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DEPENDENCE OF THE REACTIVITY OF FIVE-MEMBERED HETEROCYCLES ON THEIR STRUCTURE. 3.* PROTON AFFINITY OF AZOLES AND OXAZOLES

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The proton affinity (PA) of a number of azoles and oxazoles was calculated by MNDO and STO-3G ab initio methods. In spite of the fact that these methods predict poorly the absolute values of the PA, a good correlation between the PA values calculated by STO-3G and the experimental values of PA as well as pK_a values exists. Correlation of the experimental values with MNDO results are much worse.

Various semiempirical and nonempirical quantum mechanical methods are used for calculation of proton affinity (PA) values. We use the nonempirical method with the limited basis of STO-3G orbitals in our calculations of PA of azoles and aminoazoles. These use the geometry which is optimized by the semiempirical MNDO method [2]. Recently, reports have appeared whose authors suggest that a similar method does not permit the changes in PA of amines to be predicted correctly [3]. In order to verify the reliability of results obtained by various methods, we compared experimental and calculated values of PA for azoles and oxazoles. The values of PA which were calculated by us by MNDO and ab initio STO-3G are given in Table 1. Experimental data from the literature and results of calculations in the 6-31** basis accounting for configuration interaction based on the geometry optimized for STO-3G [4] are also given.

The PA value was determined as the difference of the absolute energies of the initial and protonated forms of the molecules. The STO-3G basis is known for a number of reasons to overestimate the PA [5], but the MNDO method, on the other hand, underestimates the PA due to underestimation of the value of enthalpy of proton formation [6]. The values of PA on the 6-31** basis are nearer to the experimental, but the error is still too large (up to 9 kcal/mole [4]) to compare directly the experimental and calculated values. However, as a rule, the succession of changes in PA for the series studied proves to be more important than the absolute value for characterization of the reactivity. In order to evaluate the accuracy of the prediction of PA change in a series of azoles and oxazoles by various methods, we used regression coefficients in equations which relate the experimental and calculated PA values (Table 1):

$$PA_{exp} = 91.1 + 0.764\,PA_{MNDO} \quad (r = 0{,}941;\ s = 3.0;\ F = 38;\ n = 7); \tag{1}$$

$$PA_{exp} = 27.9 + 0.688\,PA_{STO\text{-}3G} \quad (r = 0.990;\ s = 1.2;\ F = 242;\ n = 7); \tag{2}$$

$$PA_{exp} = 49.5 + 0.754\,PA_{6\text{-}31^{**}} \quad (r = 0{,}993;\ s = 1.1;\ F = 334;\ n = 7). \tag{3}$$

As seen from the correlation coefficients and mean square deviations, the PA calculated in the STO-3G and 6-31** bases correlate with the experimental values with practically identical accuracy. Thus, the limited STO-3G basis is practically as good as the extensive 6-31**

*For Communication 2, see [1].

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TABLE 1. PA and pK_a Values of Azoles and Oxazoles

Base	Position of NH fragments in the cation	PA, kcal/mole				pK_a	
		MNDO	STO-3G	6-31†	exp.	exp.*	Eq. (5)
Imidazole	1, 3	173,2	283,8	230,0	221,1	7,30 [7]	6,76
5-Methylimidazole	1, 3	173,7	287,9	—	224,8	7,72	7,88
4-Methylimidazole†	1, 3	175,1	288,6	233,7	—	7,95	8,07
1-Methylimidazole†	3	175,3	287,9	234,7	228,0	7,20 [8]	7,88
Pyrazole	1, 2	154,2	266,9	216,0	212,8	2,77 [9]	2,15
1H-1,2,3-Triazole	1, 2	133,0	248,6	—	—	—	−2,84
	1, 3	151,6	264,4	—	—	1,72	1,47
2H-1,2,3-Triazole	1, 2	139,2	245,5	—	—	—	−3,68
	1, 3	157,8	261,3	—	—	1,42	0,63
1H-1,2,4-Triazole	1, 4	161,2	266,6	214,5	212,4	2,22 [10]	2,07
	1, 2	145,1	250,6	201,2	—	—	−2,29
4H-1,2,4-Triazole	1, 4	157,4	274,1	—	—	—	4,12
	1, 2	141,3	258,1	—	—	—	−0,25
1H-Tetrazole	1, 2	122,3	227,4	—	—	—	−8,62
	1, 3	133,9	247,1	—	—	—	−3,25
	1, 4	143,6	252,5	—	—	−2,27 [11]	−1,77
	2, 3	113,0	227,7	—	—	—	−8,54
2H-Tetrazole	1, 2	126,3	225,0	—	—	—	−9,27
	1, 3	137,9	244,7	—	—	—	−3,90
	1, 4	147,6	250,1	—	—	—	−2,43
	2, 3	117,0	225,3	—	—	—	−9,19
Pentazole	1, 2	102,9	201,1	—	—	—	−15,74
	1, 3	119,0	224,7	—	—	—	−9,36
Isoxazole	2	144,2	253,6	202,2	202,3	−2,08 [12]	−1,47
Oxazole	3	160,0	263,3	212,0	207,8	0,88 [12]	1,17
Furazane	2	127,8	230,8	—	—	—	−7,64
1,3,4-Oxadiazole	3	144,2	253,3	—	—	—	−1,56
1,2,4-Oxadiazole	2	134,4	235,7	—	—	—	−6,36
	4	146,2	244,3	—	—	—	−4,01
1,2,3-Oxadiazole	2	120,9	237,2	—	—	—	−5,95
	3	135,0	229,7	—	—	—	−7,99

