TAUTOMERISM IN A NUMBER OF ASYMMETRICAL IMIDAZOLE SYSTEMS

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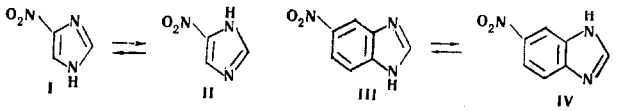
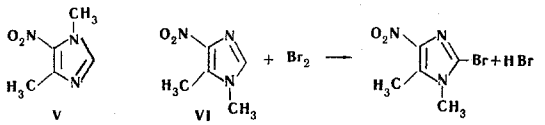
It is shown that in NH-unsubstituted asymmetrical imidazole systems the predominant tautomeric forms are those with the proton attached to the heteroatom which is most susceptible to the effect of electron-accepting substituents or least susceptible to the effect of electron-donating substituents.

The effect of substituents on the tautomerism of imidazole and benzimidazole derivatives was examined in a number of papers [1-6] in which the authors usually proceeded from a presupposition that, up to now, has not raised any doubts, viz., that the tautomeric form with the proton attached to the nitrogen atom that is subject to the maximum effect of an electron-donating substituent or to the minimum effect of an electron-accepting substituent should predominate [4-7]. However, the experimental data on the tautomerism of 4(5)-nitroimidazole [2] indicate a shift of the equilibrium to favor form I, while the pK_a values of N-methylated 5(6)-nitrobenzimidazoles indicate the higher concentration of tautomer III. The pK_a values of other isomeric pairs (Table 1, 10 and 11,



14 and 15, etc.), as well as the change in the basicity during N-methylation* convincingly indicate that the prevailing tautomeric forms are those with the proton attached to the heteroatom conjugated with the electron-accepting substituents; if, however, the substituents are electron donors, the predominant tautomeric forms are those with the proton on the unconjugated nitrogen.

In accordance with the higher concentration of form I, it was assumed that the conjugation effect is not an important factor in establishing tautomeric equilibrium. In the opinion of Ridd, Smith et al. [4,7], the inductive effect plays the decisive role. However, this assumption contradicts the higher basicity of 1-methyl-4-nitrobenzimidazole as compared with the 3-methyl-4-nitro isomer and is not in agreement with the chemical properties of the imidazole systems. For example, in the bromination of isomeric compounds V and VI, only VI reacts to form a 2-bromo derivative [8].



*See [7] for the method of analysis of tautomeric equilibria from pK_a data.

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TABLE 1. pK_a Values of N-Alkylated Derivatives of Imidazole Systems Systems in Aqueous Solutions* at 25 deg†

No.	Compound	pKa	Literature
1	Imidazole	6,95	26
2	4-Nitro-	−0,05	5
3	$N_{(1)}$-Methyl	−0,53	
4	$N_{(3)}$-Methyl	2,13	
5	Benzimidazole	5,53	27
6	4-Nitro	3,33	4
7	$N_{(1)}$-Methyl	3,86	
8	$N_{(3)}$-Methyl	3,25	
9	5-Nitro	3,48	
10	$N_{(1)}$-Methyl	3,40	
11	$N_{(3)}$-Methyl	3,67	
12	5-Amino	6,11	28
13	$N_{(1)}$-Dimethyl-	6,37	
14	1,5-Dimethyl	5,22	
15	1,6-Dimethyl-	5,17	
16	1,2,5-Trimethyl	6,07	
17	1,2,6-Trimethyl-	5,45	

*Compounds 10-17 were investigated in 50% aqueous ethanol.
†Compound 5 was investigated at 20°.

In addition, as shown in [9], the results of cyanoethylation of tautomeric nitrobenzimidazoles III and IV can be explained only if conjugation is taken into account. Thus the shift in the equilibrium to favor forms I and III is due to factors other than the absence of conjugation. It should also be noted that the predominance of tautomers I and III can by no means serve as an argument in favor of the insignificant role of conjugation. Reinforcement of the polarization of the NH bond under the influence of an electron-accepting substituent cannot unambiguously determine the direction of the shift in the tautomeric equilibrium, since the common method of evaluating the effect of substituents on the equilibrium state is a comparison of the relative stabilities of both forms [10]. The importance of precisely this sort of approach to the analysis of tautomeric equilibrium was satisfactorily demonstrated in the case of β-dicarbonyl compounds [11-13].

Analysis of the effect of electron-donating and electron-accepting substituents on the state of the imidazole grouping indicates that the energetically more stable tautomers should be those with the proton attached to the nitrogen atom subject to the minimum effect of an electron-donating substituent or to the maximum effect of an electron-accepting substituent.

Let us compare tautomeric forms I and II. If one proceeds from conjugation concepts, the effect of the nitro group in tautomer I is primarily extended to the pyrrole nitrogen atom. Also evidence in favor of this assumption is the high bond order between the C_4 and C_5 atoms of the imidazole ring [14,15]. The NH group interrupts the conjugation chain, and this effect is extended to a lesser degree to the pyridine nitrogen atom. In considering the reasons for the higher stability (and, consequently, the lower acidity) of tautomer I, one should first of all compare the states of the pyridine nitrogen atoms of structures I and II. The nitrogen atom in the first of these is attached to a less electron-accepting carbon atom, and it therefore has less p character in this orbital, which, according to Bent's rule [16], should promote greater p character of its orbitals in the N=C bond and, consequently, its high energetic stability. Similarly, in structure II the bond between the pyridine nitrogen atom and the more electron-accepting carbon of the =C−N= group has less s character, and the p character of its double bond therefore decreases. One can arrive at the same conclusion by means of somewhat different reasoning. It is well known that the electronegativity of an atom that is opposite a multiple bond increases and is stronger, the higher the bond multiplicity [17]. One can hence assume the presence of an inverse interaction; the bond multiplicity of an atom will decrease with increasing electronegativity of a substituent bonded to this atom by means of a single bond. In addition, its energetic stability should also decrease. Thus, the state of the pyridine heteroatoms is one of the reasons for the high energy stability of structure I.

