo[4.2.2]decene in solution at temperatures from 20 to —110°C. Benzo[f]-1,5-diazabicyclo[3.2.2]nonene in this temperature interval undergoes rapid conformational exchange, while the conformation ratio changes from 73:27 to 55:45. The thermodynamic characteristics of this equilibrium were obtained and some NMR parameters of the individual conformers were estimated. For benzo[g]-1,6-diazabicyclo-[4.2.2]decene it was possible to attain conditions of slow exchange between two conformations whose proportion in the temperature interval studied were almost identical. The kinetics of conformational exchange were investigated and the energy of activation of the process was found to equal 42.3 kJ/mole.

Benzo[b]-1,4-diazabicyclo[2.2.2]octene, benzo[f]-1,5-diazabicyclo[3.2.2]nonene, and benzo[g]-1,6-diazabicyclo[4.2.2]decene have been synthesized previously [2-4], and it was shown that the free electron pairs on the nitrogen atoms are conjugated with the aromatic ring to a small degree. These heterocycles are thus convenient models for investigating the influence of conjugation on the physicochemical properties of aromatic amines. With the purpose of further investigating the physicochemical properties of benzodiazabicycloalkenes, we have performed a conformational analysis of these new heterocyclic systems by the method of detailed study of the effect of temperature on the NMR spectra. Plainly the rigid bridged bicyclic structure and the benzene nucleus permit the molecule to adopt only two conformations:



I^B I^C

Here and below: the B superscript refers to the boat and the C to the chair conformation; the K subscript to the *exo-* and the H subscript to the *endo-* protons.

We were not able to detect exchange even at temperatures below —100°C, so that the NMR parameters of the individual conformers could not be obtained. We undertook to estimate simultaneously the NMR parameters of the individual conformers and the thermodynamic characteristics of the equilibrium from the change in the average

---

*For Communication 21 see [1].

Institute of Bioorganic Chemistry, Novosibirsk. Institute of Organic Chemistry, Siberian Branch, Russian Academy of Sciences, Novosibirsk 630090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1402-1407, October, 1991. Original article submitted December 26, 1989.

0009-3122/91/2710-1130$12.50

TABLE 1. NMR Parameters of Compound I, Averaged by Conformational Exchange and Recorded at Different Temperatures

T, °C	Chemical shift, δ, ppm				SSCC, J, Hz*		
	2H, 4H	2K, 4K	3H	3K	2H—3H, 4H—3H	2H—3K, 4H—3K	2K—3H, 4K—3H
21**	2,915	3,147	1,512	2,140	4,98	9,38	4,89
—90	2,787	3,170	1,651	2,331	4,18	11,62	2,63

---

*The signals of 2H, 4H, and 8H, 9H are also broadened by a weak W-type spin—spin coupling, through the nitrogen atom, of 2H—8H and 4H—9H.

**δ: 3.028 (8H, 9H); 3.81 (8K, 9K); 6.935 (10, 13); 7.010 ppm (11, 12); J: —14.28 (2H—2K; 4H—4K); 5.64 (2K—3K; 4K—3K); —15.02 (3H—3K); —13.40 (8H—8K; 9H—9K); 9.13 (8H—9H); 5.17 (8H—9K; 8K—9H); 9.14 (8K—9K); 7.59 (10—11; 12—13); 1.41 (10—12; 11—13); 0.46 (10—13); 8.52 Hz (11—12).

TABLE 2. PMR Spectra of the Individual Conformers of Compound I and Thermodynamic Parameters of Exchange Calculated by MLS

Conformer	Chemical shift, δ, ppm				SSCC, J, Hz		
	2H, 4H	2K, 4K	3H	3K	2H—3H, 4H—3H	2H—3K, 4H—3K	2K—3H, 4K—3H
I^B	3,33	3,07	1,08	1,55	6,9	2,8	11,8
I^C	2,60	3,20	1,86	2,61	3,4	14,9	—0,8
ΔH, kJ/mole	—3,27	—3,20	—3,14	—3,35	—3,14	—2,98	—3,03
ΔS, J/mole·K	—8,92	—8,46	—9,30	—9,45	—8,76	—8,86	—8,77

