A STUDY OF THE TAUTOMERISM OF THE N-ALKYL-3-METHOXYCARBONYL-4-PIPERIDINONES AND THEIR HYDROCHLORIDES

B. A. Arbuzov, O. A. Erastov, A. B. Remizov, and L. Z. Nikonova

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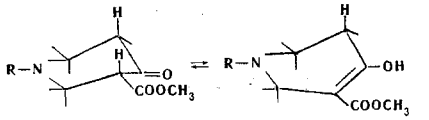
The positions of the equilibria of N-alkyl-3-methoxycarbonyl-4-piperidinones in the liquid state, in water, in alcohols, and in CCl_4 have been determined by IR and UV spectroscopy. It has been shown that Meyer's equation is not satisfied for them. This is due to the high steric requirements of the solvating electron pair of the nitrogen atom. On the basis of the fact that on passing from the methyl ester of cyclohexan-1-one-2-carboxylic acid to the N-alkyl-3-methoxycarbonyl-4-piperidones the position of the equilibrium in the liquid state and in CCl_4 does not shift in the direction of the enol it is deduced that the spatial requirements of the free electron pair of the nitrogen atom do not appreciably exceed the steric requirements of the hydrogen atom. The IR and UV spectra of the chlorides of the N-alkyl-3-methoxycarbonyl-4-piperidinones in the solid state and in water and in alcohols are given.

In recent years, the question of the spatial requirements of the free and solvated electron pair of the nitrogen atom has been discussed repeatedly in the literature [1–10]. Le Fevre and colleagues [1–3] have put forward a hypothesis according to which the steric requirements of the free electron pair of a nitrogen atom are greater than those of a hydrogen atom. Katritzky et al. [4–7] and Allinger et al. [8, 9] throw doubt on this hypothesis. Katritzky et al. [7] give the following sequence of steric requirements: solvated electron pair > hydrogen atom > free electron pair.

In connection with the question of the steric requirements of the electron pair of a nitrogen atom, it is of interest to study the tautomerism of the N-alkyl-3-methoxycarbonyl-4-piperidinones and their hydrochlorides. If the steric requirements of the free solvated electron pair of the nitrogen atom are greater than those of the hydrogen atom, in the N-alkyl-3-methoxycarbonyl-4-piperidinones (I–V) they will be less satisfied in the keto form (two 1, 3-diaxial interactions) than in the enolic form (one 1, 3-diaxial interaction), and this must have an effect on the position of the equilibrium of the forms.



I $R=CH_3$, II $R=C_2H_5$; III $R=C_3H_7$; IV $R=C_4H_9$, V $R=C_5H_{11}$.

If the steric demands of the solvated electron pair of the nitrogen atom are greater, the lower hindrance to the solvation of the heteroatom from the direction of the β-axial hydrogens in the enolic form as compared with the ketonic form must lead to a shift in the position of the equilibrium of the esters I–V in solutions in the direction of the enol to a greater degree the stronger the interaction of the solvent with the heteroatoms of the two forms. As a result, Meyer's equation will not be satisfied, and the deviations from it in a series of solvents of the same chemical type (for example, alcohols) may have an ordered nature. A dissimilar solvation of the heteroatoms in the ketonic and enolic forms of the esters I–V is also possible because of the dissimilar screening of the electron pairs of the nitrogen atoms of the radicals attached to them in the ketonic and enolic forms, as a consequence of the difference in the conformations of the forms. In this case different Brönsted-Izmailov equations will be satisfied for the esters I–V.

The atomic distances (lengths and angles of the bonds) of the $=CH_2$ and $=NR$ groups do not differ substantially [11], and therefore a change in the intrinsic (solvent-independent) equilibrium constant on passing from methyl cyclohexan-1-one-2-carboxylate (VI) to the esters I–V will be determined mainly by the steric requirements of the free electron pair of the nitrogen atom. If they are larger than those of the hydrogen atom, the constant must increase. The influence of changes of the 1, 2-interaction and ΔS on the change in the inherent equilibrium constant on passing from the ester VI to the esters I–V will depend on the nature of the radical on the heteroatom in the esters I–V. In the hydrochlorides of the esters I–IV (VII–X) respectively), there is no isolated electron pair on the nitrogen atom but there is a hydrogen atom.

