DEPENDENCE OF THE REACTIVITY OF FIVE-MEMBERED AROMATIC HETEROCYCLES ON THEIR STRUCTURE. 2.* EFFECT OF AZA SUBSTITUTION ON THE PROTON AFFINITY OF AMINOFURANS

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The proton affinities of a series of aminofurans and their aza derivatives were calculated by a nonempirical method in the STO-3G basis set. A correlation was established between the proton affinities and the position of the heteroatoms in the ring.

Earlier [1] we showed for the case of amino-substituted pyrroles and azoles that the effect of the heteroatom on the proton affinity (PA)† of the amino group is determined by its position in the ring and does not depend on the presence of other heteroatoms in the ring. While continuing these investigations, we undertook a calculation of the PA values of the amino group in aminofurans (I, II) and their aza derivatives.

I

II

As before, the calculation was performed by means of the GAUSSIAN-76 program in the STO-3G basis set with the use of the geometric parameters obtained with full optimization of the molecular geometry in terms of the semiempirical MNDO method [2]. A fairly good linear corelation exists between the proton affinities determined by the STO-3G and MNDO methods (Table 1):

$$PA_{STO\text{-}3G} = 1.162 \cdot PA_{MNDO} - 0.1268 \quad (1)$$
$$(r = 0.988; \quad s = 0.0028; \quad F = 571).$$

Assuming the nondependence of the effects of the heteroatoms on the proton affinity of the amino group for the heterocycles (I) and (II) and their derivatives produced by substitution of the —CH= fragments by nitrogen atoms, we can express the proton affinity in terms of the following equation:

$$PA = PA_0 + n_2\Delta E_2 + n_3\Delta E_3 + n_4\Delta E_4 + n_5\Delta E_5 + n_{O_{(2)}}\Delta E_{O_{(2)}}, \quad (2)$$

where PA_0 is the proton affinity of aminofuran (I), taken as reference; n_2-n_5 are the numbers of nitrogen atoms at the corresponding positions of the ring; $n_{O(2)}$ is the number of oxygen atoms at position 2; ΔE_2-ΔE_5 are the values expressing the effect of the nitrogen atom at the given position on the proton affinity; $\Delta E_{O(2)}$ is a value which expresses the change in proton affinity during the transition from isomer (I) to isomer (II).

*For Communication 1, see [1].

†In the present work the difference between the total energies of the protonated E^+ and initial E^0 molecules of the base ($PA = E^+ - E^0$), i.e., a value opposite in sign to the experimentally measured proton affinities, was used for the proton affinity (PA).

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TABLE 1. The Proton Affinities of the Amino Group in the Aminofurans (I) and (II) and their Aza Derivatives (au), Calculated by the MNDO and STO-3G Methods and by Means of the Correlation Equations

Position of heteroatoms	MNDO	Eq. (5)	STO-3G	Eq. (4)	Eq. (7)
4-O	−0,2532	−0,2551	−0,4203	−0,4224	−0,4200
4-O-2-N	−0,2454	−0,2449	−0,4142	−0,4127	−0,4135
4-O-3-N	−0,2389	−0,2378	−0,4024	−0,4017	−0,4026
4-O-5-N	−0,2369	−0,2365	−0,4029	−0,4022	−0,4030
4-O-2,3-N	−0,2283	−0,2275	−0,3930	−0,3920	−0,3929
4-O-2,5-N	−0,2271	−0,2262	−0,3927	−0,3925	−0,3933
4-O-3,5-N	−0,2195	−0,2191	−0,3822	−0,3815	−0,3823
4-O-2,3,5-N	−0,2067	−0,2089	−0,3690	−0,3717	−0,3692
2-O	−0,2457	−0,2482	−0,4108	−0,4143	−0,4118
2-O-3-N	−0,2272	−0,2308	−0,3952	−0,3935	−0,3945
2-O-4-N	−0,2359	−0,2308	−0,3951	−0,3935	−0,3945
2-O-5-N	−0,2300	−0,2295	−0,3950	−0,3941	−0,3949
2-O-3,4-N	−0,2141	−0,2135	−0,3724	−0,3728	−0,3738
2-O-3,5-N	−0,2096	−0,2122	−0,3740	−0,3733	−0,3742
2-O-4,5-N	−0,2173	−0,2122	−0,3743	−0,3733	−0,3742
2-O-3,4,5-N	−0,1922	−0,1948	−0,3510	−0,3525	−0,3501