TABLE 3. NMR Parameters of the Benzene-Ring Protons of Compound II*

Conformer	Chemical shift, δ, ppm		SSCC, J, Hz		
	H_{11}, H_{14}	H_{12}, H_{13}	$H_{11}-H_{12}$; $H_{13}-H_{14}$	$H_{11}-H_{13}$; $H_{12}-H_{14}$	$H_{12}-H_{13}$
II^B	6,794	6,951	7,53	1,51	8,20
II^C	6,844	6,950	7,65	1,23	7,54

---

*Assignment of NMR parameters to the II^B and II^C conformers may be reversed.

values of the chemical shift (δ) and spin—spin coupling constant (J) of compound I (see Table 1) with temperature, using the method of least squares (MLS). The task is essentially that of minimizing the sum of squared deviations of the calculated average values of δ and J from the corresponding experimental values:

$$D=\sum_{i=1}^{N}\left(X^{B}/(1+A_{i})+X^{C}A_{i}/(1+A_{i})-K_{i}\right)^{2}\rightarrow \min,$$

where $A_i = \exp(-\Delta H/RT_i)\exp(\Delta S/R)$; N is the number of experimental datapoints (12 in our case); X^B and X^C are the NMR parameters (δ or J) corresponding to the boat (I^B) or chair (I^C) conformation; K_i is the experimental value of the average (because of exchange) NMR parameter at temperature T_i; $\Delta H = H^C - H^B$ is the enthalpy difference between the C and B conformers, and $\Delta S = S^C - S^B$ is the entropy difference between the C and B conformers.

Calculation by MLS assumed that the desired values of X^B, X^C, ΔH, and ΔS are independent of temperature. As criteria we chose the seven most widely varying NMR parameters in the temperature interval 21 to —90°C at 10°C steps (Table 2). For assignment of signals to the individual conformers it was considered that in the boat

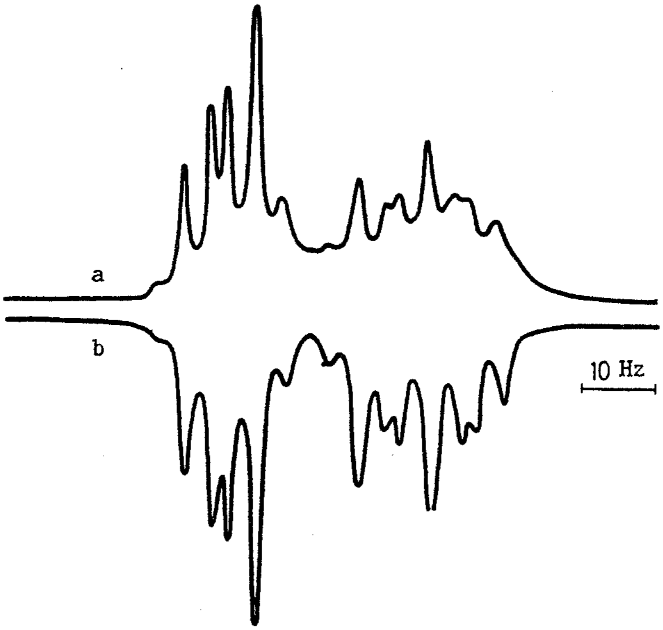


Fig. 1. Experimental (a) and theoretically calculated (b) NMR spectra of the benzene ring protons of compound II at —90°C.

