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INVESTIGATION OF THE BARRIERS TO RETARDED INTERNAL ROTATION IN N-ACYL-1-METHYL-1,2,3,4-TETRAHYDROISOQUINOLINES

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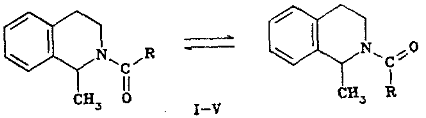
The effect of a number of alkyl substituents attached to the carbon atom of the acyl group on the activation parameters of retarded internal rotation about the C–N bond in N-acyl-1-methyl-1,2,3,4-tetrahydroisoquinolines was studied. Correlation of the free energies of activation $\Delta G^{\neq}_{298}$ with the steric factors (Es) and the σ^* substituent constants was examined.

It is known that the C–N bond in amides has partially double character, and this leads to the possibility of the existence of amides in the form of an equilibrium mixture of two relatively slowly interconverting conformers. The conformational equilibria in a number of N-acyl-1-methyl-1,2,3,4-tetrahydroisoquinolines were previously studied by NMR spectroscopy [1]. In the present research we investigated the effect of alkyl substituents attached to the carbon atom of the acyl group in I-V on the parameters of activation of retarded rotation about the C–N bond.



I–V

Z conformer E conformer

I R=H; II $R=CH_3$; III $R=C_2H_5$; IV $R=n\text{-}C_3H_7$; V $R=t\text{-}C_4H_9$

The determination of activation barriers by NMR spectroscopy with the necessary degree of accuracy requires an analysis of the complete form of the spectral line. For this, we used the DNMR3 program [2, 3], which we adapted to the technical possibilities of the BESM-6 computer. The ^{1}H NMR spectra of I-V at low exchange rates consist of two groups of signals corresponding to Z and E conformers, which exist in equilibrium. The assignment of the signals and the determination of the chemical shifts, spin–spin coupling constants (SSCC), and the parameters of the conformational equilibrium were previously accomplished in [1]. In the present research the populations of the conformers in the calculations were assumed to be independent of the temperature, since the determination of the rate constants for internal rotation for each of the examined compounds was carried out over a rather narrow temperature range, within the limits of which the equilibrium constant changes only slightly [1]. This assumption also seems justified because of the fact that the sensitivity of the form of the line to the equilibrium constants decreases sharply as the rate constant of a dynamic process increases [4].

The rate constants (k) and their temperature dependences necessary for calculation of the activation parameters were determined on the basis of a comparison of the experimental spectra with the theoretical spectra obtained by model calculations by means of the DNMR3 program (see Figs. 1 and 2). For all of the investigated compounds the dependence

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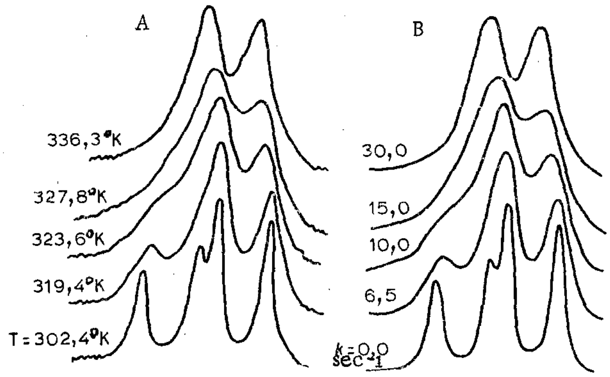

Fig. 1. Form of the line of the signals of the protons of the 1-CH$_3$ group in the experimental (A) and theoretical (B) spectra of the Z and E conformers of N-propionyl-1-methyl-1,2,3,4-tetrahydroisoquinoline (III) for a set of temperatures and rates, respectively.

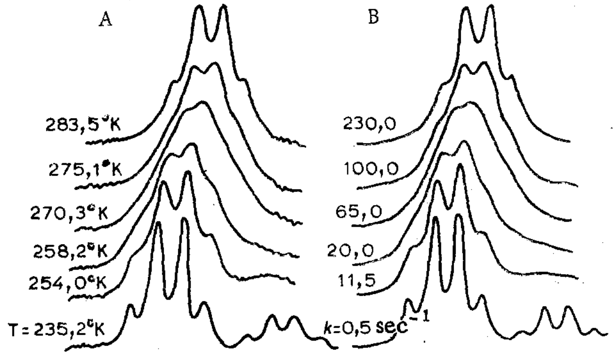

Fig. 2. Form of the line of the signals of the methylidyne 1-H proton in the experimental (A) and theoretical (B) spectra of the Z and E conformers of N-pivaloyl-1-methyl-1,2,3,4-tetrahydroisoquinoline (V).

$$\ln\frac{k}{T}=f\left(\frac{1}{T}\right) \tag{1}$$

has linear character (Fig. 3), and this constitutes evidence for the absence of any other dynamic processes that take place over the selected temperature range at the same time as retarded rotation about the C—N bond.