The values of ΔE_i and $\Delta E_{O(2)}$ in Eq. (2) were calculated by the method of least squares:

$$PA_{STO\text{-}3G} = -0.4225 + 0.0097n_2 + 0.0208n_3 + 0.0207n_4 + 0.0202n_5 + 0.0082n_O \quad (3)$$
$$(r = 0.996; \quad s = 0.0016; \quad F = 260).$$

From Eq. (3) it follows that the effect of the nitrogen atoms at positions 3 and 4 (i.e., at the β positions to the amino group) on the proton affinity are practically the same. We obtained a similar result during the examination of amino pyrroles and their aza derivatives [1]. Thus, on the assumption that $\Delta E_3 = \Delta E_4$, Eq. (3) can be simplified as follows:

$$PA_{STO\text{-}3G} = -0.4224 + 0.0097n_2 + 0.0208(n_3 + n_4) + 0.0202n_5 + 0.0081n_{O_{(2)}} \quad (4)$$
$$(r = 0.996; \quad s = 0.0016; \quad F = 358).$$

The high correlation coefficient demonstrates the reliability of Eq. (4) and, consequently, the assumptions made during its formulation.

Correlation by means of the data calculated by the MNDO method gives similar results but with a poorer correlation coefficient and a larger mean-square deviation:

$$PA_{MNDO} = -0.2551 + 0.0103n_2 + 0.0173(n_3 + n_4) + 0.0187n_5 + 0.0070n_{O_{(2)}} \quad (5)$$
$$(r = 0.988; \quad s = 0.025; \quad F = 109).$$

This is not surprising, since it has been mentioned in the literature that the MNDO method gives significant error during the prediction of the proton affinities of amines [3].

Comparison shows that the correlation for the aza derivatives of aminofuran is little worse than the correlation which we obtained earlier for the aza derivatives of amino-pyrrole [1]:

$$PA_{STO\text{-}3G} = 0.4404 + 0.0092n_2 + 0.0184(n_3 + n_4) + 0.0151n_5 + 0.0209n_{NH_2} \quad (6)$$
$$(r = 0.998; \quad s = 0.0013; \quad F = 617).$$

The reason for this may be the larger mutual effect of the aza groups in the aminofuran derivatives. Analysis of the ΔE_i contributions shows that they increase with increase in the number of aza groups and by approximately the same amount. In Eq. (4) it is therefore possible to introduce an additional term which takes account of the paired interactions between the nitrogen atoms in the ring:

$$\Delta\Delta E \times [n(n-1)]/2,$$

where $\Delta\Delta E$ is a quantity which characterizes the interaction of the two nitrogen atoms; $[n(n-1)]/2$ is the number of paired interactions in the ring in the presence of n nitrogen atoms.

The value of $\Delta\Delta E$ was determined by the method of least squares, which led to the equation

$$PA_{STO\text{-}3G} = -0.4199 + 0.0064n_2 + 0.0173(n_3 + n_4) + 0.0169n_5 + 0.0081n_{O_{(2)}} + 0.0033[n(n-1)/2]$$
$$(r = 0.9995; \quad s = 0.0006; \quad F = 1883). \qquad (7)$$

Comparison of Eqs. (4) and (7) shows that allowance for the interactions of the heteroatoms in the ring makes it possible to improve the accuracy of the calculation of the proton affinity.

Equations (4) and (6) make it possible to compare the effects of the heteroatoms in the aza derivatives of furan and pyrrole. The value of ΔE_i in these equations show identical tendencies to change, although they are larger in the case of the aminofuran derivatives. This indicates better conduction of the effects in the case of the oxygen-containing heterocycles. In order to compare the effect of the —O— and —NH— heteroatoms it is possible to neglect this difference and to combine Eqs. (4) and (6), considering that the ΔE_i values are the same for the two series:

$$PA_{STO\text{-}3G} = -0.4425 + 0.0094n_2 + 0.0196(n_3 + n_4) + 0.0177n_5 + 0.0306n_{O_{(2)}} + 0.0220n_{O_{(4)}} + 0.0204n_{NH_{(2)}}$$
$$(r = 0.995; \quad s = 0.0021; \quad F = 397), \qquad (8)$$

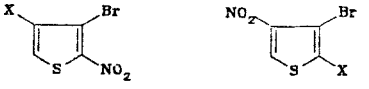
where $n_{O(2)}$, $n_{O(4)}$, and $n_{NH(2)}$ are the numbers of O or NH heteroatoms at positions 2 or 4.

