Chemistry of Heterocyclic Compounds, Vol. 30, No. 7, 1994

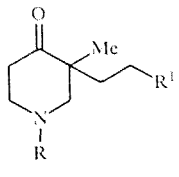
3,3-DISUBSTITUTED PIPERIDIN-4-ONES. CONFORMATIONAL ANALYSIS BY NMR AND CIRCULAR DICHROISM METHODS

E. L. Gaidarova, A. É. Aliev, T. I. Chumakov, and G. V. Grishina

Using ^1H and ^{13}C NMR spectroscopy, we have established the conformational inhomogeneity of chiral 3,3-disubstituted piperidin-4-ones. The conformer with an equatorial methyl group on the $C_{(3)}$ atom predominates in the conformational equilibrium. For (1'S, 3S)-1-(1'-phenylethyl)-3-(2-cyanoethyl)- and 1,3-dimethylpiperidin-4-ones, we found ^1H NMR spectral parameters which may serve as criteria for conformational homogeneity of piperidin-4-one molecules. The conformational composition of the (3S)-enantiomers of 1,3-dimethyl-3-(2-cyanoethyl)- and 1,3-dimethyl-3-(2-carbomethoxyethyl)piperidin-4-ones was also estimated on the basis of theoretical analysis of the circular dichroism spectra in solvents of different polarities.

Piperidin-4-ones 1-7, whose synthesis we described earlier in [1, 2], serve as convenient chiral synthons in fine organic synthesis of new chiral derivatives of the piperidine series [3].

This work is connected with conformational analysis of the series of chiral piperidin-4-ones 1-7 (containing a quaternary chiral center at the $C_{(3)}$ atom) using ^1H and ^{13}C NMR spectroscopy and circular dichroism (CD).



1-7

Compound	R	R^1
1	CH_3	CN
2	CH_3	COOMe
3	CH_3	COMe
4	$CH_2C_6H_5$	CN
5	$CH_2C_6H_5$	COOMe
6 a,b	(*S*)-$CH(CH_3)C_6H_5$	CN
7 a,b	(*S*)-$CH(CH_3)C_6H_5$	COOMe

Piperidin-4-ones 1-3 were used for the investigation in the form of the (3S)-enantiomers (98% optical purity). Piperidin-4-ones 4 and 5 were also investigated in the form of the (3S)-enantiomers, but their optical purity was 27% and 46% respectively. In the series of investigated piperidin-4-ones 1-7, compounds 6 and 7 are the most complex stereochemically: Each of them is an unresolvable 1:1 mixture of diastereomers 6a, b and 7a, b respectively. This conclusion is drawn on the basis of the doubling of the entire set of signals in the ^{13}C NMR spectrum of piperidin-4-one 6 with an equal ratio of integrated intensities and doubling of the signals from the 6-H_e, methyl, and methine protons of the phenylethyl substituent on the nitrogen atom and the CH_3 group of the methoxycarbonylethyl substituent on the $C_{(3)}$ atom in the ^1H NMR spectrum of piperidin-4-one 7. The diastereomers 6a and 7a have the (1'S, 3S)-configuration, while the diastereomers 6b and 7b have the (1'S,3R)-configuration.

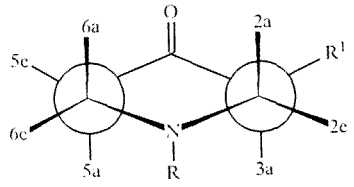
The presence of a quaternary center $C_{(3)}$ in molecules of piperidin-4-ones 1-7 significantly hinders the use of ^1H NMR spectroscopy for determination of the spatial orientation of the substituents by direct analysis of the spin–spin coupling constants of the ring protons and conformational analysis of these compounds as a whole. Accordingly, we found it necessary to first analyze the ^1H and ^{13}C data for the compounds we selected as models: (1'S,3S)-1-(1'-phenylethyl)-3-(2-cyanoethyl)-piperidin-4-one 9 and the cis-(1e,2e,5e-CH_3)- and trans-(1e,2e,5a-CH_3)-isomers of 1,2,5-trimethyl-5-(2-cyanoethyl)piperidin-4-

M. V. Lomonosov State University, Moscow 119899. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 926-940, July, 1994. Original article submitted June 11, 1994.

 0009-3122/94/3007-0800$12.50

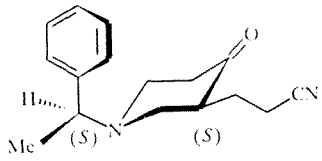
one 10a and 10b, the structures of which were rigorously established earlier using ^1H and ^{13}C NMR spectroscopy and x-ray diffraction [4, 5, 6].

According to x-ray diffraction data [6], the piperidin-4-one molecule 9 exists in the solid phase in the chair conformation with an equatorial 2-cyanoethyl group on the $C_{(3)}$ atom and an (S)-phenylethyl substituent on the nitrogen atom. The large torsional angles about the bonds $C_{(2)}-C_{(3)}$ (57.2°) and $C_{(5)}-C_{(6)}$ (53.8°) determine the dihedral angles for the interacting protons (2-H_a, 3-H_a) and (5-H_a, 6-H_a) as close to 180°, which according to the Karplus rule [7] gives the largest possible spin–spin coupling constant for piperidin-4-ones, ^3J = 11.05 and 11.56 Hz respectively (Table 2). At the same time, the values of the vicinal coupling constants ^3J(5-H_e, 6-H_a) and ^3J(5-H_e, 6-H_e), determined by the nearly 60° dihedral angles, are small (3.33 and 3.17 Hz respectively, Table 2). The fact that the coupling constants observed experimentally in the ^1H NMR spectra of piperidin-4-one 9 match the values calculated from the Karplus equation for the conformation established by x-ray diffraction unambiguously suggests that even in solution the piperidin-4-one 9 exists in the chair conformation with diequatorial substituents and is conformationally homogeneous.

