4. V. M. Berestovitskaya, A. S. Sopova, and V. V. Perekalin, Zh. Organ. Khim., 3, 1703 (1967).
5. G. Gregory, R. Moodie, and K. Schofield, J. Chem. Soc., B, 338 (1970).
6. P. W. Neber and G. Huh, Ann., 515, 283 (1935).
7. A. Hassner and F. Fowler, J. Am. Chem. Soc., 90, 2869 (1968).
8. T. Nishiwaki and T. Saito, J. Chem. Soc., C, 3021 (1971).
9. V. N. Zelmen, G. Ya. Vanag, and I. A. Stunda, Izv. Akad. Nauk LatvSSR, No. 1, 107 (1958).
10. L. S. Geita, I. É. Dalberga, and A. K. Grinvalde, Izv. Akad. Nauk LatvSSR, Ser. Khim., 114 (1973).
11. L. S. Geita, I. É. Dalberga, and A. K. Grinvalde, Zh. Organ. Khim., 11, 803 (1975).
12. I. B. Mazheika, I. S. Yankovska, S. D. Sokolov, and I. N. Yudintseva, Khim. Geterotsikl. Soedin., 460 (1972).
13. V. I. Minkin, O. A. Osipov, and Yu. A. Zhdanov, Dipole Moments in Organic Chemistry [in Russian], Khimiya, Leningrad (1968), p. 77.
14. Handbook of Dipole Moments [in Russian], Moscow (1971).

RELATIVE STABILITIES OF THE TAUTOMERIC FORMS OF CONJUGATE ACIDS AND KINETICS OF DEUTERIUM EXCHANGE IN DERIVATIVES OF INDOLIZINE, PYRROLO[1,2-a]IMIDAZOLE, AND PYRROLO[1,2-a]BENZIMIDAZOLE

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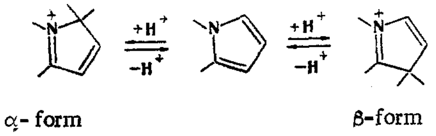
The effect of the temperature and the acidicity of the medium on the ratio of the two tautomeric forms of the conjugate acids of derivatives of indolizine, pyrrolo[1,2-a]imidazole, and pyrrolo[1,2-a]benzimidazole was investigated by PMR spectroscopy. The change in the ratio of the forms with time was studied under fixed reaction conditions. The position of the tautomeric equilibrium in a number of the investigated systems was established. A correspondence between the relative stabilities of the protonated forms and the rate constants for electrophilic deuterium exchange in the neutral molecules was observed.

A study of the protonation of indolizine (I) [1-3], pyrrolo[1,2-a]imidazole (II) [4], and pyrrolo[1,2-a]benzimidazole (III) [5] derivatives in trifluoroacetic acid showed that these systems are ambident bases capable of forming two tautomeric forms of conjugate acids.

The structure of the protonated forms corresponds to the addition of a proton to the carbon atom of the pyrrole ring in the α and β positions relative to the bridge nitrogen atom.



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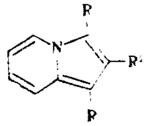
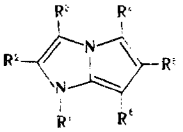
On the basis of data on the protonation of such ambident systems as enamines [6-8], methyl derivatives of pyrrole [9, 10], phenol [11, 12], and anisole [13, 14], it can be concluded that a change in the temperature and the acidity of the medium has a considerable effect on the ratio of the tautomeric forms of the cations. Differences in the relative percentages of the α- and β-protonated forms are also observed in the case of indolizine derivatives [1-3] in media with different acidities. In addition, the data available for most of the examined systems do not make it possible to solve the fundamentally important problems of whether the observed ratio of the forms is an equilibrium ratio and whether the reaction conditions affect the position of the equilibrium or the rate of conversion of one form to another.

In this connection, we studied the dependence of the relative percentage of the protonated forms of indolizine (Ia-c), pyrrolo[1,2-a]imidazole (IIa-j), and pyrrolo[1,2-a]benzimidazole (IIIa, b) derivatives on the acidity and temperature of the medium. The change in the ratio of the forms with time was examined for fixed reaction conditions.

