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MECHANISM OF THE RING-CHAIN TAUTOMERISM OF 2,3,3-TRIMETHYL-2-HYDROXY-5-PYRROLIDONES

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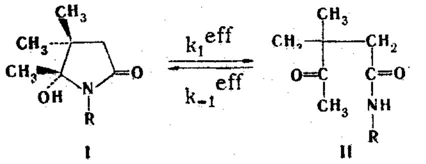
The mechanism of the prototropic equilibrium process of ring-chain tautomerization of 2,3,3-trimethyl-2-hydroxy-5-pyrrolidones is discussed on the basis of the results obtained by PMR spectroscopy. On the NMR time scale the reaction proceeds with the formation of a common intermediate anion, and the rate-determining step is the detachment of a proton.

In contrast to keto—enol tautomerism, the theory of which has been worked out in detail [1], there are an extremely limited number of studies (e.g., see [2]) devoted to the mechanism of ring-chain tautomerism.

In the present paper we examine a possible mechanism for prototropic ring-chain tautomerism and the rate-determining steps in the tautomerization on the basis of our new (and partially earlier [3, 4]) data on the tautomerism of 2,3,3-trimethyl-2-hydroxy-5-pyrrolidones.



I, II R = H or 4-XC_6H_4; X = $N(C_2H_5)_2$, OCH_3, H, Cl, Br, COOH, $COOCH_3$, CN, NO_2

In addition to the available data on the thermodynamic and kinetic parameters of the tautomerism of pyrrolidones [3, 4], we investigated the effect of the acid–base properties of the medium on the rate of tautomerization of the unsubstituted compound (R = H). The rate constants were determined by PMR spectroscopy of solutions in 50% aqueous pyridine containing HCl or $KHCO_3$. The rate constant (k_1^{eff}) is directly proportional to the bicarbonate concentration (Fig. 1). This indicates the pseudo-monomolecular character of the reaction, i.e., the bicarbonate acts as a catalyst. The decrease in the k_1^{eff} constant when hydrochloric acid is added to pyridine (Fig. 2) up to 0.2 M (the medium loses its basic character upon further addition of acid) is in agreement with the decrease in the concentration of the basic catalyst. It should be noted that k_1^{eff} decreases considerably more markedly than the pyridine concentration: When the pyridine concentration changes from 6 to 5.8 M (which corresponds to the change in the hydrochloric acid concentration), the rate constant changes by a factor of approximately four. This is associated with the existence of a reverse reaction with the participation of pyridinium ion BH^+ (see the scheme given below); the addition of hydrochloric acid leads to a substantial increase in the BH^+ concentration.

The role of bases as catalysts of the process makes it possible to assert that the rate-determining step in the tautomerization in the forward (from the chain to the open tautometer) direction is detachment of a proton under the influence of the base to give an intermediate anion. Since the tautomerization is an equilibrium process and the equilibrium constant $K_T = k_1^{eff}/k_{-1}^{eff}$ in our experiments is independent of the basicity of the medium, detachment of a proton should also be the rate-determining step for the reverse direction. The transi-

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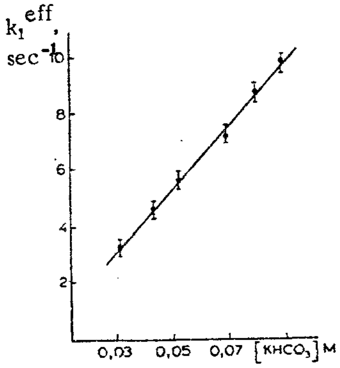

Fig. 1

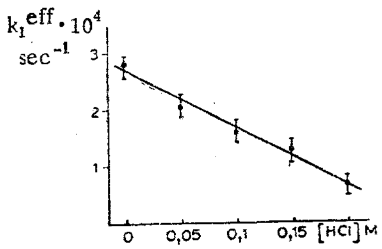

Fig. 2

Fig. 1. Dependence of the effective tautomerization rate constant (k_1^{eff}) on the potassium bicarbonate concentration in 50% aqueous pyridine.

Fig. 2. Dependence of the effective tautomerization rate constant (k_1^{eff}) on the hydrochloric acid concentration in 50% aqueous pyridine.