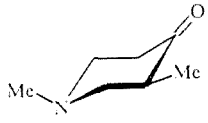


R = (*S*)-CH(Me)Ph;
R^1 = CH_2CH_2CN (8);
R = R^1 = Me (9)

The values of the coupling constants in 1,3-dimethylpiperidin-4-one 9, rather close to the considered values for piperidin-4-one 8 (Table 2), suggest that the piperidin-4-one 9 in solution exists in a chair-type conformation with diequatorial methyl groups on the $C_{(3)}$ atom and on the nitrogen atom of the piperidine ring and also is conformationally homogeneous.



8

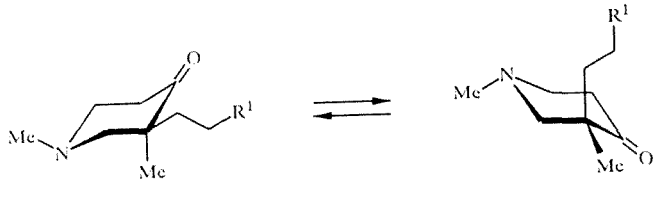


9

Consequently, for piperidin-4-ones 8 and 9 we found parameters of the ^1H NMR spectra whose values are characteristic and may serve as criteria for conformational homogeneity of piperidin-4-ones: the difference between the chemical shifts of the protons on the $C_{(2)}$ atom ($\Delta\delta = \delta(2\text{-}H_e) - \delta(2\text{-}H_a)$; 0.99 and 0.97; Table 1) and on the $C_{(6)}$ atom ($\Delta\delta = \delta(6\text{-}H_e) - \delta(6\text{-}H_a)$; 0.69 and 0.78 ppm, Table 1); the trans-vicinal coupling constant ^3J(5-H_a, 6-H_a) = 11.56 and 12.37 Hz (Table 2); the long-range spin–spin coupling constant ^4J(2-H_e, 6-H_e) = 2.68 and 2.87 Hz (Table 2), corresponding to the W rule [8], along with the very small long-range constant ^4J between the protons (2-H_a, 6-H_a) (anti-W).

In the following we used the chemical shifts and the spin–spin coupling constants of the protons for piperidin-4-ones 8 and 9 as the limiting values in determining the spatial structure of the entire series of chiral 3,3-disubstituted piperidin-4-ones 1-7.

For the investigated 3,3-disubstituted piperidin-4-ones 1-5 and 7, we note the substantial deviations of the experimentally observed values of the considered parameters from their limiting values in conformationally homogeneous piperidin-4-ones 8 and 9 (Tables 1 and 2). This is probably connected with the existence for 3,3-disubstituted piperidin-4-ones 1-5 and 7 of the conformational equilibrium $K_1 \rightleftarrows K_2$, caused by ring inversion:



K_1 K_2

TABLE 1. ^1H Chemical Shifts (δ, ppm, internal standard TMS, $CDCl_3$) in Piperidin-4-ones 1-5, 7-9

Compound	2-H_a	2-H_e	3-H_a	5-H_a	5-H_e	6-H_a	6-H_e	3-CH_3	N-CH_3	3-CH_2-CH_2	Other
1	2,37	2,50	–	2,50	2,54	2,63	2,71	1,14	2,32	1,84...2,36	–
2	2,27	2,56	–	2,61	2,42	2,51	2,80	1,08	2,32	1,80...2,30	3,66 ($COOC\underline{H}_3$)
3	2,26	2,56	–	2,58	2,40	2,50	2,79	1,04	2,32	1,70...2,40	2,13 ($COC\underline{H}_3$)
4	2,33	2,52	–	2,53	2,51	2,88	3,04	1,10	–	1,83...2,25	3,53 & 3,61 ($N-C\underline{H}_2$), 7.28-7.39 ($CH_2C_6\underline{H}_5$)
5	2,24	2,59	–	2,62	2,39	2,54	2,88	1,01	–	1,79...2,24	3,51 & 3,58 ($N-C\underline{H}_2$), 3,65 ($COOC\underline{H}_3$), 7.26-7.35 ($CH_2C_6\underline{H}_5$)
7a	2,17	2,61	–	2,63	2,36	2,46	3,05	0,95	–	1,78...2,30	1,39 ($CH(C\underline{H}_3)C_6H_5$), 3,57 ($C\underline{H}(CH_3)C_6H_5$), 3,66 ($COOC\underline{H}_3$), 7.25-7.36 ($CH_2C_6\underline{H}_5$)
7b	2,17	2,61	–	2,63	2,36	2,46	3,05	1,03	–	1,78...2,30	1,39 ($CH(C\underline{H}_3)C_6H_5$), 3,53 ($C\underline{H}(CH_3)C_6H_5$), 3,67 ($COOC\underline{H}_3$), 7.25-7.36 ($CH_2C_6\underline{H}_5$)
8	2,11	3,08	2,66	2,62	2,34	2,41	3,19	–	–	1,46...2,42	1,42 ($CH(C\underline{H}_3)C_6H_5$), 3,67 ($C\underline{H}(CH_3)C_6H_5$), 7.27-7.34 ($CH_2C_6\underline{H}_5$)
9	2,08	3,06	2,67	2,63	2,35	2,38	3,07	1,01	2,30	–	–

TABLE 2. Spin–Spin Coupling Constants $J_{H,H}$ (Hz) in Piperidin-4-ones 1-5, 7-9