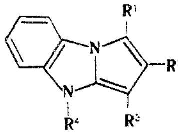
It follows from Table 1 that the ratio of the two forms of the conjugate acids observed in the PMR spectra 10 min after dissolving the pyrroloimidazoles (IIa-g, IIj) and the corresponding hydrochlorides differ sharply (Fig. 1).



I a-c



II a-j



III a, b

Ia $R^1=R^3=H$, $R^2=CH_3$; Ib $R^1=R^3=H$, $R^2=C_6H_5$; Ic $R^1=H$, $R^2=C_6H_5$, $R^3=CH_3$; IIa $R^1=CH_3$, $R^2=R^3=R^4=R^6=H$, $R^5=C_6H_4Cl$-*p*; IIb $R^1=C_6H_5$, $R^2=R^3=R^4=R^6=H$, $R^6=C_6H_5$; IIc $R^1=C_6H_5$, $R^2=R^3=R^4=R^6=H$, $R^5=C_5H_6CH_3$-*p*; IId $R^1=CH_2C_6H_5$, $R^2=R^3=R^4=R^6=H$, $R^5=C_6H_5$; IIe $R^1=CH_2C_6H_5$, $R^2=R^3=R^4=R^6=H$, $R^5=C_6H_4CH_3$-*p*; IIf $R^1=CH_2C_6H_5$, $R^2=R^3=R^4=R^6=H$, $R^5=C_6H_4OCH_3$-*p*; IIg $R^1=C_2H_5$, $R^2=Cl$, $R^3=R^4=R^6=H$, $R^5=C_6H_4CH_3$-*p*; IIh $R^1=C_2H_5$, $R^2=Cl$, $R^3=R^4=R^6=H$, $R^5=C_6H_4OCH_3$-*p*; IIi $R^1=R^2=R^3=C_6H_5$, $R^4=R^6=H$, $R^5=C_6H_4OCH_3$-*p*; IIj $R^1=C_2H_5$, $R^2=Cl$, $R^3=R^6=H$, $R^4=CH_3$, $R^5=C_6H_5$; IIIa $R^1=R^3=H$, $R^2=CH_3$, $R^4=CH_2C_6H_5$; IIIb $R^1=R^3=H$, $R^2=C_6H_5$, $R^4=CH_2C_6H_5$

Exclusively the α form of the conjugate acid is present in solutions of hydrochlorides of compounds that are unsubstituted in the α position relative to the bridge nitrogen atom (IIa-g) in CF_3COOH at 25°. A mixture of two protonated forms is observed in the spectrum of the hydrochloride of the α-methyl-substituted pyrroloimidazole IIj under similar conditions, and 10% of the β form is present in the mixture.

The ratio of the forms of all of the investigated hydrochlorides remain constant with time (Fig. 2) and consequently characterize the equilibrium state.

A mixture of the two forms of the conjugate acid is observed in the spectra of bases IIa-g and IIj in CF_3COOH (Table 1), and 10-30% of the β form is present in the case of IIa-g, whereas 90% of the β form is present in the case of IIj. The relative percentage of the forms depends substantially on the acidity of the medium and the temperature and changes with time (Table 2 and Fig. 2).

At 25° a decrease in the acidity of the medium leads to a gradual increase in the relative concentration of the α form of the conjugate acid. In 25% solutions of CF_3COOH in $CDCl_3$ the α-unsubstituted pyrroloimidazoles form only the α-protonated form, whereas the relative percentage of this form in the case of α-methyl derivatives of indolizine Ic and pyrroloimidazole IIj increases from 50 and 10% to 80 and 90%, respectively. An increase in the acidity of the medium is not accompanied by the appearance of the β form in the case of solutions of IIh, i in 25% CF_3COOH.

The concentration of the α form decreases whereas the concentration of the β form increases at a fixed acidity of the medium when the temperature is lowered. One observes 30-40% of the β form in the spectra of α,β-unsubstituted indolizine and pyrrolobenzimidazole derivatives in CF_3COOH prepared at –15°, whereas the β form is absent at room temperature under the same conditions (Table 2, Ib and IIIb). Cooling of solutions of the same substances prepared at 25° to –15° does not lead to the appearance of signals corresponding to the β form.

