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DEPENDENCE OF THE REACTIVITY OF FIVE-MEMBERED AROMATIC HETEROCYCLES ON THEIR STRUCTURE.

5.* PROTONATION OF FURAZANE, FUROXANE, AND THEIR AMINODERIVATIVES

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Proton affinity of furazane, furoxane, and their aminoderivatives for protonation at various centers was calculated by ab initio methods using the STO-3G basis set. Basicity was found to decrease in the following order: N-oxide oxygen atom, endocyclic nitrogen atom, amino group. The presence in the ring of aminogroups or N-oxide functions leads to elevated proton affinity of the basic centers which are located in the active positions of the ring.

Furazanes, furoxanes (furazane-N-oxide), and their aminoderivatives contain several potential protonation centers: the endocyclic nitrogen atoms, the amino group, and the N-oxide oxygen atom. Study of the acid-base properties of azoles, their N-oxides, and the aminoderivatives shows that, in principle, protonation can occur at any of these [2]. Besides this, experimental determination of the protonation site is encumbered with great difficulties since, for example, aminofurazanes and aminofuroxanes are weak bases and do not form stable salts with mineral acids. Therefore, we undertook a quantum mechanical study of the protonation of furazane, furoxane, and their aminoderivatives at various basic centers. The calculations were carried out nonempirically using the GAUSSIAN-76 program with the STO-3G minimal basis set according to the procedure described earlier [3]. The proton affinity (PA) was calculated as the difference of the total energies of the basic and protonated forms of the molecules (Table 1).

Optimization of the geometry, carried out by an MNDO method, showed that, in agreement with the x-ray structural analysis of 3-amino-4-methylfurazane [4], the amino group is pyramidal in aminofurazane itself and in aminofuroxanes. Protonation at the α- (relative to the amino group) nitrogen atom or at the α-N-oxide oxygen atom leads to complete flattening of the amino group and coplanarity of it with the ring. This same tendency is also observed upon protonation at the β-nitrogen atom or the β-N-oxide oxygen atom. However, in this case the amino group nevertheless retains some pyramidal character with an approximately coplanar disposition of the amino group and the ring.

Table 1 shows that the endocyclic nitrogen atom which is next to the amino group has the highest PA in aminofurazane. Its PA is much larger than for the ring nitrogen in unsubstituted furazane. An analogous increase of basicity of the endocyclic nitrogen atom upon intro-

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*For Communication 4, see [1].

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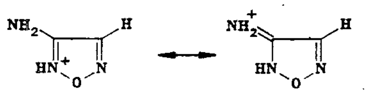
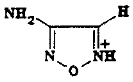
TABLE 1. Proton Affinity (kcal/mole) of Furazanes and Furoxanes

Base	Protonation center			
	NH_2	α-N	β-N	N→O
Furazane	—	230,2		—
3-Aminofurazane	239,8	251,9	233,4	—
Furoxane	—	246,2		270,3
3-Aminofuroxane	240,6	—	248,9	295,9
4-Aminofuroxane	239,0	261,2	—	272,3

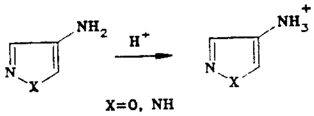
duction of amino groups into the α-position was observed, for example, in the case of imidazoles [5], pyrazoles [6, 7], and triazoles [8, 9]. This agrees with the +M effect of amino groups which facilitates delocalization of positive charge in the cation I:


Ia Ib


II

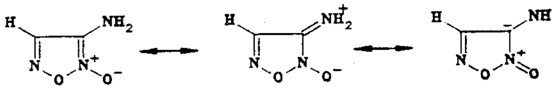
Such delocalization is impossible upon protonation of the other ring nitrogen atom. Therefore, cation II is less stable than cation I. The PA of the β-nitrogen atom is much less. Flattening of the amino group in cation I and partial retention of its pyramidal nature in cation II also indicates better conjugation upon protonation at the α-nitrogen atom.

Earlier, it was assumed that aminofurazanes in aqueous solutions are protonated first at the amino group and then on the ring [10]. However, doubts about this have already been expressed [2]. Results of the quantum mechanical calculation do not confirm such a protonation order. In general, protonation at the exocyclic amino group is observed for the five-membered aminoazoles and aminooxazoles only for the two heterocycles in which it is located on the carbon atom which is not bonded to a heteroatom [2]:



In these cases, reduced basicity of the amino group as a result of the inductive effect of the heteroatoms is minimal. On the other hand, stabilization of the cation through conjugation with the amino group is impossible upon protonation on the ring. As a result, the amino group is more basic than the atoms of the heterocycle. In all other aminoazoles and aminooxazoles, the ring nitrogen atom undergoes protonation.

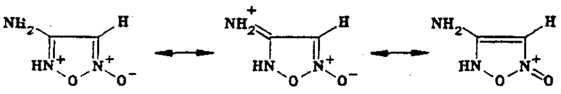
Introduction of an N-oxide oxygen atom, i.e., a change to aminofuroxanes, in general little affects the PA of the amino group. It increases somewhat with the N-oxide oxygen in the α-position and decreases as much if the oxygen is located in the β-position. In the case of 3-aminofuroxane, the +M effect of the N-oxide group leads to weakening of the conjugation between the amino group and the ring and to a decreased contribution of structure IIIb. This should lead to increased PA of the amino group.


IIIa IIIb IIIc

However, the mesomeric effect of the N-oxide oxygen atom is here compensated by its inductive effect which is opposite in sign. This also explains the small change in PA of the amino group in 3-aminofuroxane. In 4-aminofuroxane, the mesomeric effect of the N-oxide group is not exhibited due to the impossibility of its conjugation to the amino group. However, its inductive effect is weakened due to the distance from the amino group. Therefore, the sum total change of the amino group PA is also small.