Compound	Geminal				Vicinal							Long-range		
	2a2e	6a6e	5a5e	N–CH_2	2a3a	2e3a	5a6a	5a6e	5e6a	5e6e	$CH(CH_3)C_6H_5$	3a5a	2e6e	2a6a
1	-11,63	-11,22	-15,14	–	–	–	7,85	5,56	5,11	6,76	–	–	1,68	1,43
2	-11,54	-11,10	-14,94	–	–	–	9,40	5,72	4,53	5,46	–	–	2,13	1,03
3	-11,60	-11,14	-14,98	–	–	–	9,44	5,78	4,53	5,42	–	–	2,07	1,14
4	-11,60	-11,23	-15,30	-13,12	–	–	7,72	6,09	5,68	5,71	–	–	2,00	1,29
5	-11,65	-11,10	-15,05	-13,12	–	–	9,43	5,81	4,41	5,20	–	–	2,13	0,90
*7**	-11,44	-11,10	-14,62	–	–	–	9,80	6,22	4,11	4,60	6,81	–	–	–
8	-11,13	-11,34	-14,03	–	11,75	5,63	11,56	6,38	3,33	3,17	–	–	2,87	0,25
9	-11,28	-11,35	-14,26	–	11,15	6,20	12,37	6,43	3,41	2,70	–	1,34	2,68	0,25

*The sets of spin–spin coupling constants $J_{H,H}$ in diastereomers 7a and 7b completely coincide.

TABLE 3. ^{13}C Chemical Shifts (δ, ppm, $CDCl_3$) in Piperidin-4-ones 1-3, 6

Compound	C_2	C_3	C_4	C_5	C_6	N–CH_3	3-CH_3	C_7	C_8	C_9	C_{10}	(*S*)-$CH(CH_3)C_6H_5$
1	66,22	48,05	211,48	38,42	55,84	45,62	20,42	32,40	12,25	119,62	–	–
2	66,99	48,27	211,19	38,57	56,15	45,79	20,22	32,04	28,93	173,66	51,55	–
3	67,39	48,28	210,87	38,76	56,14	45,65	20,48	38,14	31,17	205,77	29,40	–
6a	59,91	48,33	210,76	38,84	50,44	63,33	20,06	32,35	12,07	119,91	–	18,11 (CH_3), 127.35-128.55 (C_6H_5), 143,11 (CH)
6b	60,53	48,38	210,65	38,84	50,59	63,13	19,64	32,35	12,05	119,91	–	18,91 (CH_3), 127.35-129.55 (C_6H_5), 143,55 (CH)

Let us estimate the fractional populations of conformers K_1 and K_2 in conformational equilibrium. To do this, let us call them n_{K1} and n_{K2} so that

$$n_{K1}+n_{K2} = 1, \tag{1}$$

$$\text{while} \quad \Delta n = n_{K2}-n_{K1}, \tag{2}$$

where Δn is the difference between the populations of the predominant and minor conformers.

The experimentally observed values of the parameters of the ^1H NMR spectrum for piperidin-4-ones 1-5 and 7 ($\hat{p}$) may be presented in the following form:

$$\hat{p} = p_{K1}^{0} \cdot n_{K1}+p_{K2}^{0} \cdot n_{K2}, \tag{3}$$

where p_{K1}^{0} and p_{K2}^{0} are the limiting values of these parameters for conformers K_1 and K_2 respectively, and the product $p_{Ki}^{0} \cdot n_{Ki}$ reflects the contribution of the conformer K_1 to the parameter $\hat{p}$.

In order to estimate the conformational composition of 3,3-disubstituted piperidin-4-ones 1-5 and 7, as the parameters $\hat{p}$ we selected the transvicinal coupling constants $^3J(5\text{-}H_a, 6\text{-}H_a)$ and $^3J(5\text{-}H_e, 6\text{-}H_e)$, the long-range coupling constants $^4J(2\text{-}H_d, 6\text{-}H_e)$ and $^3J(5\text{-}H_e, 6\text{-}H_e)$, and also the difference between the chemical shifts of the protons 6-H_e and 6-H_a ($\Delta\delta = \delta 6\text{-}H_e) - \delta(6\text{-}H_a)$), since for a change in the position of the conformational equilibrium $K_1 \rightleftarrows K_2$, it is specifically these parameters which change the most substantially (Tables 1 and 2). As the limiting values of the parameter p_{Ki}^{0} for conformers K_1 and K_2, we selected the average values of the corresponding coupling constants and $\Delta\delta$ for the conformationally homogeneous piperidin-4-ones 8 and 9 (Tables 1 and 2):

$$^3J^0\ (5\text{-}H_a, 6\text{-}H_a) = 11.75\ \text{Hz}\ (J_{aa}^{0});\ ^3J^0\ (5\text{-}H_e, 6\text{-}H_e) = 2.98\ \text{Hz}\ (J_{ee}^{0});$$

$$^4J^0\ (2\text{-}H_a, 6\text{-}H_a) = 2.78\ \text{Hz}\ (J_{aa}^{0});\ ^4J^0\ (2\text{-}H_e, 6\text{-}H_e) = 0.25\ \text{Hz}\ (J_{ee}^{0});$$

$$\Delta\delta^0 = \delta\ (6\text{-}H_e)-\delta(6\text{-}H_a) = 0.74\ \text{ppm}$$

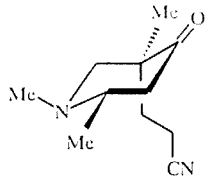
Now in solving Eqs. (1)-(3), we can easily determine the fractional populations of the conformers n_{K1} and n_{K2}. After transformation of Eq. (3), we obtain:

$$\Delta n = \frac{2\hat{J} - J_{aa}^{0} - J_{ee}^{0}}{J_{aa}^{0} - J_{ee}^{0}}; \tag{4}$$

