ORIENTATION OF THE UNSHARED ELECTRON PAIR OF THE NITROGEN ATOM IN N-SUBSTITUTED 2,5-DIMETHYL-4-PIPERIDINONES

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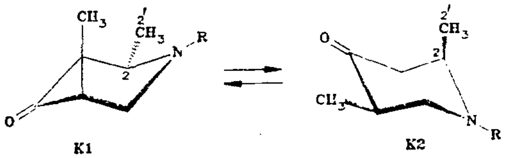
The axial orientation of the unshared electron pair of the nitrogen atom in cis isomers of N-substituted [R = H, CH_3, $CH_2C_6H_5$, or $C(CH_3)_3$] 2,5-dimethyl-4-piperidinones was proven by using the stereospecificity of the direct $^{13}C-^{13}C$ spin-spin coupling constants, vicinal $^{13}C-^{1}H$ spin-spin coupling constants, and two-dimensional nuclear-Overhauser-effect spectroscopy (NOESY).

In considering the conformational equilibrium in cis isomers of N-substituted 2,5-dimethyl-4-piperidinones [R = H, CH_3, $CH_2C_6H_5$, or $CH(CH_3)C_6H_5$], Prostakov et al. [1] and Leshcheva et al. [2] proposed different orientations of N substituents in conformer K2. Thus, in [1], on the basis of an analysis of proton NMR spectra, it was concluded that the R substituent is oriented axially, whereas in [2], in a discussion of the ^{13}C chemical shift, its equatorial orientation was considered. In both cases, the authors cited no direct proofs of either orientation of the N substituent.



For unambiguous resolution of this problem, we used the stereospecificity of the direct spin-spin coupling constant $^1J_{CC}$ with respect to the orientation of the unshared electron pair of the nitrogen atom [3]: the closeness of the unshared electron pair in the cis position to the neighboring C—C bond leads to a significant positive contribution to the value of $^1J_{CC}$. The spin-spin coupling constants $^1J_{C(2),C(2')}$ for a mixture of the cis and trans isomers of the following N-substituted 2,5-dimethyl-4-piperidinones were measured:

			$^1J_{C(2),C(2')}$, Hz				
I	R=H	cis	37.9	III	$R=CH_2C_6H_5$	cis	36.4
		trans	38.2			trans	39.0
II	$R=CH_3$	cis	36.8	IV	$R=C(CH_3)_3$	cis	35.5
		trans	38.9			trans	37.8

As is evident form the presented values of $^1J_{C(2),C(2')}$, there is a decrease of this constant both in the series of cis isomers I-IV and in going from the trans isomer to the corresponding cis isomers. The trans isomers I-III are conformationally homogeneous and are represented by a chair-like conformation with equatorial orientation of all substituents [1, 2], i.e., with a cis (a, e) position of the unshared electron pair of the nitrogen and the $C_{(2)}$—$C_{(2')}$ bond (according to [4] the trans isomer of IV has a "tapered boat" conformation with pseudoaxial orientation of the $C_{(2)}$—$C_{(2')}$ bond). Conformer K1 for the cis isomers is also characterized by a cis (a, e) arrangement of the electron pair and $C_{(2)}$—$C_{(2')}$ bond [1, 2], and therefore the decrease of $^1J_{C(2),C(2')}$ in the cis isomers can be explained by the relation of this constant to the fraction of conformer K2 with trans (a, a) orientation of the unshared electron pair and the $C_{(2)}$—$C_{(2')}$ bond. In such a conformer, there is no positive contribution from the unshared electron pair of the nitrogen atom to $^1J_{C(2),C(2')}$. In addition, according to [3], the value of $^1J_{C(2),C(2')}$ for 1,2-dimethyl-4-tert-butylpiperidine with fixed cis (a, e)

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and trans (a, a) orientations of the unshared electron pair and the $C_{(2)}-C_{(2')}$ bond is 39.3 and 35.3 Hz, respectively. The second value is close to the value of this constant measured for the cis isomer of IV, which, according to our ^1H NMR ($^3J_{2e3e}$ = 2.2 Hz and $^3J_{5a6a}$ = 11.0 Hz) and ^{13}C NMR data ($^3J_{C(2'),H(3a)}$ = 8.3 Hz) is completely represented by conformer K2. Therefore, the values of the spin-spin coupling constant $^1J_{C(2),C(2')}$ indicate equatorial orientation of the N substituent in conformer K2. According to the Karplus-type angular dependence for the spin-spin coupling constant $^3J_{CH}$ [5], this is also indicated by the spin-spin coupling constants $^3J_{C(1'),H(6(2)e)} = {}^3J_{C(1')H(6a)}$ = 2.3 Hz that we measured for the cis isomer of piperidone II.

The large content (~80%) of the cis isomer in the mixture of the isomers of piperidone IV and also the absolute predominance of conformer K2 in it assisted the analysis of the two-dimensional NOESY spectrum in this case for the cis isomer. The NOESY spectrum contained cross peaks of approximately identical intensity from the proton pairs of the cis isomer of $C(CH_3)_3-H_{(6e)}$ (0.97...2.90 ppm) and $C(CH_3)_3-H_{(6a)}$ (0.97-2.37 ppm), which is possible only with equatorial orientaiton of the tert-butyl group.

Thus, despite the increase of the steric 1,2 interaction, which was ascribed decisive significance in [1], in the cis isomers of the N-substituted 2,5-dimethyl-4-piperidinones the bulky N substituents retain equatorial orientation, and the conclusions of [1] regarding this question must be considered erroneous.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker WM-400 spectrometer. The values of the $^{13}C-^{13}C$ spin-spin coupling constants were measured with an INADEQUATE pulse sequence using mixtures of the cis and trans isomers of piperidones I-IV (in $CDCl_3$, 100.6 MHz). The two-dimensional NOESY spectrum (in C_6D_6, 400 MHz) was obtained using a standard pulse sequence and a mixing period of 1.0 sec.

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