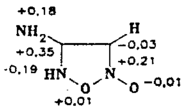
The N-oxide oxygen is the most basic atom in the aminofuroxane molecules. Its basicity is much larger when the amino group is located in the α-position. This is clearly explained by the possible delocalization of positive charge analogously to that which occurs upon protonation of aminofurazane.

The ring nitrogen atom in aminofuroxanes has much lower PA than the N-oxide nitrogen atom. Nevertheless, it is more basic than the amino group. It is interesting that the ring nitrogen atoms in amino furoxane possess larger basicity than the corresponding atoms in aminofurazane. An analogous picture is also observed for unsubstituted furoxane. The PA of its nitrogen atom is higher than for furazane. This can be explained by the fact that the N-oxide oxygen, being a mesomeric electron donor, assists delocalization of positive charge whereas its inductive effect, transmitted through the diene bond system [11], is weakened due to the distance from the protonated nitrogen atom:

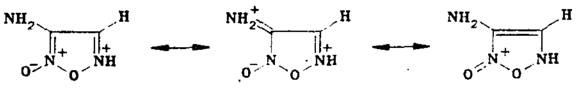


IVa IVb IVc

The ab initio calculation shows that IVb and IVc are closer to the actual structure than IVa, since according to the calculation the charge is negative and not positive on the protonated nitrogen atom:



Results of the optimization of geometry for this molecule by an MNDO method agree with this. These results indicate a lengthening of the endocylic C=N bonds and a shortening of the C–NH_2 and C–C bonds in comparison to the initial molecule. It is interesting that protonation of 3-aminofuroxane at the ring nitrogen atom leads to a significant increase of C=N bond length in the 2-3 position, from 1.41 to 1.52 Å (MNDO method). Upon protonation of furoxane itself, the length of this C=N bond increases from 1.39 to 1.44 Å. The lengthening of the C=N bond in the case of 3-aminofuroxane is explained by the participation of structures Vb and Vc in delocalization of positive charge, in which it is a single bond:



Va Vb Vc

Structure Vb is excluded for protonation of furoxane. Therefore, the lengthening of the $N_{(2)}$–$C_{(3)}$ is not as significant.

Thus, according to the calculation, the N-oxide oxygen atom possesses the largest PA in furazane, furoxane, and their aminoderivatives. The exocyclic nitrogen atoms follow next and the amino group has the lowest PA value. Introduction of an amino group leads to a large PA increase of the α-nitrogen atom and the α-N-oxide oxygen atom. The PA of the β-nitrogen atom and the β-N-oxide oxygen atom in this case change little. A change from furazanes to their N-oxides, furoxanes, increases significantly the PA of the second nitrogen atom in the ring but weakly affects the PA of the exocyclic amino group due to compensation of the opposing mesomeric and inductive effects of the N-oxide fragment.

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REACTION OF 6-ARYL-2,2-DIMETHYL-1,3-DIOXIN-4-ONES WITH CYANOAMINO COMPOUNDS

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6'387:543.51'422

Aroylketenes have been generated by thermolysis of 6-aryl-2,2-dimethyl-1,3-dioxin-4-ones. They take part in a 1,4-cycloaddition reaction at the C≡N bond of N-aryl or N,N-dialkyl-N-cyanoamines and of N'-phenyl-N-cyanoguanidine to form the corresponding 2-N-aryl-amino, 2-N,N-dialkylamino, and 2-N-phenylguanidino-6-aryl-1,3-oxazin-4-ones. p-Aminobenzonitrile and cyanoacetamide are acylated by aroylketenes to form the p-cyanophenylamide of p-toluylacetic acid and the cyano-acetamide of benzoylacetic acid.

Aroylketenes can be conveniently generated by the thermolysis of 5-aryl-2,3-dihydrofuran-2,3-diones [1] and they can then take part in 1,4-cycloadditions with aldehydes, ketones [2], azomethines [3], isocyanates [4], and other compounds containing multiple bonds [5]. The ability of compounds with the C≡N bond to take part in this reaction is restricted to those with a strongly activating electron donating group (N,N-dialkylcyanamines, cyanoic esters) [6]. Unsubstituted and monosubstituted cyanamides cannot take part in the cycloaddition reaction because their properties as BH nucleophiles cause opening of the 5-aryl-2,3-dihydrofuran-2,3-dione ring under conditions considerably milder than those demanded for generation of the aroylketene [7]. Aminonitriles containing unsubstituted or monosubstituted amino groups react in a similar manner [8].

In order to study the reaction of cyanoamino compounds with aroylketenes another method of generating the latter was used based on the thermolysis of 6-aryl-2,2-dimethyl-1,3-dioxin-4-ones (I). This occurs under significantly more severe conditions (140-145°C) than for the thermolysis of 5-aryl-2,3-dihydrofuran-2,3-diones (80-85°C). BH nucleophiles do not react with compounds I below the temperature for generating the aroylketenes [9]. (Formula, following page, below Table 1.)

Both mono and di-substituted cyanamides react with Ia-d to form 2-N-mono (II) and 2-N,N-disubstituted-6-aryl-1,3-oxazin-4-ones (III-VII). Unsubstituted cyanamide could not be used due to its very ready dimerization even with gentle heating.

The IR and PMR spectra of the compounds corresponded to those given in [6, 10-12].

Aroylketenes generated by thermolysis of Ia-e react at the C≡N bond of N'-phenyl-N-cyanoguanidine to form 2-N-phenylguanidino-6-aryl-1,3-oxazin-4-ones VIII-XI (Table 1).

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