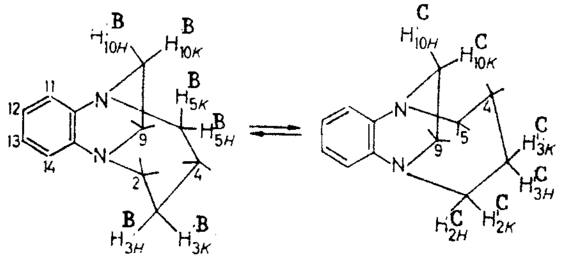
conformation I^B the $H_{3H}{}^B$ signal should be shifted upfield because of the anisotropy of the magnetic receptivity of the benzene ring, while the SSCCs $J_{H_{2K}{}^B-H_{3H}{}^B}$ and $J_{H_{4K}{}^B-H_{3H}{}^B}$ between the protons in the *anti* position should be about 10-15 Hz. Analogously, the SSCC between the *anti*-situated protons $H_{2H}{}^C$, $H_{3K}{}^C$ and $H_{4H}{}^C$, $H_{3K}{}^C$ in the I^C conformation should also be about 10-15 Hz.

The good convergences of the values of ΔH and ΔS obtained by optimization using different NMR parameters confirmed the correctness of our results and gave the values, averaged for all choices of parameter:

$$\Delta H = H^C - H^B = -3{,}2 \pm 0{,}2 \text{ kJ/mole}\ ; \Delta S = S^C - S^B = -8{,}9 \pm 0{,}4 \text{ J/mole·K}$$

The proportion of the thermodynamically favored conformation I^C at 21°C is 55 ± 2%; at —90°C, 73 ± 2%. Since at —110°C exchange is still rapid on the NMR time scale ($\Delta\nu_{1/2} < 1$ Hz), we can estimate the upper limit of the activation energy of the process as $E_a < 30$ kJ/mole.

Analogously to compound I, the probable conformations of benzo[g]-1,6-diazabicyclo[4.2.2]decene (II) are



II^B II'^C

The ^1H NMR spectra of a solution of II in carbon disulfide at temperatures near —50°C show a transition from rapid to slow exchange, so that at lower temperatures we were able to observe the NMR signals of either conformer in isolation. Interestingly, at all temperatures in the range 23 to —90°C these two conformers of II are present in a 1:1 ratio to 2% accuracy, as was shown by comparison of the integrated signals under conditions of slow exchange and by the averaged chemical shifts under conditions of rapid exchange, in the ^{13}C NMR spectra. Thus for compound II, $\Delta H = H_{II}{}^C - H_{II}{}^B = 0.0 \pm 0.2$ kJ/mole; $\Delta S = S_{II}{}^C - S_{II}{}^B = 0.0 \pm 0.7$ J/mole·K.

Analysis of the NMR spectrum of the benzene ring protons at —90°C indicated that compound II does not possess enantiomerically skewed conformations. This spectrum is the sum of the spectra of two AA'BB' systems (see

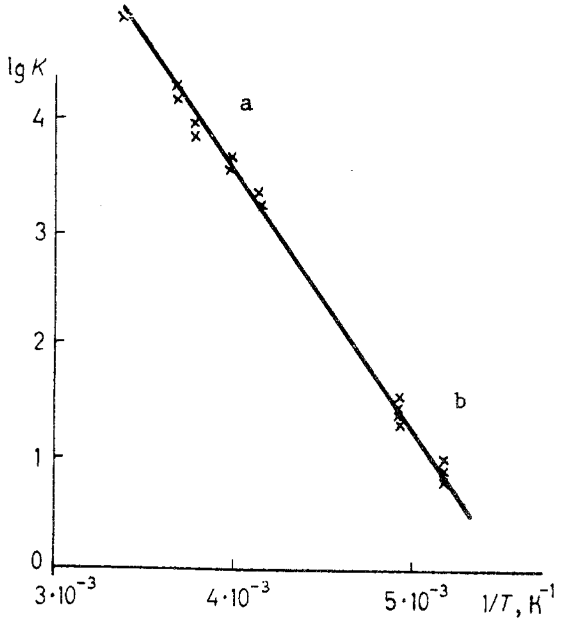


Fig. 2. Arrhenius dependence of log K on 1/T for conformational exchange of compound II: a) region of rapid exchange; b) region of slow exchange.