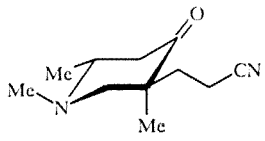
$$\Delta n = \Delta\delta/\Delta\delta^0. \tag{5}$$

For the piperidin-4-ones 1-5 and 7, the values of Δn were calculated using all five selected parameters. The averaged values of Δn and their variances are presented in Table 5, where n_{K1} and n_{K2} are the average values of the fractional populations of conformers K_1 and K_2 respectively, calculated from the five parameters, and $K_{eq} = n_{K1}/n_{K2}$ is the conformational equilibrium constant. Based on the values of K_{eq} for 3,3-disubstituted piperidin-4-ones 1-5 and 7, we determined the differences between the free energies of conformers K_1 and K_2, respectively containing an axial and an equatorial 3-CH_3 group: $\Delta G = -RT\ln K_{eq}$.

We estimated the conformational composition in 3,3-disubstituted piperidin-4-ones 1 and 2 and also in the (1′S, 3S)- and (1′S,3R)-diastereomers of 1-(1′-phenylethyl)-3-methyl-3-(2-cyanoethyl)piperidin-4-one 6a and 6b also on the basis of analysis of the parameters of their ^{13}C NMR spectra. In Table 5, for these compounds we present the values of the direct spin–spin coupling constants ^1J (C, C). In this case, the coupling constant $^1J_{(C_{(3)},3\text{-}\underline{C}H_3)}$ is the most sensitive to the position of the conformational equilibrium. Based on these data, using formula (4) we estimated the difference between the populations of the conformers Δn (Table 5). As the limiting values in this case we used the values of the coupling constants $^1J_{(C_{(5)},5\text{-}\underline{C}H_{3,ax})} = 34.2$ and $^1J_{(C_{(5)},5\text{-}\underline{C}H_{3,eq})} = 37.6$ Hz for the axial and equatorial methyl groups on the quaternary $C_{(5)}$ atom in the conformationally homogeneous trans-(1e,2e,5a-CH_3)- and cis-(1e,2e,5e-CH_3)-isomers of 1,2,5-trimethyl-5-(2-cyanoethyl)-piperidin-4-one 10b and 10a [5].



10 a



10 b

The results obtained suggest significant predominance of the conformer K_2 for the (1′,3S)- and (1′S,3R)-diastereomers of 1-(1′-phenylethyl)-3-methyl-3-(2-cyanoethyl)piperidin-4-one 6a and 6b and support the conclusion that the same conformer predominates for the piperidin-4-ones 1 and 2.

In establishing the orientation of substituents on the quaternary center $C_{(3)}$ in the predominant conformer K_2 and the minor conformer K_1 of piperidin-4-ones 1-7 using ^1H NMR spectroscopy, as the criterion we used the stereoselective effect of the magnetic anisotropy of the carbonyl group, manifested in the shielding of the equatorial protons and groups on the adjacent carbon atom [9]. This effect is observed, for example, for the protons 5-H_a and 5-H_e in piperidin-4-ones 8 and 9 (Table 1) and for the axial and equatorial 5-CH_3 groups in diastereomers 10a and 10b: $\delta_{(5\text{-}CH_{3,ax})} = 1.28$, $\delta_{(5\text{-}CH_{3,eq})} = 1.00$ ppm [9]. The same should be also observed for protons of the 3-CH_3 group in piperidin-4-ones 1-7. If as the starting value we take the chemical shift of the equatorial 5-CH_3 group in cis-(2e,5e-CH_3)-piperidin-4-one 10b (1.00 ppm, [5]), then the downfield shift for the 3-CH_3 group in piperidin-4-ones 1-4 may be connected with the appearance of a certain fraction of conformer with an axial methyl group in the 3 position. In this case, the change in chemical shift values for the 3-CH_3 group upon going from compound 1 to compounds 2-4 suggests that for piperidin-4-ones 2-4, the population of conformer K_2 with an equatorial methyl group on the $C_{(3)}$ atom is greater than for piperidin-4-one 1. Consequently, in the conformer K_2 predominant in the conformational equilibrium $K_1 \rightleftarrows K_2$ for 3,3-disubstituted piperidin-4-ones 1-7, the group 3-CH_3 is in an axial position.

However, we cannot draw a conclusion concerning the preferred orientation of substituents on the quaternary $C_{(3)}$ atom in the predominant and minor conformers of 3,3-disubstituted piperidin-4-ones 1-7 on the basis of analysis of their ^{13}C NMR spectra: the ^{13}C chemical shifts of the 3-CH_3 groups in piperidin-4-ones 1-3 and 6a, b (Table 3) occupy an intermediate position between the values characteristic for equatorial (18.61 ppm) and axial (21.76 ppm) CH_3 groups bonded to a quaternary carbon center in diastereomers 10a and 10b [5].

Thus, based on conformational analysis of 3,3-disubstituted piperidin-4-ones 1-7 done using ^1H and ^{13}C NMR spectroscopy, we can draw the conclusion that these compounds are conformationally inhomogeneous, and that the conformational equilibrium is shifted toward the conformer K_2 with an equatorial methyl group on the $C_{(3)}$ atom.

We observe a dependence of the position of the conformational equilibrium on the nature of the substituent on the nitrogen atom of the piperidine ring: with an increase in the bulk of the substituent, the fractional population of conformer K_2 with an equatorial 3-CH_3 group increases in equilibrium.

