EFFECT OF THE MEDIUM ON THE REACTION OF 4-METHYL-7-AZAINDOLINE WITH ACETIC AND TRIFLUOROACETIC ACIDS

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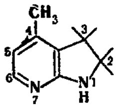
The effect of the medium on the equilibrium involved in proton transfer via a hydrogen bond and dissociation of ion pairs in systems composed of 4-methyl-7-azaindoline and acetic and trifluoroacetic acids was examined by means of PMR and IR spectroscopy. The position of the molecular H complex ⇌ ion pair equilibrium depends on the proton-donor–acceptor properties of the solvent and is shifted to favor the ionic form in the order $CH_3CN < CH_2Cl_2 < CDCl_3$. A change in the dielectric constant of the medium affects mainly the degree of dissociation of the ion pairs.

We have previously studied the reaction of 4-methyl-7-azaindoline



with acetic and trifluoroacetic acids in methylene chloride [1]. The relative position of equilibria (1)-(3)

$$B + AH \underset{1}{\rightleftharpoons} B\ldots HA \underset{2}{\rightleftharpoons} BH^{+}\ldots A^{-} \underset{3}{\rightleftharpoons} BH^{+} + A^{-}$$

was established on the basis of a comparative examination of the dependence of the chemical shift of the proton of the pyridine ring in the position relative to the protonation center (6-H) and the J_{56} spin–spin coupling constant (SSCC) on the reagent molar ratio (C_{AH}/C_B) and the IR spectra of solutions of the amine–acid systems at 1400-1800 cm^{-1}. It was shown that when $C_{AH}/C_B \leq 1$ in the amine–CF_3COOH system, equilibria (1) and (2) are shifted to favor H complexes of the ion pair type. Equilibrium (2) is observed under the same conditions in the system with CH_3COOH.

In the present research the same method was used to study the effect of the medium on the position of equilibria (1)-(3) in these systems. For this, we measured the PMR and IR spectra of the amine–acid systems at various reagent molar ratios in $CDCl_3$, CH_2Cl_2, CH_3CN, CD_3OD, and 80% CD_3OD/D_2O.

The results of the measurements showed that the $\Delta J_{56} = f(C_{AH}/C_B)$ dependences for the 4-methyl-7-azaindoline–trifluoroacetic acid system coincide in $CDCl_3$, CH_2Cl_2, and CH_3CN (see Fig. 1, curve a). Absorption in the region of the $\nu_{C=O}$ vibrations of the molecular form of the acids (1750-1800 cm^{-1}) is absent in the IR spectra of an equimolar mixture of the reagents in these media (Fig. 2, curve a), and the ν_{as} band of the vibrations of the trifluoroacetate ion (1676 cm^{-1}), the position and intensity of which are close to those of the analogous band in the spectra of the same system measured in CD_3OD and 80% CD_3OD/D_2O appears. Absorption bands at ~1540, 1630, and 1650 cm^{-1},* which are characteristic for the protonated form of the heterocycle

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*In some media the bands of the protonated heterocycles at 1630-1650 cm^{-1} are overlapped by an intense band at 1676 cm^{-1}.

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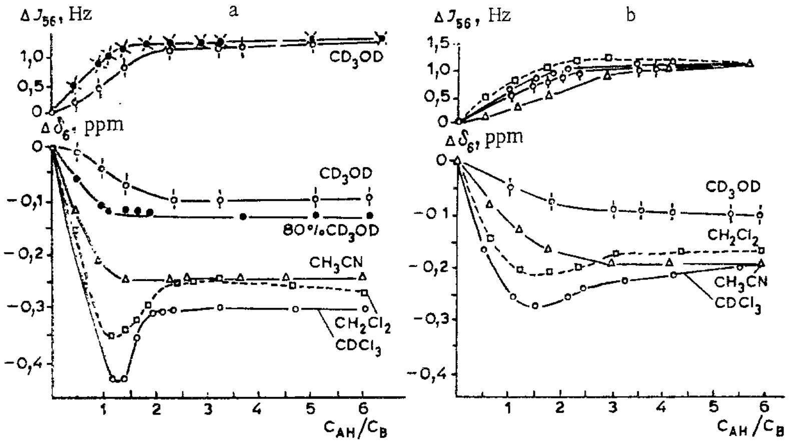


Fig. 1. Dependence of $\Delta\delta_6$ and ΔJ_{56} on the molar reagent ratio in systems composed of 4-methyl-7-azaindoline and trifluoroacetic (a) and acetic (b) acids in $CDCl_3$ (O), CH_2Cl_2 (□), CH_3CN (Δ), CD_3OD (O), and 80% CD_3OD (●).