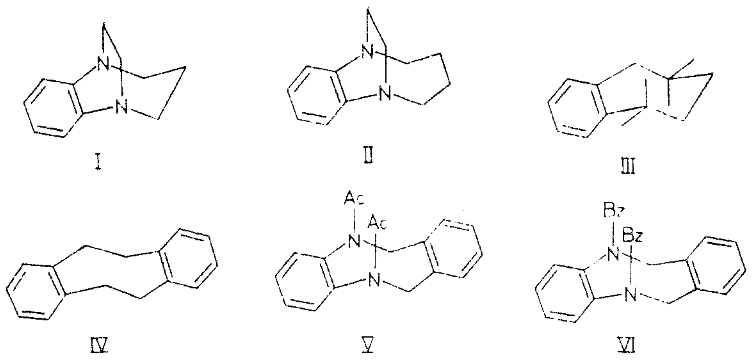


Fig. 3. Structures adduced for comparison of the conformational equilibrium parameters: I) $E_a < 30$ kJ/mole; II) $E_a = 42.3$ kJ/mole; III) $E_a = 40.9$ kJ/mole [6]; IV) $E_a = 42.7$ kJ/mole [7]; V) $E_a = 54.0$ kJ/mole [8]; VI) $E_a = 58.8$ kJ/mole [8].

Table 3 and Fig. 1), not the spectrum of an ABCD system, and this is possible only if compound II possesses two symmetrical unskewed conformations.

To determine the kinetic characteristics of exchange, we measured the signal broadening of the aliphatic $C_{(2)}$ and $C_{(5)}$, $C_{(3)}$ and $C_{(4)}$, and $C_{(9)}$ and $C_{(10)}$ atoms at various temperatures relative to the solvent (carbon disulfide) line width taken as a standard (Table 4). The exchange rate constants were calculated on the basis of these signal broadenings, taking into account the equality of the conformer contributions, using the formulas of [5]:

$$K = \pi\Delta\nu_{1/2} \text{ (under slow-exchange conditions);}$$

$$K = \pi(\nu^C - \nu^B)^2/2\Delta\nu_{1/2} \text{ (under rapid-exchange conditions),}$$

where $\Delta\nu_{1/2}$, Hz, is the signal broadening of the corresponding nucleus at peak half height, and ν^C, ν^B are the chemical shift of that nucleus for the II^C and II^B conformers, respectively.

The calculated rate constants were handled by the linearized method of least squares to give the Arrhenius approximation, $\log K = \log A - E_a/2.3RT$ (Fig. 2), which yielded the following results: activation energy $E_a = 42.3 \pm 0.4$ kJ/mole; logarithm of the preexponential multiplier, $\log A = 12.4 \pm 0.1$, corresponding to a preexponential multiplier of $A = (2.2 \pm 0.4)\cdot 10^{12}$.

TABLE 4. Signal Broadening ($\Delta\nu$) of Compound II Relative to Signal Width of CS_2 due to Conformational Exchange*

$T_{r.e}$ °C**	$\Delta\nu$, Hz			$T_{s.e}$, °C**	$\Delta\nu$, Hz					
	$C_{(2)}^{br}$, $C_{(5)}^{br}$	$C_{(3)}^{br}$, $C_{(4)}^{br}$	$C_{(9)}^{br}$, $C_{(10)}^{br}$		$C_{(2)}^{B}$, $C_{(5)}^{B}$	$C_{(2)}^{C}$, $C_{(5)}^{C}$	$C_{(3)}^{B}$, $C_{(4)}^{B}$	$C_{(3)}^{C}$, $C_{(4)}^{C}$	$C_{(9)}^{B}$, $C_{(10)}^{B}$	$C_{(9)}^{C}$, $C_{(10)}^{C}$
23	—	—	2,4	−70	8,5	8,3	11,0	7,5	9,0	8,0
0	3,5	1,8	10,5	−80	2,5	2,3	2,9	2,5	2,4	2,4
−10	6,7	3,5	22,0							
−20	13,8	6,3	—							
−30	25,7	14,9	—							

