Chemistry of Heterocyclic Compounds, Vol. 39, No. 4, 2003

SPATIAL STRUCTURE OF ISOMERS OF 3,7-DIALKOXYALKYL-3,7-DIAZA-BICYCLO[3.3.1]NONAN-9-OLS

S. G. Klepikova[1], V. A. Solomin[1], T. K. Iskakova[1], V. K. Yu[1], K. D. Praliev[1], N. A. Zhumanova[1], and K. D. Berlin[2]

The spatial structure of 3,7-dialkoxyalkyl-3,7-diazabicyclo[3.3.1]nonan-9-ols has been investigated with the aid of ^{1}H and ^{13}C NMR spectroscopy. It was shown that the secondary alcohols studied exist in solution predominantly in a chair-boat conformation which proved to be energetically more favorable than a chair-chair conformation due to the formation of an intramolecular hydrogen bond (IMHB) between the unshared pair of electrons on the nitrogen atom and the hydrogen atom of the hydroxyl group.

Keywords: 3,7-dialkoxyalkyl-3,7-diazabicyclo[3.3.1]nonan-9-ol, *chair-boat*, conformation, ^{1}H and ^{13}C NMR spectroscopy, structure.

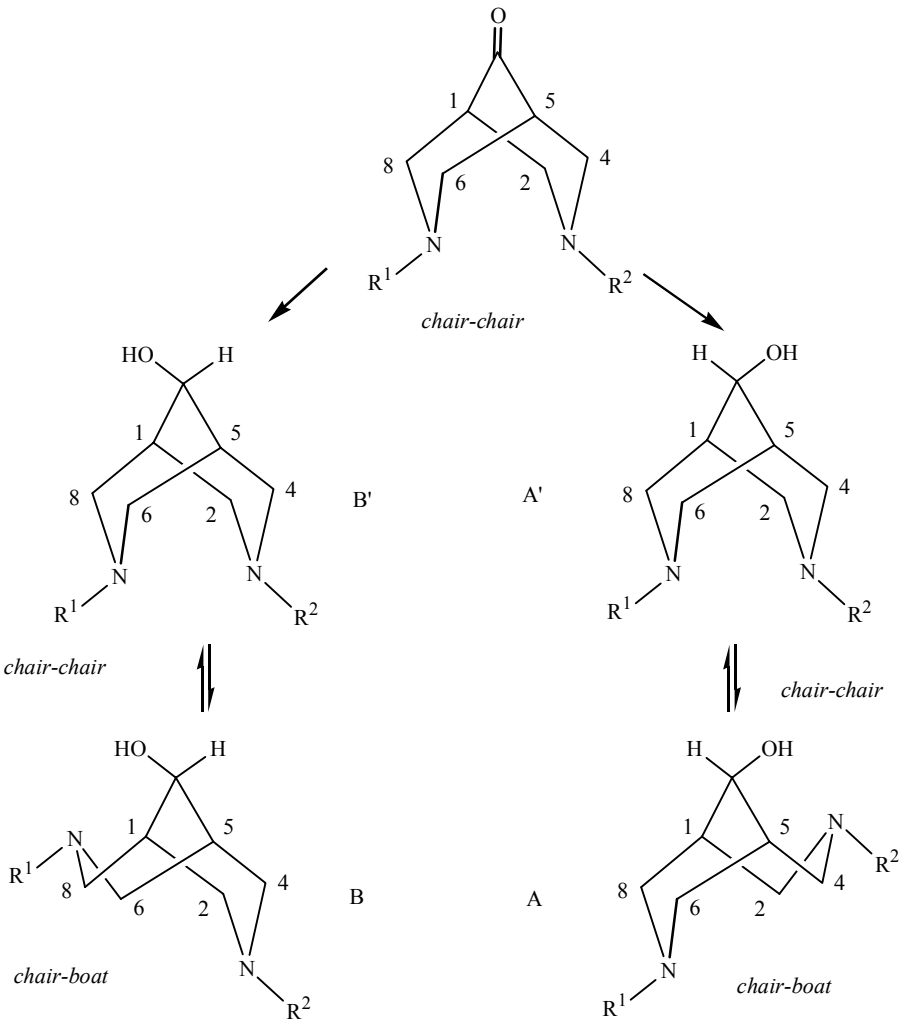
Derivatives of 3,7-dialkoxyalkyl-3,7-diazabicyclo[3.3.1]nonan-9-ons possess pharmacological activity over a wide spectrum of action [1-3]. A distinct dependence of the pharmacological activity on the length of the alkyloxyalkyl substituent at the nitrogen atom can be traced. The spatial structure of these molecules plays an important role in the appearance of biological properties. Methods of ^{1}H and ^{13}C NMR spectroscopy were used to demonstrate the structures of the substances synthesized.