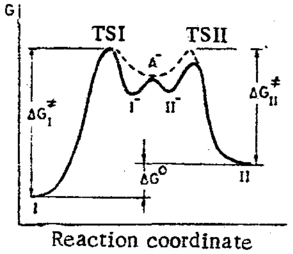

Fig. 3. Energy profile of the tautomerization reaction: I) chain form of the tautomer; II) open form; TSI and TSII are the corresponding transition states, the continuous line corresponds to tautomerization via scheme (1) with two intermediates I$^-$ and II$^-$, and the dashed line corresponds to tautomerization via scheme (2) with common intermediate A$^-$.

tion state of this process should depend markedly on the electronic properties of substituent X and should have a positive ρ constant in the Hammett equation [5] for rate constants, since the detachment of a proton is a special case of a general equilibrium of the form $BH^{(n+1)} \rightleftarrows B^{(n-1)+} + H^+$ when n = 0. We obtained [4] ρ = +3.6 and +4.7 for correlations with the k_1^{eff} and k_{-1}^{eff} constants, respectively; this is in agreement with the conclusion presented above.

In an examination of the formal kinetic scheme of the equilibrium reaction one should take into account the factor that distinguishes ring-chain tautomerism from other types of tautomerism, viz., the sharp difference in the configurations of starting tautomers I and II. It would be natural to assume that the intermediates formed in the deprotonation of the starting tautomers have structures that are close to that of the chain tautomer for one of the intermediates and close to the open form for the other and that the reaction in general form can be described in accordance with the Pedersen—Martius scheme [1], to which the energy profile shown in Fig. 3 by means of the continuous line corresponds:

$$I + B \underset{k'_1}{\overset{k_1}{\rightleftarrows}} I^- + BH^+ \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} II^- + BH^+ \underset{k_{-1}}{\overset{k'_{-1}}{\rightleftarrows}} II + B \qquad (1)$$

Here, B is the catalyst, BH^+ is the conjugate acid, and I^- and II^- are the corresponding intermediates. As we have shown, the step involving the detachment of a proton is the rate-determining step, i.e., k_1 and k_{-1} are much smaller than the remaining constants and approximately equal to the corresponding effective constants k_1^{eff} and k_{-1}^{eff}.

An analysis of the free energies of activation $\Delta G_I^{\neq}$ and $\Delta G_{II}^{\neq}$ and the difference in the free energies of the starting tautomeric forms (ΔG°) [3, 4] makes it possible to shed some light on the problem as to whether the steps that follow the detachment of a proton are consecutive or synchronous, or, in other words, as to whether there are two intermediates in the reaction or one that is a common mesomeric ion. However, the solution of this problem can be found only within the framework of the method used with the given time resolution. For the investigated compounds the difference in the free energies of activation within the limits of the experimental error is equal to the difference in the free energies (ΔG°) of the tautomers. The same relationship is satisfied for the entropies [3, 4]. Thus, on the one hand, transition states TSI and TSII (Fig. 3) have identical energies, whereas on the other hand, the entropy of activation $\Delta S_I^{\neq}$ (i.e., the difference in the entropies between starting tautomer I and transition state TSI) differs from $\Delta S_{II}^{\neq}$ by a value that is equal to the transition from the chain form to the open form, and TSI is consequently similar to TSII not only with respect to energy but also with respect to structure, i.e., it is close to the open form. Since it is difficult to imagine that the already opened ring recloses along the pathway from TSI to intermediate I^-, intermediates I^- and II^- evidently also have a similar structure that is close to the structure of the open form. Consequently, it may be stated that on the NMR time scale the reaction proceeds with the formation of one common intermediate anion, i.e., in a manner similar to that of keto–enol tautomerism; the structure of the common anion is close to that of the open form. The reaction can be written in the form of the Ingold–Shopley–Thorne scheme [1] with the energy profile depicted in Fig. 3 by means of the dash line:

$$I + B \underset{k'_1}{\overset{k_1}{\rightleftarrows}} A^- + BH^+ \underset{k_{-1}}{\overset{k'_{-1}}{\rightleftarrows}} II + B \qquad (2)$$

Here, A^- is the common intermediate anion.