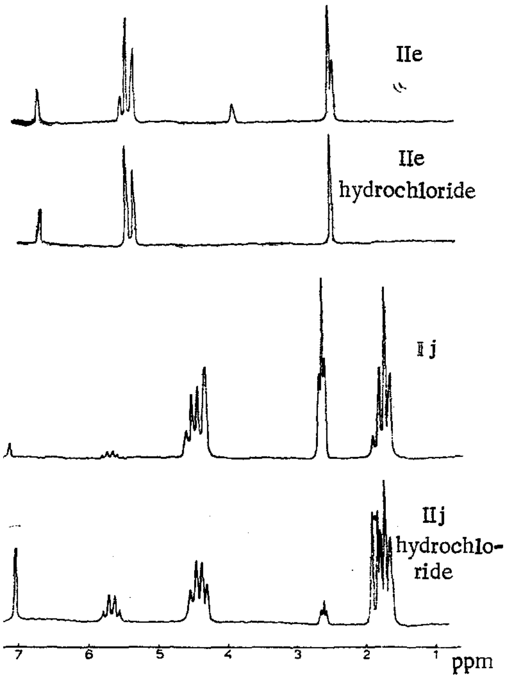


Fig. 1. PMR spectra of 1-benzyl-6-(p-tolyl)pyrrolo[1,2-a]imidazole (IIe), 1-ethyl-2-chloro-5-methyl-6-phenylpyrrolo[1,2-a]-imidazole (IIj), and their hydrochlorides in CF_3COOH at 25° 10 min after preparation of the solutions.

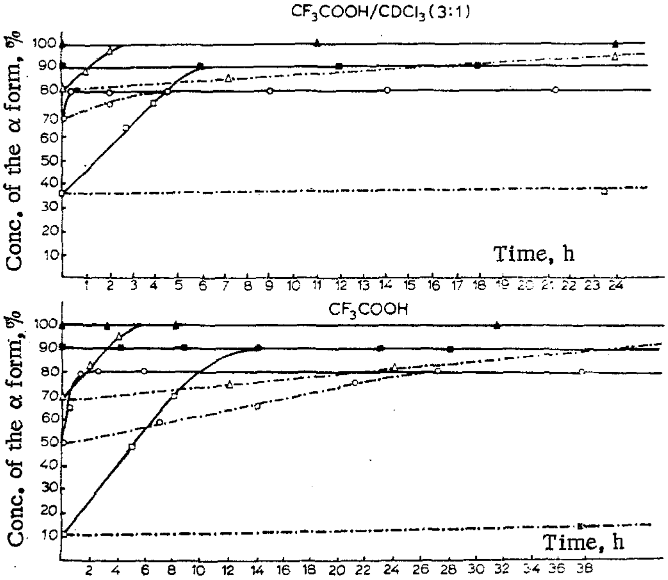


Fig. 2. Dependence of the relative percentage of the α form of the conjugate acid on the time: —) 70°C; — · —) 25°; Δ) 1-benzyl-6-(p-tolyl)pyrrolo[1,2-a]imidazole (IIe); ▲) hydrochloride of IIe; □) 1-ethyl-2-chloro-5-methyl-6-phenylpyrrolo[1,2-a]imidazole (IIj); ■)hydrochloride of IIj; ○) 2-phenyl-3-methylindolizine (Ic).

Thus the ratio of the two protonated forms of the conjugate acids observed immediately after dissolving compounds of the investigated type in CF_3COOH is not an equilibrium ratio, and the effect of the temperature and the acidity of the medium on the ratio of the forms is evidently due to the dependence of the rate of conversion of one form to the other on these parameters.