The activation parameters were calculated on the basis of the equations [5]

$$\Delta G^{\neq}=RT\left(\ln\frac{k_B}{h}-\ln\frac{k}{T}\right) \tag{2}$$

$$\Delta H^{\neq}=-R\cdot\mathrm{tg}\,\alpha \tag{3}$$

$$\Delta S^{\neq}=R\cdot\ln\frac{k}{T}+\frac{\Delta H^{\neq}}{T}-R\cdot\ln\frac{k_B}{h}, \tag{4}$$

where tan α is the slope of linear dependence (1), k_B is the Boltzmann constant, and h is the Planck constant. The free energies ($\Delta G_{298}^{\neq}$), enthalpies ($\Delta H^{\neq}$), and entropies ($\Delta S^{\neq}$) of activation found are presented in Table 1.

The observed regular decrease in the free energy of retarded rotation as the volume of the substituent increases in the I-V series can be explained by two reasons. First, the role of steric hindrance, which increases the energy of the ground state to a greater extent

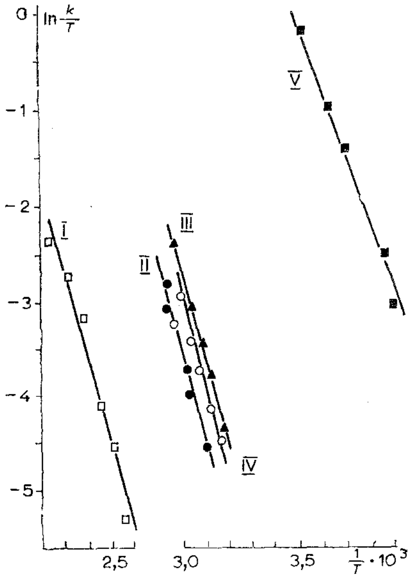

Fig. 3. Temperature dependence of the rate constants for retarded rotation for I-V.

TABLE 1. Parameters of the Conformational Equilibria and Free Energies, Enthalpies, and Entropies of Activation for Retarded Internal Rotation in N-Acyl-1-methyl-1,2,3,4-tetrahydroisoquinolines

Compound	Coalescence temp., K	Amt. of the conformer, %		$K=\frac{[Z]}{[E]}$	$\Delta G^{\neq}_{298}$, kJ/mole	$\Delta H^{\neq}$, kJ/mole	$\Delta S^{\neq}$, J/mole-deg
		Z	E				
I	375	60	40	1,50	89,4±0,4	74,5±4,9	−48,2±11,9
II	309	61	39	1,56	76,1±0,3	79,6±7,5	10,4±13,0
III	301	63	37	1,70	73,9±0,4	79,6±8,0	17,8±14,2
IV	302	61	39	1,56	74,3±0,4	74,9±9,2	1,7±14,3
V	233	78	22	3,55	56,8±0,3	56,9±3,3	0,3±12,6

TABLE 2. Comparison of the Free Energies of Activation of Retarded Internal Rotation about the C—N Bond in I-V (A) and $(CH_3)_2NCOR$ (B)

R	Substituent parameters [8]		$\Delta G^{\neq}_{298}$, kJ/mole	
	E_s	σ^*	A	B [7]
H	0	0	89,4	87,5
CH_3	−1,24	−0,49	76,1	72,4
C_2H_5	−1,31	−0,59	73,9	72,9
n-C_3H_7	−1,60	−0,61	74,3	75,4
t-C_4H_9	−2,78	−0,79	56,8	49,8

than the energy of the transition state, increases. Second, the contribution of the +I effect, which decreases the energy of the transition state to a greater degree than the energy of the ground state, increases in the same order of substituents. It follows from the data in Table 1 that the free energy of activation decreases by 13.3 kJ/mole on passing from N-formyl derivative I to N-acetyl derivative II. This is evidently explained by the fact that the planar structure of the amide fragment is disrupted as a consequence of steric interaction of the bulkier methyl group attached to the carbon atom of the N-acyl substituent with the CH_3 group in the 1 position of the tetrahydroisoquinoline two-ring system. This in turn leads to a decrease in the conjugation of the unshared electron pair of the nitrogen atom with the π electrons of the carbonyl group and a decrease in the barrier to rotation about the C–N bond. A similar effect was observed in a study of retarded rotation about the amide bond in the N-acyl-1,2,3,4-tetrahydroquinoline series [6].

The free energies of activation of retarded rotation about the C–N bond in I-V and in the corresponding aliphatic N,N-dimethylamides [7] are compared in Table 2. Two fundamental conclusions follow from the data presented in Table 2. First, in both series of compounds the barriers to activation correlate better with the steric factors (E_S) than with the σ^* substituent constants: The corresponding coefficients of linear correlation for the I-V series are 0.99 and 0.92, as compared with 0.96 and 0.85 for aliphatic N,N-dimethylamides. Second, the barriers to activation for substituents of the same type in the two compared series of compounds are relatively close. These data constitute evidence that the $\Delta G_{298}^{\neq}$ values are determined chiefly by the character of the substituent attached to the amide carbonyl.

EXPERIMENTAL

The ^1H NMR spectra were recorded with a Varian HA-100D spectrometer. The samples were solutions of the investigated substances (1 mole/liter) in d_6-DMSO (I) or $CDCl_3$ (II-V) with the addition of tetramethylsilane (TMS) (5% by volume) as the internal standard.

The temperature was measured by means of temperature standards (methanol for low temperatures and ethylene glycol for high temperatures) with the aid of the van Geet calibration curve [9]. The effective relaxation times (T_2°) were estimated from the half-widths of the lines of the experimental spectra at the temperatures and were assumed to be independent of the temperature in the calculations.

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