Moreover, we observe an increase in the fractional population of conformer K_2 for piperidin-4-ones 2,3,5, and 7, containing carbomethoxy- and acetylethyl substituents on the $C_{(3)}$ atom, compared with their 3-(2-cyanoethyl)-substituted analogs 1,4, and 6. This suggests a decrease in the conformational energy of the substituents on the quaternary carbon atom in the α-position relative to the carbonyl group in piperidin-4-ones in the series:

$$CH_3 > CH_2CH_2CN > CH_2CH_2COOMe \sim CH_2CH_2COMe$$

In the second part of this work, we carried out conformational analysis of (+)-(3S)-enantiomers of piperidin-4-ones 1 and 2 on the basis of circular dichroism (CD) data in solvents of different polarities.

In the CD spectrum of the (+)-(3S)-enantiomer 1 in heptane, in the 300 nm region we observe a positive Cotton effect (CE) for the $n \rightarrow \pi^*$ transition of the carbonyl chromophore with molecular ellipticity $[\theta]$ equal to +1100°. In methanol, the trend in the CD curve does not change, but we observe a marked decrease in the intensity and a hypsochromic shift of the maximum ($\Delta\lambda_{max} \approx 10$ nm) (Fig. 1). Analogous behavior of the CD curves and the sign of the Cotton effect for the $n \rightarrow \pi^*$ transition of the carbonyl chromophore in solvents of different polarities is also observed for the (+)-(3S)-enantiomer 2 (Fig. 2).

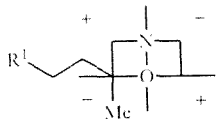
TABLE 4. Spin–Spin Coupling Constants $^1J(C,C)$ (Hz) in Piperidin-4-ones 1,2,6

Compound	C_2–C_3	C_3–C_4	C_4–C_5	C_5–C_6	C_3,C_3-CH_3	C_3–C_5	C_3,C_3-CH_2-CH_2
1	34,7	—	38,0	33,8	36,1	9,3	—
2	34,9	38,1	38,1	34,0	36,7	9,1	—
*6*a	34,6	37,7	38,2	34,8	36,3	—	34,9
*6*b	34,4	37,7	38,2	34,8	36,8	—	34,9

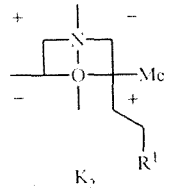
TABLE 5. Results of Calculations of Conformational Equilibrium $K_1 \rightleftarrows K_2$ for 3,3-Disubstituted Piperidin-4-ones 1-7

Compound	Δn, %	n_{K2}, %	n_{K1}, %	K_{eq}	ΔG_{298}, kJ/mole
1	11,2 ± 2,8	55,6	44,4	1,25	-0,54
2	43,2 ± 4,6	71,6	28,4	2,52	-2,29
3	40,8 ± 3,9	70,4	29,6	2,38	-2,15
4	24,8 ± 4,9	62,4	37,6	1,66	-1,26
5	48,0 ± 1,4	74,0	26,0	2,85	-2,59
*6*a	23,5 ± 4,8	61,7	38,3	1,61	-1,18
*6*b	52,9 ± 2,5	76,5	23,5	3,26	-2,93
7	65,8 ± 4,9	82,2	17,1	4,85	-3,91

For the (+)-(3S)-enantiomers of conformationally inhomogeneous 3,3-disubstituted piperidin-4-ones 1 and 2, in the CD spectra we might expect the appearance of two dichroism bands, each of which should correspond to the $n \rightarrow \pi^*$ transition of the carbonyl chromophore in an individual conformer. Let us consider the octant diagrams for both conformers K_1 and K_2.



K_1



K_2

According to the octant rule, for conformer K_1 the octant sign is determined only by the position of the axial 3-CH_3 group. Consequently, this conformer should be characterized by a negative Cotton effect in the region of the $n \rightarrow \pi^*$ transition. However, the integrated intensity of this Cotton effect R_{K1} will be less than the rotatory power of the pure conformer R_{K1}^*, since

$$R_{K1} = n_{K1} \cdot R^*_{K1}, \tag{6}$$

where n_{K1} is the fractional population of conformer K_1 in conformational equilibrium, and $n_{K1} \cdot R^*_{K1}$ is the A "component", making a negative contribution to the overall CD band.

In conformer K_2, the contribution to the Cotton effect for the $n \rightarrow \pi^*$ transition of the carbonyl chromophore comes from the axial 2-cyanoethyl group falling within the positive octant, and therefore for this conformer we can expect a positive sign of the Cotton effect. Its integrated intensity R_{K2} is:

$$R_{K2} = n_{K2} \cdot R^*_{K2}, \tag{7}$$

where n_{K2} is the fractional population of conformer K_2 in conformational equilibrium, and $n_{K2} \cdot R^*_{K2}$ is the B "component", making a positive contribution to the overall CD band.

Consequently, the positive Cotton effect bands for the $n \rightarrow \pi^*$ transition of the carbonyl chromophore experimentally observed for the (+)-(3S)-enantiomers of piperidin-4-ones 1 and 2 are the result of superposition of the dichroism bands for components A and B of opposite signs.

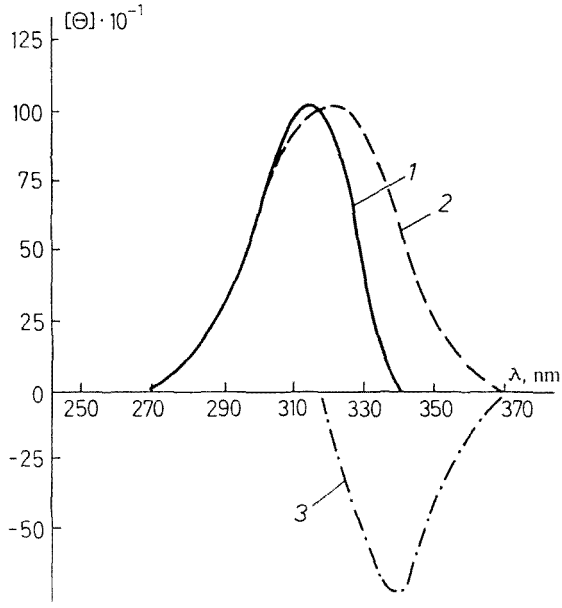


Fig. 1. Experimental CD curve for (+)-(3S)-dimethyl-3-(2-cyanoethyl)piperidin-4-one 1 in heptane (1, ——); Gaussian curve of component B (2, – – –); calculated curve of component A (3, –·–).