The subjects investigated in the present work were 3,7-di-(2-ethoxyethyl)-, 3,7-di-(3-isopropoxypropyl)-, and 3-(2-ethoxyethyl)-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1]nonan-9-ols. Results are given on the investigation of their spatial structure with the aid of ^{1}H and ^{13}C NMR spectroscopy. On the basis of the data obtained on the vicinal coupling constants of protons, which bear important information on the geometry of the molecules [4], it was established that the secondary alcohols studied exist in solution predominantly in a *chair-boat* conformation, which proved to be energetically more favorable than the *chair-chair* conformation, due to the formation of IMHB between the unshared pair of electrons on the nitrogen atom and the hydrogen atom of the hydroxyl group. In alcohols having the same substituents one conformer is observed, since in this case conformers A and B are identical. If the substituents are different then the alcohols are a mixture of two conformers, the relative content of which depends on the nature of the substituents. In agreement with the results obtained the following scheme may be suggested for the formation of stable conformers in the *chair-boat* form.

---

[1] A. B. Bekturov Institute of Chemical Sciences, Kazakh Ministry of Education and Science, Republik of Kazakhstan, Almaty 480100; e-mail: yu_vk@rambler.ru. [2] Chemical Faculty, Oklahoma State University, Stillwater, 74078, USA. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 586-593, April, 2003. Original article submitted April 5, 2002.

 0009-3122/03/3904-0504$25.00

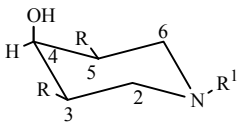


1 $R^1 = R^2 = CH_2CH_2OCH_2Me$, **2** $R^1 = R^2 = CH_2CH_2CH_2OCHMe_2$;
3 $R^1 = CH_2CH_2OCH_2Me$, $R^2 = CH_2CH_2CH_2OCHMe_2$

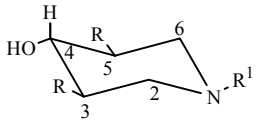
It is interesting to note the doubling of the signals in the ^{13}C NMR spectra with identical substituents with the exception of the signals of the $C_{(1)}$, $C_{(5)}$, and $C_{(9)}$ atoms. In order to explain this we suggest that the main reason for the difference in chemical shifts is firstly the presence of an OH group axially disposed to one of the rings and consequently equatorial to the other. To check this hypothesis spectra were recorded for the pair of 3,5-dibenzyl-1-(2-ethoxyethyl)piperid-4-ols epimeric at $C_{(4)}$ with a rigid *chair*-like conformation of the piperidine ring [1]. It is seen from the data of Table 1 that the effect on the ^{13}C chemical shifts of the hydroxyl group, depending on its orientation, is significant for the $C_{(2)}$ and $C_{(6)}$ atoms and diminishes with distance. The effect on the $C_{(3)}$, $C_{(4)}$, and $C_{(5)}$ atoms is not considered, since in the bicyclic alcohols the corresponding atoms $C_{(1)}$, $C_{(9)}$, and $C_{(5)}$ are common.

In the spectrum of compound **1** the difference between the chemical shifts of the $C_{(6)}$, $C_{(8)}$ and $C_{(2)}$, $C_{(4)}$ atoms was 4.73 ppm while for the outlying methyl groups of the ethoxyethyl substituents the difference was 0.07 ppm (Table 2). This is in good agreement with values of 4.64 and 0.07 ppm found from the spectra of model compounds differing only in the orientation of the OH group. The observed agreement of the values points in favor of the assumption made by us.