---

*Assignment of the ^{13}C NMR signals to II^B and II^C, as well as of the NMR signals to the $C_{(2)}$, $C_{(5)}$, $C_{(9)}$, and $C_{(10)}$ nuclei, may be reversed. Chemical shifts 61.47 ($C_{(2)}^{br}$, $C_{(5)}^{br}$); 59.56 ($C_{(2)}^{B}$, $C_{(5)}^{B}$); 63.47 ($C_{(2)}^{C}$, $C_{(5)}^{C}$); 28.44 ($C_{(3)}^{br}$; $C_{(4)}^{br}$); 29.61 ($C_{(3)}^{B}$, $C_{(4)}^{B}$); 27.04 ($C_{(3)}^{C}$, $C_{(4)}^{C}$); 52.76 ($C_{(9)}^{br}$, $C_{(10)}^{br}$); 55.95 ($C_{(9)}^{B}$, $C_{(10)}^{B}$); 49.03 ppm ($C_{(9)}^{C}$, $C_{(10)}^{C}$).

**$T_{r.e}$) Temperature of rapid exchange; $T_{s.e}$) temperature of slow exchange.

Comparison of the kinetic characteristics of the conformational equilibria of compounds I and II and their close analogs [6-8] leads to some qualitative conclusions about the structural influence of the cyclic system, and the presence in it of nitrogen atoms, on the rigidity of the conformationally mobile seven-(eight-)membered ring (see Fig. 3).

1. The eight-membered ring of II is conformationally more rigid than the seven-membered ring of I.
2. Introduction of the nitrogen atoms into the ring increases its rigidity (compare the activation energies of compounds IV-VI).
3. Introduction of the CH_2CH_2 bridge to form a bicyclic system facilitates conformational transitions (compare the activation energies of compounds II, V, and VI, as well as of I and III).

EXPERIMENTAL

NMR spectra were recorded on a Bruker WP-200 SY (200.13 MHz for ^1H nuclei; 50.33 MHz for ^{13}C nuclei) in the temperature interval —110 to 21°C. The solvent was carbon disulfide with acetone-d_6 for stabilization and TMS as the standard for chemical shift measurement (^{13}C NMR chemical shifts were measured relative to the CS_2 signal at $\delta_{^{13}C}$ (192.8 ppm). PMR spectra were analyzed on an ASPECT-2000 personal computer with the standard iteration program PANIC in order to derive chemical shift and SSCC values; the error in estimating these parameters was $\approx$0.04 to 0.07 Hz. The derived parameters were handled by the method of least squares on the computer.

Benzo[f]-1,5-diazabicyclo[3.2.2]nonene and benzo[g]-1,6-diazabicyclo[4.2.2]decene were obtained as in [2-4].

LITERATURE CITED

1. A. G. Gall', A. S. Trachum, V. A. Romantsev, and G. V. Shishkin, *Khim. Geterotsikl. Soedin.*, No. 6, 798 (1991).
2. G. V. Shishkin, A. A. Gall', and G. A.Zloba, *Khim. Geterotsikl. Soedin.*, No. 11, 1538 (1981).
3. A. A. Gall' and G. V. Shishkin, *Khim. Geterotsikl. Soedin.*, No. 5, 677 (1983).
4. A. A. Gall' and G. V. Shishkin, *Khim. Geterotsikl. Soedin.*, No. 5, 682 (1983).
5. G. Emsley, G. Finey, and L. Sutcliffe, *High-Resolution Nuclear Magnetic Resonance Spectroscopy*, Pergamon Press, Oxford (1965).
6. E. Grunwald and E. J. Price, *J. Am. Chem. Soc.*, **87**, 3139 (1965).
7. D. Montecalvo, M. St. Jacques, and R. Wasylishen, *J. Am. Chem. Soc.*, **95**, 2023 (1973).
8. R. Grossley, A. P. Downing, M. Nogradi, A. B. de Oliveira, W. D. Ollis, and J. O. Sutherland, *J. Chem. Soc. Perkin Trans. I*, 205 (1973).