In fact, measurement of the spectra of these compounds with time (Fig. 2) showed that

TABLE 1. Percentage of the Protonated Forms (%) in the PMR Spectra of Pyrrolo[1,2-a]imidazole Derivatives (IIa-j) and Their Hydrochlorides in CF_3COOH at 25°C (10 min after dissolving)

Compound	Bases		Hydrochloride	
	α-form	β-form	α - form	β-form
IIa	78	22	100	—
IIb	91	9	100	—
IIc	87	13	100	—
IId	90	10	100	—
IIe	68	32	100	—
IIf	85	15	100	—
IIg	80	20	100	—
IIj	10	90	90	10

TABLE 2. Percentage of the α Form of the Conjugate Acid (%) as a Function of the Temperature and the Acidity of the Medium (10 min after dissolving)

Compound	Acidity of the medium and temperature			
	CF_3COOH, —15°	CF_3COOH, 25°	$CF_3COOH/CDCl_3$ (3 : 1), 25°	$CF_3COOH/CDCl_3$ (1 : 3), 25°
I b	62	100	100	100
I c	10	50	65	80
II e	55	68	80	100
II i	78	85	100	100
II j		10	37	90
III a	70	90	100	100
III b	77	100	100	100

conversion of the β form to the α form of the conjugate acid is observed up until the equilibrium state is established, in which state the ratio of the form, within the limits of the accuracy of the measurements, coincides with the ratio of the forms observed in the spectra of the corresponding hydrochlorides. The rate of establishment of the equilibrium state increases as the temperature and acidity of the medium are increased (Fig. 2).

The position of the equilibrium for all of the investigated systems is determined mainly by the presence or absence of a substituent attached to the carbon atom of the pyrrole ring in the α position relative to the bridge nitrogen atom. In the case of α-unsubstituted compounds the equilibrium is shifted completely to favor the α form, and this corresponds to a considerable difference in the basicities of the α- and β-carbon atoms.

An equilibrium between two tautomeric forms of conjugate acids in which the relative percentages of the α and β forms are 80-20 and 90-10%, respectively, is observed for the investigated α-methyl-substituted indolizines (Ic) and pyrroloimidazoles (IIj). Similar data were observed for pyrazole derivatives with alkyl groups in the α positions.

A study of the protolytic equilibrium in series of indolizine, pyrrolo[1,2-a]imidazole, and pyrrolo[1,2-a]benzimidazole derivatives showed that the α form of the conjugate acid is thermodynamically more favorable in all three heterocyclic systems.

In addition, it is interesting to note that under conditions of slow conversion of the β form to the α form, the percentage of the thermodynamically less favorable β form for α,β-unsubstituted compounds is 30-40%, whereas for α-methyl-substituted derivatives it reaches 90% (Table 2). Insofar as one can judge from the relative percentage of the protonated forms that is observed immediately after preparation of solutions of the compounds under these conditions, protonation takes place at a higher rate at the less basic center (C_β). A similar Brönsted disparity has been observed in a number of other ambident bases [9, 10].

In addition, it is well known that the relative stabilities of isomeric carbonium ions

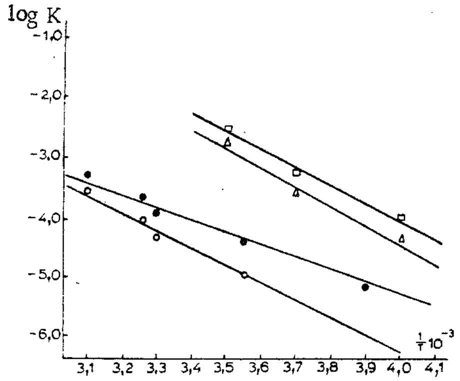


Fig. 3. Depencence of log K on 1/T for 2-methylindolizine (Ia), 2-methyl-4-benzylpyrrolobenzimidazole (IIIa), and 1-benzyl-6-(p-tolyl)pyrroloimidazole (IIe): ●) α proton (Ia); Δ) β proton (IIIa); O) β proton (Ia); □) β proton (IIe).

TABLE 3. Rate Constants for Deuterium Exchange in Neutral I-III Molecules

Compound	Position	log K	$L^{+}\beta$	Δ pK_a (in nitromethane
I a	α	−5,30	1,82	3,53
	β	−6,30	1,88	
III a	α	−3,43	1,77	−0,39
	β	−4,40	1,85	
II e	α	−3,00	1,72	−0,99
	β	−3,99	1,81	

formed during the protonation of various atoms of the same aromatic **base, in the general case** follow the trend of the relative rates of deuterium exchange at these positions [15]. In order to verify whether this sort of conformity is observed in the compounds that we investigated, we studied the rate of deuterium exchange of Ia, IIIa, and IIe in $CDCl_3/CD_3OD$ (4:1) at 50 to –25°. Under these conditions deuterium exchange occurs only at the α and β atoms of the pyrrole fragment.