In addition, because of the high electronegativity of the σ bonds of the pyridine nitrogen atom as compared with the pyrrole nitrogen atom [25.74 (4.13) and 24.63 (3.94)* [18]), the $O_2N-C=CH-NH-$ grouping of

*The first number is the values in the Mulliken scale, while those in parentheses are values in the Pauling scale.

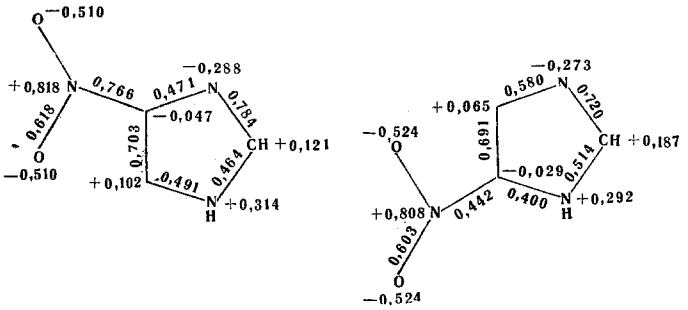
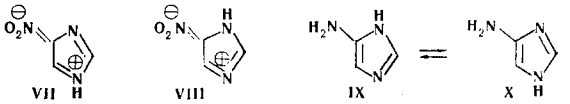


Fig. 1. π-Electron densities and bond orders in the 4(5)-nitroimidazole molecule.

tautomer I should be more stable than the $O_2N-C=CH-N=$ grouping of structure II in which two electron acceptors (the nitro group and the pyridine nitrogen atom) are conjugated.

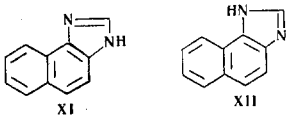
The difference in the interaction of an electron-accepting substituent with pyrrole and pyridine nitrogen atoms is satisfactorily illustrated by resonance structures VII and VIII. The lower weight of the latter under hybridization conditions does not raise any doubts.



Thus if one proceeds from the assumption that the effect of the nitro group is transmitted along the system of conjugated bonds, structure I should be more energetically stable.

Similarly, if there is an electron-donating substituent in the 4(5) position of the imidazole ring, tautomer IX should be more energetically stable. The $H_2\ddot{N}-\underset{|}{C}=CH-N=$ grouping in it is energetically more favorable than the $H_2\ddot{N}-\underset{|}{C}=CH-\ddot{N}H-$ grouping in which two donor groups (amino and pyrrole) are conjugated. In addition, conjugation of the pyridine nitrogen atom with the amino group in structure IX should promote an increase in the multiplicity of the $-N=CH-$ bond and in its energy stability.

The proposed explanation for the tautomerism can also be applied to derivatives of more complex imidazole systems. For example, the unexpected decrease in the dipole moment of naphth [1,2-d]imidazole when it is methylated in the 3-position [19] attests to a high concentration of tautomer XII, according to the old concepts [4-7], one should have expected a high concentration of XI in view of the high basicity of β-aminonaphthalene as compared with the α isomer.



The point of view set forth in this paper is confirmed by MO calculations of 4(5)-nitroimidazole [20] (Fig. 1). They indicate that: a) the hydrogen atom in the most stable tautomeric form of 4(5)-nitroimidazole is bonded to the atom with the lower electron density as compared with the nitrogen atom of the tautomer which is present in lower concentrations; b) the π-electron density of the pyridine nitrogen atom adjacent to the nitro group is greater than that of the nitrogen atom removed from it; c) the order of the bond of the pyridine nitrogen atom with the α-carbon atom of the imidazole ring is higher in the predominant tautomer; d) the NH group in the stable tautomer is situated at the most electron-accepting carbon atom.

This representation of the predominance (in solutions) of the tautomeric forms with the proton attached to the nitrogen atom with the lower electron density also agrees with the difference in the results of alkylation [21-25] in neutral and alkaline media.* Alkylation of 5(6)-nitrobenzimidazoles in the absence of alkali

*See [3] for data on the kinetics and mechanism of alkylation of 4(5)-nitroimidazole.

leads to the formation of primarily 1,6-disubstituted isomers [23,24], while 1,5-disubstituted isomers are the major products in alkaline media [25]. The increase in the yields of 1,2-dimethyl-5-nitrobenzimidazole and 1-methyl-5-nitrobenzimidazole on alkylation in alkaline media [4] also attests to the predominance of tautomeric forms of the III type.

The results of [6] on the benzylation of benzimidazoles, which deviate from the usual principles of orientation in N-substitution, should, one would think, be interpreted with allowance for the fact that the reaction was carried out in benzene in the presence of fused sodium acetate, which is an alkaline reagent.

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