As expected, in Eq. (8) the correlation coefficient is somewhat lower, and the mean-square deviations are higher than in Eqs. (4) and (6).

From the ΔE_O and ΔE_{NH} values it follows that the proton affinity decreases successively in the series of 4-NH, 2-NH, 4-O, and 2-O derivatives. This sequence coincides with the direction of change in the σ constants determined for the heteroatoms as substituents in the five-membered heterocycles: —0.75 (4-NH), —0.15 (2-NH), 0.25 (4-O), 1.04 (2-O) [4, 5].

As follows from Eq. (8), increase in the number of heteroatoms in the ring is accompanied by a decrease in the proton affinity, and this is clearly due to increase in the electron-withdrawing characteristics of the heterocycle. Unfortunately, there are no published data on the σ values for five-membered heterocycles as substituents. There are also no data on the σ values for aza groups as substituents at the various positions of five-membered heterocycles [6]. As already mentioned, the effect of aza substitution at positions 3 and 4 is practically the same. This result is not consistent with the widespread view of position 3 in the isomer (II) as a para position and position 3 in isomer (I) and 4 in isomer (II) as meta positions [6]. However, it must be borne in mind that this applies to substituents in a heterocyclic ring and not to heteroatoms directly included in the ring.

Attention is drawn to the large difference in the effects of the α-aza groups. The nonequivalence of the positions is determined by the fact that the bonds between atoms 1—2 and 1—5 in the molecule are nonequivalent. The 1—5 bond has a higher order (and, consequently, a shorter length) than the 1—2 bond. The difference in the conduction of the electronic effects along the bonds of various orders in the series of five-membered heterocycles was recorded experimentally for the case of thiophene derivatives [7]:



Study of the dependence of the rate constant for the substitution of the bromine atom on the σ constants of the substituent X showed that the constant ρ, which reflects the conduction of the electronic effect, is 3.95 in the first case and 8.18 in the second, i.e., the effect of the substituents differs by more than twice. Approximately the same relationship was obtained in our case during aza substitution at the positions of the furan and pyrrole rings.

Thus, the proton affinity of aza-substituted aminofurans can be calculated to a first approximation by a simple additive scheme as the sum of the contributions from the heteroatoms

at the various positions. Inclusion of the paired interactions of the heteroatoms makes it possible to improve the accuracy of the calculation. The proton affinities of the aminoheterc cycles decreases progressively in the series of 4-NH, 2-NH, 4-O, and 2-O derivatives. During aza substitution the β positions are equivalent, while the α positions are nonequivalent, and substitution at the formal double bond has an effect approximately twice as large as substitution at a single bond.

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ELECTROPHILIC SUBSTITUTION REACTIONS OF 3-ACETYLAMINO-5-METHOXYBENZOFURAN

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The formylation, aminomethylation, azo coupling, and bromination reactions of 3-acetylamino-5-methoxybenzofuran have been investigated.

We have previously developed two methods for the preparation of 3-acetylaminobenzofurans with an unsubstituted 2 position; one of these methods is based on the Schmidt rearrangement of 3-(azidoacetyl)benzofurans [1], whereas the other is based on the decarboxylation of 3-acetylaminobenzofuran-2-carboxylic acids [2, 3]. The literature does not contain any reports concerning the chemical properties of these substances.

It was of interest to us to examine the effect of the acetylamino group on electrophilic substitution reactions and also, more importantly, to study the feasibility of using these compounds in Mannich and azo coupling reactions; benzofuran itself is known not to undergo these reactions. It was anticipated that the acetylamino group would activate the 2-position with respect to electrophilic reagents due to resonance participation of the unshared pair of electrons on the nitrogen atom. In the present paper we demonstrate that formylation, aminomethylation, bromination, and azo coupling reactions are directed exclusively to the 2-position of the heterocycle.

The Villsmeier reaction occurs at 20°C and results in the formation of 3-acetylamino-2-formylbenzofuran (II) in 50% yield. The position of the formyl group was established on the basis of formation of a pyrimidine ring upon treatment of the formylation product II with ammonium acetate; this resulted in the formation of 2-methyl-8-methoxybenzofuro[3,2 d]pyrimidine (III). The IR spectrum of compound II contains absorption bands due to the aldehyde (1710 cm^{-1}) and amide (1580 and 1650 cm^{-1}) groups; these bands are not present in the spectrum of compound III. The UV spectral characteristics of this compound and its comparison with the spectral data of other structurally analogous benzofuro[3,2-d]pyrimidines [4] confirmed the structure

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