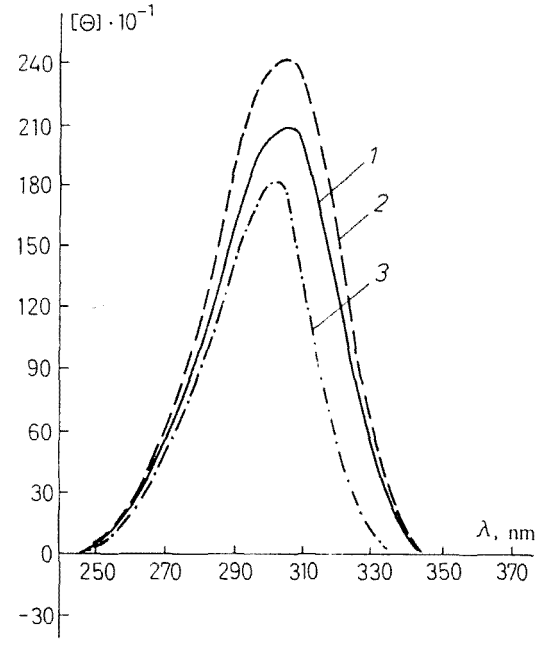


Fig. 2. CD curves for (+)-(3S)-1,3-dimethyl-3-(2-methoxycarbonylethyl)piperidin-4-one 2 in heptane (1, ——), in methylene chloride (2, in methylene chloride (2, – – –), in methanol (3, –·–).

In order to determine the ratio of conformers K_1 and K_2, we need to calculate the rotatory powers R_{K1} and R_{K2} of the corresponding electronic transitions of components A and B. The rotatory power of the electronic transition R for a CD band of Gaussian shape is defined as its integrated intensity and is calculated from the formula

$$R = 0.407 \cdot 10^{-38} \cdot \frac{\Delta\varepsilon_0 \cdot \Delta}{\nu_0} \quad \text{or} \quad R = 1.234 \cdot 10^{-42} \cdot \frac{[\Theta]_0 \cdot \Delta}{\nu_0} \,, \tag{8}$$

where ν_0, $[\theta]_0$, and $\Delta\varepsilon_0$ are the wavenumber, ellipticity, and dichroism absorption at the maximum of the band, while Δ is its reduced halfwidth.

However, as we see from Figs. 1 and 2, the experimental CD curves for (+)-(3S)-enantiomers of piperidin-4-ones 1 and 2 have an irregular shape. Therefore in our case, in order to calculate R on the experimental CD curves we need to isolate the individual Gaussian band of one of the components. Then the rotatory power of the electronic transition of the second component can be determined as the difference between the rotatory powers of the overall band and the Gaussian band of the first component.

As an example, let us consider the case of determination of the ratio of conformers K_1 and K_2 for the (+)-(3S) enantiomer of piperidin-4-one 1 based on CD data in heptane (Fig. 1). The calculations were done using the technique in [10].

In order to determine the satisfactory criterion for a Gaussian shape of the homogeneous section on the experimentally observed spectral line, we tested the linearity of the function

$$\frac{d\lg\Delta\varepsilon}{d\nu} = f\ (\nu) \text{ (first derivative method)} \tag{9}$$

both for the long-wavelength (335-325 nm) and for the short-wavelength (295-275 nm) branches of the Cotton effect for the $n \rightarrow \pi^*$ transition of the carbonyl chromophore. For each case, we can write the regression equation:

$$\Delta\lambda = 335 - 325 \text{ nm}: \frac{\Delta\lg\Delta\varepsilon}{\Delta\nu} = 2.961 + 0.094\ \nu_m \quad \text{and} \tag{10}$$

$$\Delta\lambda = 295 - 275 \text{ nm}: \frac{\Delta\lg\Delta\varepsilon}{\Delta\nu} = -21.568 - 0.679\ \nu_m \,. \tag{11}$$

However, the regression characteristics for the two cases are quite different:

$$\sigma_1 = 0.041 \text{ and } r_1 = 0.86;$$
$$\sigma_2 = 0.214 \text{ and } r_2 = 0.21.$$

The values obtained for the correlation coefficient and the standard error suggest that in the first case, we observe a relationship between the parameters

$$\nu_m \quad \text{and} \quad \frac{\Delta\lg\Delta\varepsilon}{\Delta\nu} \,,$$

while in the second case such a relationship is absent. On this basis, the section of the "pure" band is isolated specifically on the short-wavelength branch of the experimental curve (293-275 nm).

For this section, the dependence

$$\lg\Delta\varepsilon = f[(\nu-\nu_0)^2] \text{ (trial-and-error method)} \tag{12}$$

also is linear and can be represented in the form of a first-order equation:

$$\lg\Delta\varepsilon = -0.600+0.045\ (\nu-\nu_0)^2 \tag{13}$$

In the graphical variant, by the first-derivative method we find two parameters of the Gaussian band:

$$\nu_0 = 31.51 \text{ kK and } \Delta = 3.04 \text{ kK}.$$

By the trial-and-error method for $\nu_0 = 31.51$ kK we find the following parameters for the same band:

$$\Delta = 3.10 \text{ kK and } \Delta\varepsilon_0 = 0.2512 \text{ deg}.$$

The average value of the halfwidth is equal to $\Delta = 3.07$ kK.