TABLE 1. Chemical Shifts of Carbon Atoms of the Isomers of 1-(2-Ethoxyethyl)dibenzylpiperid-4-ol and Their Change as a Function of the Orientation of the OH Group



a



e

$R = {}^{7}CH_2Ph,\ R^1 = {}^{8}CH_2{}^{9}CH_2{}^{10}OCH_2{}^{11}CH_3$

Isomer	Chemical shifts, δ, ppm						
	$C_{(2)}$, $C_{(6)}$	$C_{(3)}$, $C_{(5)}$	$C_{(4)}$	$C_{(8)}$	$C_{(9)}$	$C_{(10)}$	$C_{(11)}$
a (ax)	52.81	42.71	68.18	57.50	67.78	65.96	14.71
e (eq)	57.45	44.95	76.97	57.05	67.86	65.82	14.64
$\Delta\delta = \delta_e - \delta_a$, ppm	4.64	2.24	8.79	-0.45	0.08	-0.14	-0.07

It is necessary to note that the $C_{(2)}$, $C_{(4)}$ and $C_{(6)}$, $C_{(8)}$ atoms of symmetrical molecules, such as 3,7-diazabicyclo[3.3.1]nonan-9-one (or its reduced analog) [2,3], are displayed as one signal at 58.49 (57.92 ppm), while in the spectrum of alcohol **1** two signals at 52.84 and 57.57 ppm correspond to these atoms. Since conformers A and B of alcohols with the same substituents at the nitrogen atoms are identical, we will carry out all the discussion on conformer A. Comparison with the values of the chemical shifts of the $C_{(2)}$, $C_{(6)}$ atoms in the isomers taken as models enables assignment of the first signal at 52.84 ppm to the $C_{(2)}$, $C_{(4)}$ atoms and the second signal at 57.57 ppm to the $C_{(6)}$, $C_{(8)}$ atoms. The lower value therefore indicates an axial orientation of the hydroxyl group in relation to the ring containing the $C_{(2)}$, $C_{(4)}$ pair of atoms.

The ^{1}H NMR spectra of alcohols **1** and **2** (see Table 3) show the presence of one isomer having a *chair-boat* conformation. Proof of this assertion is given by the presence in the spectra of a triplet with splitting somewhat exceeding 10 Hz and an intensity of two protons. The triplet form of the signal arises when the two coupling constants coincide. It is known that for rigid *chair*-form piperidine systems the constants are fairly characteristic and values greater than 10 Hz may correspond to the interaction of both geminal and vicinal protons disposed diaxially relative to the plane of the ring [4].

If it is considered that the 1- and 5-H protons in the studied compounds are equatorial as a result of the prescribed method of linking the rings and it is assumed that both rings are in the *chair* form then the appearance of a large vicinal constant is impossible since there are no *trans*-diaxially disposed protons. For 3,7-diazabicyclo[3.3.1]nonanes having a *chair-chair* conformation the vicinal constants lie in the range 1 to 7 Hz [5,6]. This means that only one variant of the explanation remains acceptable, which is the fact that one of the rings takes up the *boat* form. Consideration of the classical model shows that in this case the dihedral angles between the protons at $C_{(2)}$ ($C_{(4)}$) and the neighboring protons at $C_{(1)}$ ($C_{(5)}$) are 0 and 120° [7,8]. Calculations carried out by us with the Chem3D program with optimization on energy with the aid of the MOPAC/PM3 method gave the following values: 10-12° for the dihedral angle between the 1-, 5-H and 2-, 4-H_{pe} protons and 105-106° for the dihedral angle between the 1-, 5-H and 2-, 4-H_{pa} protons in alcohols **1-3** having a *chair-boat* structure. The calculated values show a small deviation from ideal angles. From the Karplus–Conroy curve [9] for the known value of the angles, the mean values for the vicinal constants of 10 and 12 Hz respectively are readily determined. On the basis of the obtained data the triplet signal in the spectrum of compound **1** at 3.02 ppm with a splitting of 10.8 Hz and the triplet in the spectrum of alcohol **2** at 3.09 ppm with splitting of 10.2 Hz must belong to two protons 2- and 4-H, which form dihedral angles of 105° with the 1- and 5-H protons. A doublet of doublets with chemical shift 2.15 ppm and constants 10.2 and 1.5 Hz in the spectrum corresponds

