Reports of the Academy of Sciences of the USSR

CHEMISTRY

1957

Abstract

Full Text

Reports of the Academy of Sciences of the USSR
1957. Vol. 113, No. 5

CHEMISTRY

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TAUTOMERISM OF ACYLATED HETEROCYCLIC AMINES AND ITS STUDY BY MEANS OF SPECTRA

(Presented by Academician I. L. Knunyants, 4 XII 1956)

In earlier studies ([1]–[4]), spectra were used to show that α- and γ-amino derivatives of the N-heteroaromatic series exist in the form of amino compounds, and not imino compounds.

An explanation of this fact can be obtained by applying the laws of acid–base equilibrium to amino–imino tautomeric equilibrium. The existence of heterocyclic amines in the amino form is thereby regarded as a consequence of the considerably higher basicity of the exocyclic imino nitrogen atom in comparison with the basicity of the ring nitrogen, which causes a strong (practically complete) shift of the equilibrium toward the amino tautomeric form ([4]).

From these concepts follows the possibility of influencing the position of the amino–imino tautomeric equilibrium by changing the ratio of the basicities of the two nitrogen atoms responsible for tautomerism—the ring and the exocyclic nitrogen. Such a change could be expected to be achieved by replacing one of the hydrogen atoms of the amino group with electronegative groups of the acid-residue type, which could substantially lower the basicity, above all, of the exocyclic nitrogen directly bonded to them.

For this purpose, acid residues of acetic and benzoic acids, mono-, di-, and trichloroacetic acids, trifluoroacetic acid, benzenesulfonic and sulfanilic acids, and nitric acid were used in the work. Upon introduction into the amino group of 2-aminopyridine and 2-aminothiazole, these residues formed the corresponding amides.

In studying the infrared and ultraviolet spectra of the indicated compounds, it was shown that, indeed, depending on the "acidifying" (acidifying) ability of the acid residues (an estimate of this ability could be made from the strength of the corresponding acids), the heterocyclic amides exist not only in the amino form, but also in the imino form or as a mixture of two tautomeric forms. These data were obtained by comparing the spectra of the amides with the spectra of

Fig. 1. Infrared absorption spectra of some 2-acylaminopyridines and N-methyl-2-trichloroacetylpyridonimine

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their methyl derivatives having a fixed amino or imino structure, and also by considering individual characteristic bands in the infrared spectra.

Thus, acetylamino- and benzoylaminopyridines, as well as mono-, di-, and trichloroacetylaminopyridines, in the infrared spectra (in the crystalline state) possess a characteristic band of the amide carbonyl group at 1686–1718 cm^{-1} (raised in the chloroacetamides owing to the inductive effect of the electronegative chlorine atoms).

In contrast to the analogous pyridine derivative, 2-trichloroacetylaminothiazole has in its spectrum a carbonyl band only at 1616 cm^{-1}, which indicates the imino structure of this compound in the solid state. Indeed, in model compounds with a fixed imino structure (N-methyl-2-acetylpyridonimine, N-methyl-trichloroacetylpyridonimine, N-methyl-2-trichloroacetyliminothiazoline) the carbonyl band is found in the region 1605–1630 cm^{-1}, being substantially shifted into the region of lower frequencies owing to conjugation.

The action of the more strongly acidifying trifluoroacetic-acid residue leads to the fact that not only 2-trifluoroacetylaminothiazole, but also 2-trifluoroacetylaminopyridine in the crystalline state exists in the imino form (carbonyl bands at 1630–1640 cm^{-1}, see Fig. 1).

In solutions, such compounds as 2-acetyl-, 2-monochloroacetyl-, and 2-dichloroacetyl-aminopyridines in various solvents have the amino structure (absorption bands in the ultraviolet at 235 and 278 mμ, as in substances with a fixed amino structure). Trichloroacetylaminopyridine, being an amide in heptane solutions, in alcoholic and especially aqueous solutions, along with the amide form, shows a noticeable content of the imide tautomeric form (an absorption band appears at 315–325 mμ, as in N-methyl-2-trichloroacetyl- or N-methyl-2-acetylpyridonimines). 2-Trichloroacetylaminothiazole in alcoholic and aqueous solutions exists practically entirely in the imine tautomeric form (band in the ultraviolet spectrum at 305 mμ) and only in heptane solution is an amide; 2-dichloroacetylaminothiazole already in alcoholic and aqueous solutions contains the amino form in rather large amounts. In crystals dichloroacetylaminothiazole is an amide (carbonyl band in the infrared spectra at 1702 cm^{-1}).