Thus the parameters of the partial band are:

$$\nu_0 = 31.51 \text{ kK}, \lambda_0 = 317.36 \text{ nm}; \Delta\varepsilon_0 = 0.2512 \text{ deg};$$
$$[\Theta]_0 = 828.96 \text{ deg}; \Delta = 3.07 \text{ kK}. \tag{14}$$

Based on the parameters in (14) found by the combined first-derivative and trial-and-error methods, using Eq. (15) we calculated the complete band of Gaussian shape (Fig. 1).

$$\Delta\varepsilon = \Delta\varepsilon_0 e^{-\left(\frac{\nu - \nu_0}{\Delta}\right)^2}. \tag{15}$$

In Fig. 1, in graphical form we present the results of subtraction of the partial band from the overall spectrum. The calculated positive Gaussian band (Fig. 1) is assigned to the $n \rightarrow \pi^*$ transition of the carbonyl chromophore of component B, formed by conformer K_2. The rotatory power of the transition R_{K2} is determined from the formula

$$R_{K_2} = 1.234 \cdot 10^{-42} \frac{898.96 \cdot 3.07}{31.51} = 10.8 \cdot 10^{-41} \text{ CGSE}. \tag{16}$$

The rotatory power R of the CD band of irregular shape observed experimentally for the (+)-(3S)-enantiomer 1 was determined using the trapezoidal rule

$$R = 0.696 \cdot 10^{-42} \cdot \Delta\nu \cdot \sum_{k=2}^{n-1} \left(\frac{[\Theta]}{\nu}\right)_k \text{ CGSE}. \tag{17}$$

For a step $\Delta\nu = 0.5$ kK, we obtain:

$$R = 5.72 \cdot 10^{-41} \text{ CGSE}.$$

The rotatory power of the experimental CD band represents the overall rotatory power of the $n \rightarrow \pi^*$ transition of the carbonyl chromophore in components A and B:

$$R = R_{K1} + R_{K2}.$$

Then we can write:

$$5.72 \cdot 10^{-41} = 10.8 \cdot 10^{-41} + R_{K1}.$$

Consequently,

$$R_{K1} = -5.08 \cdot 10^{-41} \text{ CGSE}.$$

According to (6) and (7), we can write:

$$n_{K1} \cdot R^*_{K1} = 10.80 \cdot 10^{-41} \text{ CGSE},$$
$$n_{K2} \cdot R^*_{K2} = -5.08 \cdot 10^{-41} \text{ CGSE}.$$

Then

$$\frac{n_{K_2} \cdot R^*_{K_2}}{n_{K_1} \cdot R^*_{K_1}} = 2.13.$$

TABLE 6. Rotatory Powers of Components A and B and the Experimental CD Curve of the (+)-(3S)-Enantiomer 2, 10^{-41} (CGSE)

Component	Rotatory power	Heptane	Methylene chloride	Methanol
B	R_{K2}	4,85	3,93	2,60
Experimental curve	R	2,06	2,09	1,80
A	R_{K1}	-2,79	-1,84	-0,80

Obviously, not knowing the values of the rotatory powers for each of the conformers R^*_{K1}, we cannot solve the problem of the fractional populations of the conformers in conformational equilibrium. Therefore to solve this problem, we made use of the following hypotheses.

According to [10, 11], in the CD spectra of α-substituted cyclohexanones, the contributions (Δa) to the Cotton effect at 300 nm from the axial methyl and isopropyl groups found in the α-position relative to the carbonyl group are +67 and +98 respectively. In other words, the contributions to the Cotton effect for the $n \rightarrow \pi^*$ transition of the carbonyl chromophore from the single carbon atom of the CH_3 group and the three carbon atoms of the isopropyl group are comparable in magnitude and are assigned as

$$\Delta a_{i\text{-}Pr} / \Delta a_{Me} = 1.46 \tag{18}$$

Accordingly, the rotatory power of the conformer K_2, containing an axial 2-cyanoethyl substituent in the 3 position (3 carbon atoms) and the rotatory power of the conformer K_1 with an axial 3-CH_3 group (1 carbon atom) also is assigned as

$$R^*_{K2}/R^*_{K1} = 1.46.$$

Then we can write:

$$n_{K2}/n_{K1} = 1.46,$$
$$n_{K2} + n_{K1} = 1.$$

From this $n_{K2} = 0.59$ and $n_{K1} = 0.41$ (Table 7). Thus if the hypothesis in (18) is satisfied, then for the (+)-(3S)-enantiomer of piperidin-4-one 1, the equilibrium mixture in heptane contains 41% conformer K_1 with an axial 3-CH_3 group and 59% conformer K_2 with an equatorial 3-CH_3 group.

If we assume that the rotatory powers of conformers K_1 and K_2 are approximately identical, i.e.,

$$R^*_{K2}/R^*_{K1} = 1.0, \tag{19}$$

then the fractional populations of the conformers in the equilibrium mixture in heptane are

$$n_{K2} = 0.68 \text{ and } n_{K1} = 0.32 \text{ (Table 7).}$$

Analogous calculations of the rotatory powers for the $n \rightarrow \pi^*$ transitions of the carbonyl chromophore of components A and B were also done for the (+)-(3S)-enantiomer of piperidin-4-one 2 on the basis of analysis of the CD spectra in solvents of different polarities. The results are presented in Table 6.