In contrast to keto–enol tautomerism, which proceeds, as a rule, with a negative entropy of activation (e.g., see [6]), the entropy of the starting tautomers is lower than that of the transition states for the investigated case of ring-chain tautomerism because of the greater solvation by the solvent of the transition state (the anion) than of the neutral starting compound. The average (with respect to the investigated substituents) entropies of activation of the process in the forward and reverse directions ($\Delta S_I^{\neq}$ and $\Delta S_{II}^{\neq}$) are, respectively, 16 ± 3 eu and 6 ± 3 eu [4]. It is known [5] that both external (interaction with the solvent) and internal (a change in the configuration) factors make a contribution to $\Delta S^{\neq}$. In our case the small positive $\Delta S_{II}^{\neq}$ values are probably explained primarily by the external factor and may be associated with the greater solvation of tautomer II (which has the dipolar $-\overset{\delta+}{N}=C-\overset{\delta-}{O}$ structure) as compared with the transition state. The greater positive $\Delta S_I^{\neq}$ values evidently confirm the open structure of transition state I, since in this case, in addition to the external factor (similar to the factor mentioned above for $\Delta S_{II}^{\neq}$), an internal factor associated with the greater conformational lability of TSI as compared with cyclic tautomer I should also make a large contribution to the $\Delta S^{\neq}$ value.

We concluded that the step involving the detachment of a proton is the rate-determining step on the basis of data obtained for the pyridine–water system, which contains an excess of proton donors. It might be expected that the rate-determining step in a medium with a low percentage of donors may be the step involving the addition of a proton to intermediate A^- [scheme (2)]. In fact, according to the data in [7], the time required to establish equilibrium between the tautomers in pure pyridine is 260 h, as compared with 8 h in pure water.

EXPERIMENTAL

2,3,3-Trimethylene-2-hydroxy-5-pyrrolidone was obtained by the method in [3]. The PMR spectra of the compounds were recorded with an R-20A spectrometer at 34°C. The effective rate constants in 50% aqueous pyridine with the addition of sodium bicarbonate were obtained by dynamic NMR spectroscopy by the method described in [4]. In experiments with the addition of hydrochloric acid the constants were obtained from the time change with time in the integral intensities of the signals of the corresponding tautomeric forms. The reaction was begun with the chain tautomer and was first-order in both the tautomer and bicarbonate. The ρ constants in the Hammett equations at various temperatures were calculated by the method of least squares; the correlation coefficients ranged from 0.960 to 0.996.

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STRONG BASE-CATALYZED THERMAL REARRANGEMENTS OF AZINES OF BENZYL ALKYL KETONES

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Azines of benzyl alkyl ketones undergo cyclization in the presence of strong basic catalysts to give mixtures of compounds of the pyrrole and pyrazole series. The formation of pyrazole products probably proceeds via the scheme of the Fischer reaction taking into account the concept of a [3,3] sigmatropic shift. However, the presence of nitriles and hydrocarbons among the products of the reaction of pyrazole derivatives indicates the ambiguous character of the proposed scheme. The rearrangement of azines to pyrazole compounds probably proceeds through a step involving the formation of a carbanion, while the formation of nitriles and hydrocarbons can be explained by radical processes. The dependence of the ratio of the pyrolysis products (pyrrole/pyrazole) on the amount of catalyst and its basicity (LiH, NaH, KH, NaOH, KOH, PhOK, and CH_3OK) makes it possible to assume that the occurrence of the reaction through a step involving a [3,3] shift is realized thermally and that small amounts of the catalyst promote the realization of this reaction pathway; however, a high percentage of the catalyst and the use of the most basic catalysts lead to an increase in the yields of the pyrazole products.

One of us has previously proposed that the Fischer reaction and some related processes (e.g., the synthesis of pyrroles from azines under the influence of acidic agents) be regarded as sigmatropic [3,3] rearrangements [1]. We were later able to confirm this assumption for the Fischer reaction experimentally [2, 3].

An examination of the mechanism of the Piloty reaction from the point of view of a sigmatropic [3,3] shift and recognition of the decisive role in this reaction of tautomeric

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