The tautomerism of the esters I–V and VII–X has not previously been studied. For its study we used IR and UV spectroscopy. From the absorption in the UV spectra, the contents of the enols in alcoholic solutions of the esters I–V and in a hexane solution of the III were calculated. For the molar absorption coefficient of the enolic form of the esters I–V we used the molar absorption coefficient of the enolic form of ethyl cyclohexan-1-one-2-carboxylate (ε_{enol} 10850) [12]. It is considered that the molar absorption coefficient of the enolic form of a β-keto ester does not depend on the nature of the solvent, with constancy of the absorption maximum [13]. The results are given in Table 1.

The constants of the tautomeric equilibrium (K_T) of the esters I–V in alcoholic solutions were determined and a graph was constructed of their dependence on the enolizing capacity of the solvent (L). In all cases Meyer's equation was not satisfied, while an equation of the type $Y = AX + B$ was satisfied (Fig. 1). Since one and the same Brönsted-Izmailov equation is satisfied for the esters I–V (Fig. 2), their failure to satisfy Meyer's equation can be explained by the high steric

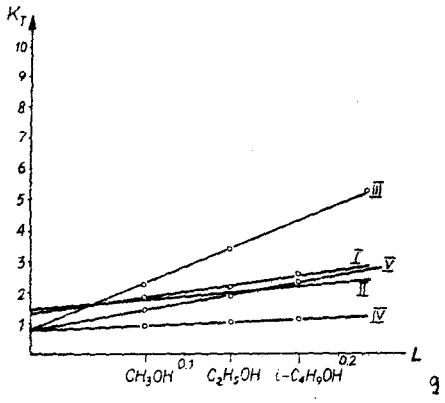


Fig. 1. Constants of the tautomeric equilibrium of esters I–V in alcoholic solutions.

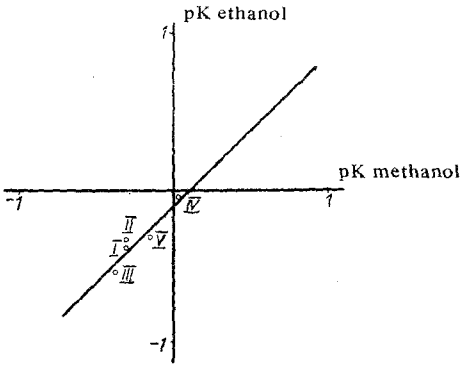


Fig. 2. Brönsted-Izmailov equation for the esters I–V.