According to hypothesis (18), the conformational composition for the (+)-(3S)-enantiomer 2 in solvents of different polarities can be represented as follows:

$n_{K2}:n_{K1}$ (%)
Heptane 55:46
Methylene chloride 60:40
Methanol 69:31

TABLE 7

Compound	Solvent	Conformational composition, %		Hypothesis	Method
		n_{K1}	n_{K2}		
1	Heptane	41,0	59,0	(18)	CD
	$CDCl_3$	44,4	55,6		NMR
2	Heptane	33,3	67,0	(20)	CD-NMR
		36,0	64,0	(19)	CD
		45,0	55,0	(18)	CD
	$CHCl_3$	28,4	71,6		NMR
	CH_2Cl_2	28,4	71,6	(20)	CD-NMR
		32,0	68,0	(19)	CD
		40,0	60,0	(18)	CD
	CH_3OH	21,0	79,0	(20)	CD-NMR
		24,0	76,0	(19)	CD
		31,0	69,0	(18)	CD

Based on the hypothesis (19) that the rotatory powers of the individual conformers K_1 and K_2 are equal, for the (+)-(3S)-enantiomer 2, we obtain the following conformational composition:

$n_{K2}:n_{K1}$ (%)
Heptane 64:36
Methylene chloride 68:32
Methanol 76:24

In the third variant of the solution, to estimate the fractional populations of conformers K_1 and K_2 we drew on data on the conformational composition of the (+)-(3S)-enantiomer 2, obtained from analysis of its NMR spectra. Apparently the conformational composition of piperidin-4-one 2 changes very insignificantly upon going from chloroform to methylene chloride. Accordingly, we can write:

$$n_{K2}(CDCl_3) = n_{K2}(CDCl_2) = 0.716 \text{ and } n_{K1}(CDCl_3) = n_{K1}(CD_2Cl_2) = 0.284.$$

Then based on CD data in methylene chloride, we can determine the rotatory powers of the conformers R_{K2}^* and R_{K1}^*:

$$R^*_{K2} \cdot 0.716 = 3.93 \cdot 10^{-4} \text{ CGSE and } R^*_{K1} \cdot 0.284 = -1.84 \cdot 10^{-41} \text{ CGSE},$$

from which

$$R^*_{K2} = 5.49 \cdot 10^{-41} \text{ CGSE}, \quad R^*_{K1} = -6.48 \cdot 10^{-41} \text{ CGSE} \quad \text{and} \quad R^*_{K2} / R^*_{K1} = 0.85 \tag{20}$$

The fractional populations of conformers K_1 and K_2 calculated on the basis of hypothesis (20) for the (+)-(3S)-enantiomer 2 in heptane and methanol are presented in Table 7.

The results of the conformational analysis of 3,3-disubstituted piperidin-4-ones 1 and 2 carried out by NMR spectroscopy and CD methods, presented in Table 7, suggest that:

1) data on the conformational composition of piperidin-4-ones obtained for solvents close in polarity on the basis of analysis of the NMR and CD spectra agree reasonably well;

2) spectropolarimetry can be used with a high degree of reliability for stereochemical analysis of conformationally inhomogeneous piperidine systems. Moreover, application of spectropolarimetry for solving conformational analysis problems allows us to significantly expand the number of solvents we can use for this purpose;

3) the most accurate results for calculation of the composition of conformational equilibrium of piperidin-4-ones in different solvents when using spectropolarimetry can be obtained only when we draw on data on the conformational composition of the substrate obtained for one of the solvents using NMR spectroscopy (hypothesis (20));

4) the fraction of conformer K_2 with an axial 3-CH_3 group increases with an increase in the polarity of the solvent.

EXPERIMENTAL

The ^1H NMR spectra were taken on a Bruker WM-400 spectrometer with operating frequency for the protons 400 MHz with internal standard TMS. The ^{13}C NMR spectra were obtained on a Bruker WM-400 spectrometer with operating frequency for the ^{13}C 100.6 MHz. The chemical shifts are given on the δ scale.

The circular dichroism spectra were registered on a Jasco J-20 spectropolarimeter in cuvets with $l = 0.1$ cm at 20°C.

REFERENCES

1. G. V. Grishina and E. L. Gaidarova, Khim. Geterotsikl. Soedin., No. 8, 1072 (1992).
2. E. L. Gaidarova and G. V. Grishina, Synlett., No. 1, 89 (1992).
3. E. L. Gaidarova, K. Rosher, A. É. Aliev, and G. V. Grishina, Khim. geterotsikl. Soedin., No. 10, 1379 (1992).
4. A. J. Jones and M. M. A. Hassan, J. Org. Chem., **37**, 2332 (1972).
5. G. V. Grishina, E. L. Gaidarova, and A. É. Aliev, Khim. Geterotsikl., No. 10, 1369 (1992).
6. G. V. Grishina, S. A. Abdulganeeva, V. M. Potapov, I. A. Ivanova, A. A. Espenbetov, Yu. T. Struchkov, I. A. Grishina, and A. T. Lutsenko, Khim. Geterotsikl. Soedin., No. 12, 1656 (1985).
7. M. Karplus, J. Am. Chem. Soc., **85**, 2870 (1963).
8. M. Barfield and B. Chakrabarti, Chem. Reviews, **18**, 2870 (1969).
9. H. Günther, Introduction to an NMR Spectroscopy Course [Russian translation], Mir, Moscow (1984), p. 86.
10. V. V. Dunina, E. G. Rukhadze, and V. M. Potapov, Synthesis and Investigation of Optically Active Substances [in Russian], Izdat. MGU, Moscow (1979), p. 5.
11. H. Ripperger, Z. Chemie, **6**, 161 (1966).