It was observed that deuterium exchange in all of the investigated systems follows a first-order equation. A linear dependence of the logarithm of the rate constants on 1/T is observed (Fig. 3).

The dependence of log K was extrapolated to –25° in order to estimate the rates of deuterium exchange in indolizine. At this temperature the exchange rate constants (Table 3) for both positions of the pyrrole fragment increase by two orders of magnitude on passing from indolizine to pyrrolobenzimidazole and pyrroloimidazole.

The established deuterium exchange rates (Table 3) in the α position of the investigated compounds change linearly with the basicity constants determined in nitromethane. One should bear in mind that these constants characterize the basicity of the α center, inasmuch as the equilibrium of the two tautomeric forms of the conjugate acid in these compounds is shifted completely to favor the α form.

The results make it possible to assume that the change in the basicities of the β center also follow the trend of the rate of exchange of the protons in the β position. From the change in the rate constants for deuterium exchange it can be concluded that the basicity and, consequently, the stability of the β form of the conjugate acid increase on passing from indolizine (I) to pyrrolobenzimidazole (III) and pyrroloimidazole (II); this is in agreement with the percentage of the β form of the conjugate acid observed for these compounds in CF_3COOH at 25°.

The correlation between the exchange rate constants and the basicity constants makes it possible to accurately use the energies of electrophilic localization as reactivity indexes of the investigated systems. The values of these indexes calculated by the Hückel method are in agreement both with the relative reactivities of the α and β positions and with the increase in the reactivities of these positions in the order indolizine, pyrrolobenzimidazole, and pyrroloimidazole.

EXPERIMENTAL

The PMR spectra of the investigated compounds in mixtures of deuterochloroform and trifluoroacetic acid with various percentages of trifluoroacetic acid (from 25 to 100%) and deuterochloroform with alcohol (4:1) were measured with a C-60 spectrometer (JEOL, Japan). All of the measurements were made at the same concentration of the investigated substance in solution (0. 15 M). The ratio of the protonated forms was determined by means of an integrator. The accuracy in the measurements was ± 5%.

LITERATURE CITED

1. W. L. F. Armarego, J. Chem. Soc., 4226 (1964).
2. W. L. F. Armarego, J. Chem. Soc., B, 191 (1966).
3. M. Fraser, I. McKenzie, and D. H. Reid, J. Chem. Soc., B, 44 (1966).
4. L. M. Alekseeva, G. G. Dvoryantseva, I. V. Persianova, Yu. N. Sheinker, A. A. Druzhinina, and P. M. Kochergin, Khim. Geterotsikl. Soedin., 492 (1972).
5. L. M. Alekseeva, G. G. Dvoryantseva, I. V. Persianova, Yu. N. Sheinker, R. M. Palei, and P. M. Kochergin, Khim. Geterotsikl. Soedin., 1132 (1972).
6. G. Opitz and W. Merz, Ann., 652, 139 (1962).
7. G. Opitz and A. Griesinger, Ann., 665, 101 (1963).
8. J. E. Jonson, M. E. Herr, J. C. Babcock, and A. E. Fonken, J. Am. Chem. Soc., 78, 430 (1956).
9. Y. Chiang and E. B. Whipple, J. Am. Chem. Soc., 85, 2763 (1963).
10. E. B. Whipple, Y. Chiang, and R. L. Hinman J. Am. Chem. Soc., 85, 26 (1963).
11. A. J. Kresge, Y. Chiang, and L. E. Hakka, J. Am. Chem. Soc., 93, 6167 (1971).
12. T. Birchall and R. J. Gillespil, Can. J. Chem., 42, 502 (1964).
13. T. Birchall, A. N. Bourns, R. J. Gillespil, and P. J. Smith, Can. J. Chem., 42, 1433 (1964).
14. J. W. Larsen and M. Eckert-Maksic, Tetrahedron Lett., 15, 1477 (1972).
15. D. Bethell and V. Gold, Carbonium Ions, Academic Press, New York (1970).