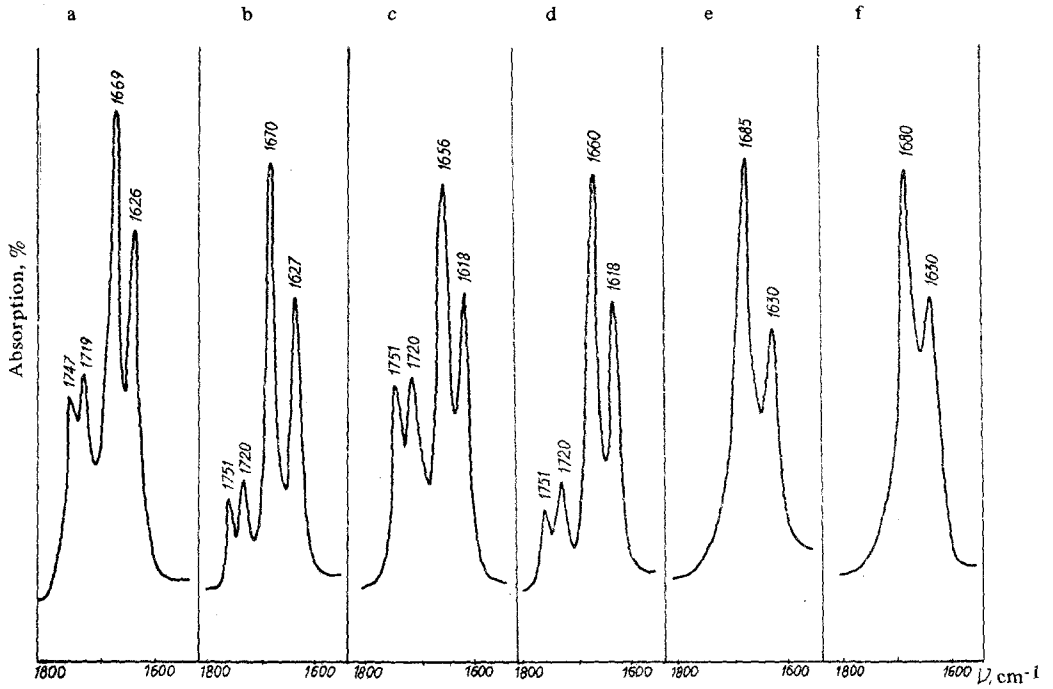


Fig. 3. IR spectra: a) III in the liquid state; b) III in CCl_4; c) VI in the liquid state; d) VI in CCl_4; e) VII–X in the solid state; f) VII–X in isobutanol.

Table 1

UV Absorption and Content of the Enolic Form in Solutions of Esters I–V

Solvent	λ_{max}, nm	I		II		III		IV		V	
		ε	%	ε	%	ε	%	ε	%	ε	%
Methanol	252	7200	66.3	7200	66.3	7600	70.0	5400	49.7	6300	58.6
Ethanol	252	7500	69.1	7200	66.3	8400	77.4	5700	52.5	7250	66.8
Isobutanol	252	7900	72.8	7700	70.9	9050	83.4	6000	55.3	7650	70.5
Hexane	252					10000	92.1				

Table 2

UV Absorption of the Hydrochlorides VII–X in Solvents

Compound	Solvent	λ_{max}, nm	ε after the following intervals of time from the preparation of the solution, hours							
			1–5	24	48	72	120	144	168	264
VII	Water	245	3300*	3300	3300					
	Methanol	245	10000	8000	6000	6000		5600		
	Ethanol	245	9100	8600	8300	8100				
	Isobutanol	245	9700	8500	8400	8400				
VIII	Water	245		3900		3900				
	Methanol	245		7350		6500	6200		5850	5600
	Ethanol	245		8150		8000	8000			
	Isobutanol	245	9200			9000	8300			
IX	Water	245	4300		4300		4200			
	Methanol	245	9000		7000					
	Ethanol	245	8500		8350					
	Isobutanol	245			8600		8500		8500	
X	Water	245	3900	3900	3900	3900		3900		3700
	Methanol	245	9600	7300	6400	5900				5700
	Ethanol	245	10000	9000	9000	9000		8000		7850
	Isobutanol	245	9500	8700	8700	8400		8400		8400

*Only 30 min after the preparation of the solution, ε = 3300.

requirements of the solvated electron pair of the nitrogen atom. The differences in the contents of the enolic form in the esters I–V in alcoholic solution are apparently due to the influence of the radical on the nitrogen atom on the intrinsic equilibrium constants of the esters. From the IR spectra in the liquid state and CCl_4, in the ester IV the amount of enolic form is somewhat less, and in the ester III somewhat greater, than in the esters I, II, and V.