TABLE 2. ^{13}C NMR Spectra of the Isomers of 3,7-Diazabicyclo[3.3.1]nonan-9-ols and Their Relative Content

Compound	Isomer	Orientation of OH	Chemical shifts, δ, ppm													Content, %
			$C_{(1)}$, $C_{(5)}$	$C_{(2)}$, $C_{(4)}$	$C_{(6)}$, $C_{(8)}$	$C_{(9)}$	$C_{(10)}$	$C_{(11)}$	$C_{(12)}$	$C_{(13)}$	$C_{(14)}$	$C_{(15)}$	$C_{(16)}$	$C_{(17)}$	$C_{(18)}$	
1	A	*a*		52.84			56.37	67.95	65.90	14.80						
			35.01			71.40										50
		e			57.57		56.50	67.58	65.95	14.87						
		a			52.84		56.50	67.58	65.95	14.87						
	B		35.02			71.40										50
		e		57.57			56.37	67.95	65.90	14.80						
2		*a*		53.28							53.28	27.49	65.82	71.01	21.84	
	A		34.73			72.47										50
		e			57.34						53.72	27.44	65.74	71.11	21.76	
		a			53.28						53.72	27.44	65.74	71.11	21.76	
	B		34.73			72.47										50
		e		57.34							53.28	27.49	65.82	71.01	21.84	
3		*a*		53.04							53.65	27.23	65.93	70.96	21.79	
	A		4.88			71.58										60
		e			57.23		56.30	67.83	67.72	14.79						
		a			52.62		56.63	67.42	65.80	14.84						
	B		34.88			71.29										40
		e		57.52							54.07	27.08	65.88	71.04	21.73	

TABLE 3. ^{1}H NMR Spectra and Relative Contents of Conformers in 3,7-Diazabicyclo[3.3.1]nonan-9-ols

Compound	Chemical shifts,* δ, ppm (coupling constants, *J*, Hz)										Content of isomers A and B, %
	1-, 5-H_e	2-, 4-H_{pe}	2-, 4-H_{pa}	6-, 8-H_a	6-, 8-H_e	10-CH_2	13-CH_3	14-CH_2	18-CH_3	9-OH br. s	
1	2.17 (br. d, *J* = 10.2)	3.02 (t, *J* = 10.2; *J* = 10.2)	2.15 (dd, *J* = 10.2; *J* = 1.5)	2.57 (dd, *J* = 11.1; *J* = 2.4)	2.74 (dd, *J* = 11.1; *J* = 2.7)	2.49 (*J* = 6.0); 2.52 (t, *J* = 6.0)	1.18 (*J* = 6.9); 1.18 (t, *J* = 6.9)			5.39	50:50
2	2.25 (br. d, *J* = 10.8)	3.09 (t, *J* = 10.8; *J* = 10.8)	1.99 (dd, *J* = 10.8; *J* = 1.5)	2.39 (dd, *J* = 11.4; *J* = 3.0)	2.62 (dd, *J* = 11.4; *J* = 3.3)			2.36 (*J* = 6.9); 2.37 (t, *J* = 6.9)	1.13 (*J* = 6.0); 1.14 (d, *J* = 6.0)	5.62	50:50
3	2.18 (br. s)	3.02 (*J* = 9.3; *J* = 9.3); 3.06 (br. t, *J* = 9.6; *J* = 9.6)	2.04 (*J* = 11.1); 2.16 (br. d, *J* = 11.1)	2.50 (*J* = 10.5); 2.55 (br. d, *J* = 10.5)	2.71 (*J* = 10.5); 2.75 (*J* = 10.5)	2.52 (br. t, *J* = 6.0)	1.18 (*J* = 6.9); 1.19 (t, *J* = 6.9)	2.36 (br. t, *J* = 6.9)	1.12 (*J* = 6.0); 1.14 (d, *J* = 6.0)	5.51	38:62