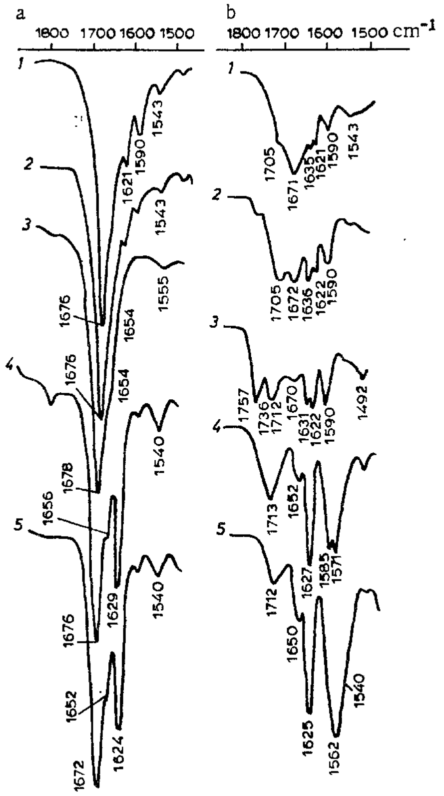
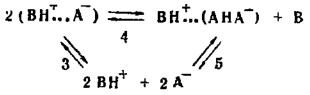


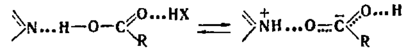
Fig. 2. IR spectra of systems composed of 4-methyl-7-azaindoline and trifluoroacetic (a) and acetic (b) acids in $CDCl_3$ (1), CH_2Cl_2 (2), CH_3CN (3), CD_3OD (4), and 80% CD_3OD (5) (the reagent concentration was 0.13 M, the cuvette was constructed from CaF_2, and the layer thickness was 0.05 mm).

[1], are simultaneously present. A similar pattern is also observed when $C_{AH}/C_B < 1$. It follows from these data that in $CDCl_3$ and CH_3CN, as in CH_2Cl_2, equilibria (1) and (2) in the amine-CF_3COOH system are shifted to the right completely. The sharp differences in the character of the curves for the chemical shift $\Delta\delta_6 = f(C_{AH}/C_B)$ (Fig. 1, curve a) are due to different positions of equilibrium (3) in these media. An increase in the contribution of dissociation leads to a decrease in the difference between the observed chemical shifts of 6-H in the amine–acid system and the value characteristic for the solvated ion in a given solvent. In conformity with this, the depth of the minimum on the $\Delta\delta_6 = f(C_{AH}/C_B)$ curve, which corresponds to the formation of an H complex with proton transfer, decreases as the dielectric constant of the solvent increases. In $CDCl_3$ and CH_2Cl_2 (ε = 4.8 and 8.9) the dependences of the relative chemical shift of 6-H on the reagent molar ratio coincide when $0 < C_{AH}/C_B < 1$. The shift of the minimum on the $\Delta\delta_6 = f(C_{AH}/C_B)$ curve in chloroform in the region of large C_{AH}/C_B values as compared with methylene chloride indicates an increase in the relative percentages of 2 : 1 complexes of the BH^+ (AHA^-) type as the dielectric constant of the solvent decreases.

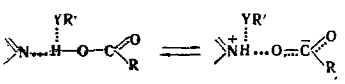


The presence in the IR spectra of an equimolar mixture of the reagents of weak bands of the molecular form of the base (~1590 and 1620 cm^{-1}), the relative intensity of which decreases on passing from solutions in $CDCl_3$ to solutions in CH_2Cl_2, constitutes evidence for the presence of equilibrium (4) in these media. The stability of complexes of the BH^+ (AHA^-) type decreases sharply as the polarity of the medium increases. The absence of bands of the molecular form of the base in the IR spectrum of an equimolar mixture of the reagents in acetonitrile (ε = 37.5) attests to complete shifting of equilibria (4) to the left. In addition, the dependence for the chemical shift of 6-H in this medium (Fig. 1, curve a) corresponds to a considerable shift of equilibrium (3) to favor dissociated ions in the neighborhood of an equimolar reagent ratio.

On the basis of measurements of the PMR and IR spectra of the 4-methyl-7-azaindoline–acetic acid system in $CDCl_3$, CH_2Cl_2, CH_3CN, and CD_3OD (Figs. 1b and 2b), we examined the effect of the medium on the position of the molecular H complex⇌ion pair equilibrium (2). The character of the dependence for the chemical shifts of 6-H (Fig. 1, curve b) changes substantially in the indicated series of solvents. On passing from CH_2Cl_2 to $CDCl_3$, the depth of the minimum on the $\Delta\delta_6 = f(C_{AH}/C_B)$ curve increases substantially. The relative $\Delta\delta_6$ and ΔJ_{56} values in the case of an equimolar reagent ratio in $CDCl_3$ indicate a shift in equilibrium (2) to favor an H complex of the ion pair type. This is confirmed by an increase in the relative intensity of the bands of the ionic form (1543 and 1671 cm^{-1}) in the IR spectrum of an equimolar mixture of amine and acetic acid in this medium as compared with CH_2Cl_2 (Fig. 2, curve b). The observed effect provides evidence that it is not the polarity of the solvent that affects the position of equilibrium (2) to a great degree, but rather its ability to form H bonds with the reagents as a proton donor or acceptor. On the basis of data from the IR spectra of aliphatic amine–carboxylic acid systems it has been shown [2, 3] that the molecular complex⇌ion pair equilibrium is shifted to the right as the proton-donor properties of the solvents increase. Solvation of the amine–acid molecular complex by protonated solvent molecules (HX) with the formation of a H bond leads to a shift of the electron density from the oxygen atom of the carbonyl group of the acid and, as a consequence, facilitates transfer of a proton from the acid to the amine:



The formation of H bonds between molecules of the proton-acceptor solvents and the hydroxyl group of the acid should lead to destabilization of the amine–acid molecular complex and should facilitate its dissociation to the starting components, i.e., it should promote a shift of equilibrium (1) to the left. On the other hand, the effects of solvation of the protonated amine in such media should facilitate dissociation of the H complexes of the ion pair type to ions:



Since acetonitrile can participate in the formation of H bonds with the reagent only as a proton acceptor, one should have expected a shift in equilibria (1) and (2) to the left in this solvent as compared with chloroform and methylene chloride. In fact, bands of $\nu_{C=O}$ vibrations of an acid bonded to the solvent (1757 and 1736 cm^{-1}), the $\nu_{C=O}$ band of an amine–acid molecular complex (1712 cm^{-1}), and the band of a carboxylate ion (1670 cm^{-1}) are observed in the IR spectrum of the amine–acetic acid system in CH_3CN in the case of an equimolar reagent ratio (Fig. 2, curve b). Bands of both the molecular form (1492, 1590, and 1620 cm^{-1}) and the ionic form (1535 and 1631 cm^{-1}) of the heterocycle are observed simultaneously. The relative intensities of the bands of the molecular and ionic forms of the acid and amine correspond to a considerable shift of equilibria (1) and (2) to the left in CH_3CN as compared with solutions in $CDCl_3$ and CH_2Cl_2. A comparison of the dependence of the parameters of the PMR spectra on the amine–acid molar ratio in these media (Fig. 1, curve b) leads to a similar conclusion. The ΔJ_{56} value for an equimolar reagent ratio in CH_3CN corresponds to the presence of ~70-80% of the molecular form in the system, whereas the reaction involving proton transfer is shifted to the right by more than 50% in CH_2Cl_2 and $CDCl_3$ under the same conditions. The observed shift in equilibrium (2) in the order $CH_3CN < CH_2Cl_2 < CDCl_3$ makes it possible to conclude that chloroform participates in the acid–base interaction as an active proton donor and that it is a medium that has strong ionizing and weak dissociating abilities. This result is in agreement with the data in [4]. Acetonitrile, on the other hand, affects the system of equilibria of the protolytic reaction as a weakly ionizing and strongly dissociating solvent. The character of the curve for the chemical shift of 6-H of the amine–acetic acid system does not make it possible to disregard the contribution of equilibrium (3) in this medium even at low acid concentrations.

In methanol ($\varepsilon = 33.6$) the character of the dependence of the parameters of the PMR spectra on the amine–acid molar ratio in systems with acetic acid and trifluoroacetic acid (Figs. 1a and 1b) corresponds to the simple protolytic equilibrium

$$B + AH \rightleftharpoons BH^+ + A^-$$

In both systems the changes in the chemical shift of the ring α-H atom are proportional to the amount of added acid. A linear dependence over the entire range of changes in these parameters is observed between the $\Delta\delta_6$ and ΔJ_{56} values. Bands of acid $\nu_{C=O}$ vibrations (1713 cm^{-1}) and acetate ions ν_{as} vibrations (1571 cm^{-1}) of comparable intensity are present in the IR spectrum of an equimolar mixture of amine and acetic acid in CD_3OD (Fig. 2, curve b). On passing from methanol to aqueous methanol the relative intensity of the bonds of the ionic form increases, and this indicates a shift of the protolytic equilibrium to the right. A comparison of the J_{56} values and the intensities of the bands of the molecular and ionic forms in the IR spectra shows that the ionization reaction is shifted to the right as compared with methanol in chloroform and methylene chloride in the case of an equimolar reagent ratio. This corresponds to the appreciable increase in the relative strength of the acids and the base in proton-donor media with low dielectric constants.

EXPERIMENTAL

The PMR spectra of the investigated systems were measured with a C-60 HL spectrometer at a base concentration of 0.3 M and at various acid concentrations. Tetramethylsilane was used as the internal standard. The IR spectra of solutions of the acid-amine systems were measured with a Perkin–Elmer 457 spectrometer.

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