Fig. 3 gives the IR spectra in the 1800–1600 cm^{-1} region of the esters III and VI. They show that the position of the equilibrium of ester III in the liquid state (Fig. 3, a) and in CCl_4 (Fig. 3, b) is not displaced appreciably in the direction of the enolic form as compared with the position of the equilibrium of ester VI in the liquid state (Fig. 3, c) and in CCl_4 (Fig. 3, d), respectively. The features of the UV spectra confirm the information derived from the IR spectra on the absence of a shift in the position of the equilibrium in the direction of the enol in nonpolar solvents on passing from ester III to ester VI: in hexane ester III contains 92.1% of enol (Table 1) and ester VI contains 94% of enol (from the UV absorption given in [14–15]). Thus, the steric requirements of the free electron pair of the nitrogen atom are apparently low.

It is known that the absorption maxima of cyclic β-keto esters in the UV spectra remain constant in water, alcohols, and hexane [13]. It is assumed that this is due to a particularly strong chelate hydrogen bond in the cyclic β-keto esters [13]. In the esters I–V, on passing from alcohols (λ_{max} 252 nm) to water (λ_{max} 276 nm, ε 7300–8900), the absorption maxima in the UV spectra shifts in the direction of long wavelengths. The anions of the esters I–V absorb at 280 nm (ε 12000), and it is possible that the esters I–V undergo dissociation in aqueous solutions.

According to the IR spectra, the hydrochlorides VII–X in the solid state (Fig. 3, e; spectra of the hydrochlorides VII–X identical) and in isobutanol (Fig. 3, f; spectra of the hydrochlorides VII–X identical; the solutions stood for 2 days), consist of the enolic form.

Table 2 gives information on the UV absorption of the hydrochlorides VII–X in aqueous alcoholic solutions. In contrast to the N-alkyl-3-ethoxycarbonyl-4-piperidinones (I–V), in their hydrochlorides (VII–X) the absorption maxima in the UV spectra undergo no shift on passing from water to alcohols. In agreement with the IR spectra, it is possible to take the extremely high absorption observed in solutions of the hydrochlorides as the absorption of the 100% enols and to calculate the contents of the enolic forms in the equilibrium mixture. However, the nature of the equilibrium in alcoholic solutions of the hydrochlorides is obscure, since the observed rate of establishment of the equilibrium is too low for keto-enol systems.

Attempts are being made to connect the nature of the absorption in the 2700–2820 cm^{-1} region in saturated cyclic nitrogen-containing compounds with the orientation of the electron pair of the nitrogen atom [3]. The esters I–V have the following absorption bands in the 2700–2800 cm^{-1} region: I—2678, 2765, 2797; II—2780, 2820; III—2683, 2746, 2800; IV—2743, 2780, 2810; V—2765, 2785, 2815.

EXPERIMENTAL

The N-alkyl-3-methoxycarbonyl-4-piperidinones and their hydrochlorides were obtained by methods given by Preobrazhenskii et al. [16]. They had the following constants: I—bp 61–62° C (0.3 mm), n_D^{25} 1.4882, d_4^{25} 1.0661. Found, %: C 56.11; H 7.72. Calculated, %: C 56.09, H 7.65; II—bp 110° C (8 mm), n_D^{25} 1.4895. Found, %: C 58.16; H 8.21. Calculated, %: C 58.35; H 8.16; III—bp 95° C (1 mm), n_D^{25} 1.4860, d_4^{25} 1.0523; IV—bp 112° C (0.3 mm), n_D^{25} 1.4829, d_4^{25} 1.0494. Found, %: C 61.74; H 9.16. Calculated, %: C 61.95; H 8.98; V—bp 101° C (0.5 mm). Found, %: C 63.31; H 9.3. Calculated, %: C 63.41; H 9.3; VII—mp 166° C; VIII—mp 144–145° C; IX—mp 141–141.5° C; X—mp 134–135° C.

The IR spectra were recorded on a Hilger H-800 spectrophotometer, and the UV spectra on an SF-4 spectrophotometer. The spectra were recorded after predetermined intervals of time until they ceased to change, which showed the establishment of equilibrium.

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Arbuzov Institute of Organic and Physical Chemistry AS USSR

Kazan State University