Fig. 1. Infrared absorption spectra of some 2-acylaminopyridines and N-methyl-2-trichloroacetylpyridonimine

Sulfamidopyridine and sulfanilamidopyridine in crystals possess, in the infrared spectra, a band characteristic of the imino grouping N–C = N–SO_2–(940 cm^{-1})

and do not show the bands characterizing the amino configuration N = C–N –SO_2–(1040 cm^{-1} and 850-860 cm^{-1}). In the ultraviolet region, in aqueous solutions they absorb analogously to fixed model imino forms; they show a small content of the amino form in alcoholic solutions and a predominant content in dioxane-heptane solutions (Fig. 2). In contrast to the pyridine derivatives, 2-sulfamidothiazole* both in the crystalline state and in all solvents retains the imino structure.

2-Nitraminothiazole behaves in the same way, whereas 2-nitraminopyridine, having the imino structure in the crystalline state and in aqueous and alcoholic solutions (bands at 1615 cm^{-1}, 1542 cm^{-1} in the infrared spectra and at 273 mμ, 350 mμ in the ultraviolet spectra), in dioxane solution reveals a noticeable content of the amino tautomeric form.

Thus, by having residues differing in acidifying ability, it is possible, as it were, to influence the position of the tautomeric equilibrium, obtaining derivatives having one or the other tautomeric structure.

The quantitative data obtained from the ultraviolet spectra on the equilibrium content of the amino and imino tautomeric forms of the compounds studied in various solvents are given in Table 1.

* The study of sulfamides of the thiazole series was carried out jointly with I. Ya. Postovskii and V. V. Kushkin in a work whose detailed results will be reported later.

From these data it follows that, for the tautomeric equilibrium to be shifted toward stability of the imino form, the acyl group introduced must have

Table 1

Content of the amino form (%)

Compound	R	Solution in *n*-heptane	Solution in dioxane	Solution in alcohol	Solution in water
2-aminopyridine derivative	$COCH_3$	~100	~100	~100	~100
2-aminopyridine derivative	$COCHCl_2$	~100	~100	99.9	99.0
2-aminopyridine derivative	$COCCl_3$	~100	99.8	99.0	93.7

Compound	R	Solution in *n*-heptane	Solution in dioxane	Solution in alcohol	Solution in water
2-aminopyridine derivative	$SO_2C_6H_4NH_2$	–	99.1	76.0	18.5
2-aminopyridine derivative	$SO_2C_6H_5$	99	95.5	45	11
2-aminopyridine derivative	NO_2	–	87.4	17	~0
2-aminothiazole derivative	$COCH_3$	~100	~100	~100*	~100
2-aminothiazole derivative	$COCHCl_2$	~100	99.6	90	45
2-aminothiazole derivative	$COCCl_3$	93	60	3.5	~0
2-aminothiazole derivative	$SO_2C_6H_4NH_2$	~0	~0	~0	~0
2-aminothiazole derivative	$SO_2C_6H_5$	~0	~0	~0	~0
2-aminothiazole derivative	NO_2	~0	~0	~0	~0

* The previously noted [5] presence of several percent of the imino tautomeric form in an alcoholic solution of 2-acetylaminothiazole was not confirmed in repeated measurements.

a high acidifying ability; moreover, the minimum value of this acidifying ability is different for different heterocyclic amines. The transition to the imino form

Fig. 2. Ultraviolet absorption spectra. 1 —2-methylsulfonamidopyridine in alcohol, 2 —2-sulfonamidopyridine in *n*-heptane, 3 —the same in dioxane, 4 — the same in alcohol, 5 —the same in water, 6 —N-methyl-2-sulfonpyridonimine in alcohol

Figure 2: Fig. 2. Ultraviolet absorption spectra. 1 —2-methylsulfonamidopyridine in alcohol, 2 —2-sulfonamidopyridine in *n*-heptane, 3 —the same in dioxane, 4 —the same in alcohol, 5 —the same in water, 6 — N-methyl-2-sulfonpyridonimine in alcohol

proceeds more readily in derivatives of 2-aminothiazole than in derivatives of 2-aminopyridine.

Solvents, in their ability to influence the position of the amino–imino tautomeric equilibrium, are arranged in the series heptane—dioxane—alcohol—water, in which each subsequent member possesses a stronger ability to shift the equilibrium toward the imino tautomeric form. In the crystalline state, the substances exist only as one tautomeric form: the amino form for compounds with acyl residues of relatively low and medium acidifying ability, and the imino form for compounds with residues of high acidifying ability.