*Chemical shifts are given for isomer A; *pa* are pseudoaxial, *pe* are pseudoequatorial protons.

to the other 2- and 4-H pair of protons of compound **1**. An analogous signal at 1.99 ppm with splitting 10.8 and 1.5 Hz is observed in the spectrum of compound **2**. Two doublets of doublets in the spectrum of alcohol **1** at 2.57 and 2.74 ppm with constants 11.4, 3.0, and 2.7 Hz belong to the geminal protons at 6- and 8-H occupying axial and equatorial positions relative to the plane of the *chair*-form ring. In the spectrum of compound **2** two signals as a doublet of doublets with chemical shifts of 2.39 and 2.62 ppm and constants 11.4, 3.0, and 3.3 Hz belong to them. The 1- and 5-H protons of alcohol **1** (and alcohol **2**) give a doublet at 2.17 (2.25 ppm) in the spectrum with unresolved components. The complex structure of the signal is caused by the interaction of each of these protons with five neighbors. However the splitting of the signal into a doublet is displayed in the spectrum due to the large coupling constant of 10.2 (10.8 Hz) of the 1- and 5-H protons with the pseudoequatorial protons of the ring having a *boat* shape. The signal of the 9-H proton was not detected since it falls in the resonance region of the methylene groups found beside the oxygen atom in the N-substituents. An analysis of the coupling of the terminal protons therefore showed that the synthesized alcohols **1** and **2** are represented in solution mainly by one *chair-boat* conformer.

An additional stabilization factor is necessary to accomplish the conformational transition from a *chair-chair* into a *chair-boat* conformation. The stabilizing factor in the investigated alcohols is the IMHB arising between the hydrogen atom of the hydroxyl group and the unshared electron pair of the nitrogen atom. It is natural that the ring in relation to which the OH group is axial will take up the form of a *boat*. In this case the the distances and angles are optimal for forming IMHB. In fact the presence in the spectra of the alcohols in $CDCl_3$ of low field broadening of the hydroxyl proton signal in the 5-6 ppm region (Table 3), its position practically unchanged on heavily diluting the solution, indicates the formation of IMHB. We note that the bispidinones, from which these alcohols are obtained, have a *chair-chair* conformation [3]. Consequently, on the basis of the ^{1}H and ^{13}C NMR spectral data obtained, it is possible to draw the conclusion with confidence that the absolute predominance of the *chair-boat* conformer in solution is explained by the presence of the OH group the proton of which interacts with the free electron pair of the nitrogen atom with the formation of an IMHB.

The ^{13}C NMR spectrum of alcohol **3** with different N-substituents is even more complex. In the spectrum of compound **3**, as in the spectra of alcohols **1** and **2**, doubled signals were observed, but in difference to the latter the line intensities in these signals were different. Moreover an additional doubling occurs of the already previously doubled signals of the ring atoms $C_{(2)}$, ($C_{(4)}$), $C_{(6)}$, $C_{(8)}$, and $C_{(9)}$, which proved to be sensitive to the different substituents. This is not remarkable, because these carbon atoms are in spatial proximity to the heteroatoms participating in the formation of IMHB. We note that the change in chemical shift caused by a different orientation of the OH group to the ring exceeds by far the change caused by the different N-substituents. For the OH group it is more than 4 ppm, but for the different N-substituents it did not exceed 0.5 ppm. All three changes indicate that the synthesized alcohol **3** is a mixture of two stereoisomeric compounds, one of which is in conformation A and the other in conformation B. Assignment of the signals was carried out allowing for the data of ^{13}C NMR spectra of model compounds and of alcohols **1** and **2**. The relative content of conformers A and B, determined from the integrated intensities of the signals, was 60 and 40% respectively (Table 2). From the ratio obtained it follows that the 3-isopropoxypropyl substituent, compared to 2-ethoxyethyl, favors the formation of conformer A (60%) in which the nitrogen atom with a 3-isopropoxypropyl substituent is included in an IMHB, and the nitrogen atom with a 2-ethoxyethyl substituent remains unbonded. The ratio of isomers most probably depends on the basicity of the nitrogen atom, which in its turn is influenced by the substituent.