Fig. 2. Ultraviolet absorption spectra. 1 —2-methylsulfonamidopyridine in alcohol, 2 —2-sulfonamidopyridine in *n*-heptane, 3 —the same in dioxane, 4 — the same in alcohol, 5 —the same in water, 6 —N-methyl-2-sulfonpyridonimine in alcohol.

All the data obtained, in our opinion, confirm the correctness of the approach to the amino–imino (and, in general, protolytic) tautomeric equilibrium as an equilibrium of acid–base character.

This conclusion is also confirmed by the following quantitative comparisons. If the found values of the negative logarithms of the tautomeric equilibrium constants in different solvents, pK_S, are plotted on a graph whose coordinate axes give the values of pK_S in two solvents, then the points for the various compounds studied fall on one straight line, located

under an angle of 45° to the abscissa axis (Fig. 3) and, consequently, corresponding to the equation $pK_{S_1} = pK_{S_2} + \text{const}$.

The existence of such a dependence between the constants of tautomeric equilibrium in two solvents, as was first shown by M. I. Kabachnik ([6]) as applied to keto–enol equilibria, indicates that the tautomeric systems investigated obey the Brønsted–Izmailov rule ([7]), and hence the general relations determining acid–base equilibria.

Taking into account that the constant term in the above equation of the straight line is equal to $\dfrac{\Delta F_{S_2} - \Delta F_{S_1}}{2.3\,RT}$, where $\Delta F_{S_2} - \Delta F_{S_1}$ is the change in the free energy of the tautomeric system on passing from one solvent to another, it is

easy to calculate this quantity, which, as follows from the graph, has a constant value for the whole series of compounds studied (for the given pair of solvents). The value $\Delta F_{S_2} - \Delta F_{S_1}$ calculated from the experimental data is 2.1 kcal/mole for the transition from dioxane to alcoholic solutions and 1.2 kcal/mole for the transition from alcoholic to aqueous solutions.

Fig. 3. Dependence between pK_S in two solvents. S_1—ethyl alcohol; S_2—dioxane (**a**) and water (**b**).
1—2-trichloroacetylaminopyridine, 2—2-dichloroacetylaminothiazole, 3—2-sulfanilamidopyridine, 4—2-sulfonamidopyridine, 5—2-nitraminopyridine, 6—2-trichloroacetylaminothiazole, 7—2-dichloroacetylaminopyridine.

Experimental Part

The infrared absorption spectra were recorded on an IKS-11 infrared spectrometer; the ultraviolet spectra, by means of an SF-4 spectrophotometer. Acylated heterocyclic amines were obtained by the interaction of the acid chlorides of the corresponding acids with 2-aminopyridine and 2-aminothiazole in pyridine or benzene. In this way the following were obtained: 2-chloroacetylaminopyridine, m.p. <110° (decomp.), found %: Cl 20.8, calculated %: Cl 20.8; 2-dichloroacetylaminopyridine, m.p. 69–70.5°, found %: Cl 34.5, calculated %: Cl 34.6; 2-dichloroacetylaminothiazole, m.p. 180–180.5°, found %: Cl 33.9, calculated %: Cl 33.6; 2-trichloroacetylaminopyridine, m.p. 84–85°, found %: Cl 44.4, calculated %: Cl 44.5; 2-trichloroacetylaminothiazole, m.p. 194–195°, found %: Cl 43.5, calculated %: Cl 43.4; 2-sulfonamidopyridine, m.p. 171°; 2-sulfonamidothiazole, m.p. 170°. By interaction of the corresponding amide with an acid anhydride, 2-trifluoroacetylaminopyridine, m.p. 98–101°, found %: C 44.0; H 2.49, calculated %: C 44.2; H 2.63; 2-trifluoroacetylaminothiazole, m.p. 156–157°, found %: C 30.32; H 1.59, calculated %: C 30.60; H 1.53; 2-acetylaminopyridine, m.p. 71°. By nitration of the corresponding amines with concentrated nitric acid according to Chichibabin and Razorenov ([8]), 2-nitraminopyridine, m.p. 184°, and 2-nitraminothiazole, m.p. <180° (decomp.), were synthesized.

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named after S. Ordzhonikidze

Received
2 XII 1956

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Note: Figure translations are in progress. See original paper for figures.