In the ^{1}H NMR spectrum of alcohol **3** there were two triplets at 3.02 and 3.06 ppm, with large coupling constants, assigned to the 6- and 8-H protons of isomer B and to the 2- and 4-H protons of isomer A, which make dihedral angles of 120° with the 1- and 5-H protons. These are displaced relative to one another by the size of the coupling constant as a result of which a quartet is observed. The signals of the methyl group of the 2-ethoxyethyl substituent are particularly clearly separated. Integration of these signals gives the relative content of isomers, which, within the limits of error of the measurements, agree with the results obtained from the ^{13}C NMR spectra (Tables 2 and 3).

From a consideration of the geometry of bispiperidines it follows that transition from the *chair-chair* form to the *chair-boat* form aids not only IMHB but also repulsion between the free electron pairs of the nitrogen atoms, proving to have a destabilizing action and aiding extrusion of the $C_{(2)}$–N–$C_{(4)}$ fragment. As a result of this the *chair-boat* form is formed. But it is insufficient in the case of ketones and their reduced analogs, which have a *chair-chair* conformation. It is also useful to note that in the *boat* conformation the pseudoequatorial protons are deshielded by 0.4-0.7 ppm, but the pseudoaxial protons are displaced towards high field by 0.5-0.7 ppm in comparison with the axial and equatorial protons in the *chair* conformation. This fact will evidently be useful when assigning signals in the spectra of compounds being studied.

REFERENCES

1. T. K. Iskakova, N. A. Zhumanova, V. K. Yu, K. D. Praliev, S. G. Klepikova, and K. D. Berlin, *Izv. MON, Nats. Akad. Nauk Rep. Kaz., Ser. Khim.*, No. 3, 93 (2002).
2. K. D. Praliev, T. K. Iskakova, N. A. Ismagulova, V. K. Yu, S. G. Klepikova, and K. D. Berlin, in: *Chemistry of Natural and Synthetic Biologically Active Compounds (Structure, Conversions, and Properties)* [in Russian], Sb. Nauch. Tr. Inst. Khim. Nauk MON Rep. Kaz., Alma-Ata (2001), p. 198.
3. T. K. Iskakova, K. D. Praliev, V. K. Yu, N. A. Ismagulova, S. G. Klepikova, and K. D. Berlin, in: *Chemistry of Natural and Synthetic Biologically Active Compounds (Structure, Conversions, and Properties)* [in Russian], Sb. Nauch. Tr. Inst. Khim. Nauk MON Rep. Kaz., Alma-Ata (2001), p. 157.
4. B. I. Ionin, B. A. Ershov, and A. I. Kol'tsov, *NMR Spectroscopy in Organic Chemistry* [in Russian], Khimiya, Leningrad (1983), p. 268.
5. N. S. Zefirov, *Usp. Khim.*, **44**, 413 (1975).
6. G. L. Garrison, K. D. Berlin, J. B. Scherlag, R. Lazzara, E. Patterson, T. Fazekas, S. Sangiah, Chen Chun-Lin, F. D. Schubot, D. van der Helm*, J. Med. Chem.*, **39**, 2559 (1996).
7. C. S. Smith, M. D. Thompson, K. D. Berlin, E. M. Holt, B. J. Scherlag, E. Patterson, and R. Lazzara, *Eur. J. Med. Chem.*, **25**, 1 (1990).
8. R. A. Apleton, S. G. Egan, J. M. Evans, S. H. Graham, and J. R. Dixon, *J. Chem. Soc.*, 1110 (1968).
9. H. Gunter, *Introduction to a Course on NMR Spectroscopy* [Russian translation], Mir, Moscow (1984), p. 478.