*Values of pK_a are converted to 25°C and statistically corrected.

†According to the authors of [4], methylimidazole exists as the 4-isomer, therefore, the experimental value of PA from (3) is taken in a pair with that calculated for 4-methylimidazole.

basis accounting for configuration interaction for prediction of relative PA values of azoles. Also, the MNDO method gives significantly poorer results.

The relation between the calculated PA values and the pK_a values is interesting in order to predict the pK_a values of azoles upon protonation by various nucleophilic centers. For this, it is necessary to know the tautomeric form in which the more interesting compounds occur in aqueous solution and at what center the protonation cocurs. The 1H-tautomer is known to be predominant for 1,2,4-triazole [13] and tetrazole [14] and the protonation occurs at the nitrogen atom in position 4. For 4(5)-methylimidazole pK_a = 7.52 [15] and 5-methylimidazole predominates over 4-methylimidazole in aqueous solution. Knowledge of the equilibrium constant (K = 0.66 [16]) allows the pK_a values of both tautomers to be calculated (Table 1). 1,2,3-Triazole in aqueous solution is found as a mixture of equal quantities of the 1H- and 2H-tautomers [17] whose protonation can lead to two cations:

I

II

Results of quantum chemical calculations show that cation II is much more stable than cation I. The large difference of pK_a values of 1-methyl- and 2-methyl-1,2,3-triazoles supports this. If for the 1-methyl derivative pK_a = 1.25 [17], then for the 2-isomer pK_a cannot be determined due to its very low basicity. According to [17], pK_a = −3.5 for the 2-methyl derivatives. The large difference in stability of cations I and II leads to formation of a mixture of tautomers upon protonation only for cation II. Since the pK_a value of 1,2,3-triazole is known (1.17 [18]), it is possible to calculate the pK_a values for the 1H- and 2H-tautomers. They are equal to 1.77 and 1.47, respectively.

When carrying out the correlation it is necessary to consider that dissociation of the cations of imidazole, pyrazole, and tetrazole can proceed with loss of either of the two protons with an identical result. Introduction of the corresponding statistical correction [16] leads to an increase of pK_a for these azoles by a value of log 2 = 0.30.

Since the values of pK_a of azoles are determined at various temperatures, they are converted to 25°C for comparison. For this, an increase of temperature by 1°C was taken to cause a lowering of pK_a by 0.01 [19].

Treatment of the data by a least squares method leads to the equations

$$pK_a = 0.304 \cdot PA_{MNDO} - 45.82 \quad (r = 0.959;\ s = 1{,}03;\ F = 103;\ n = 11); \tag{4}$$

$$pK_a = 0{,}273 \cdot PA_{STO\text{-}3G} - 70{,}65 \quad (r = 0.991;\ s = 0.49;\ F = 496;\ n = 11). \tag{5}$$

It is interesting that the correlation with the pK_a values is better than with the experimental PA values. This is probably related to the high accuracy of measurement of basicity constants, the error is usually 0.05-0.10 units, which is significantly smaller than the mean square deviation in (5). At the same time, the error of PA measurement (1-2 kcal/mole) is larger than the mean-square deviation for (2).

Equation (5) predicts pK_a = −7.64 for furazane, and −7.34 accounting for the statistical factor. Although the pK_a value for unsubstituted furazane is not determined, it is known that $-pK_a$ = 4.68-5.11 (40°C) for monomethylfurazane and some other alkyl derivatives [20]. It can be assumed with sufficient certainty that pK_a of unsubstituted furazane is of the same order of magnitude, however, the value of pK_a predicted by (5) is significantly lower than the experimental. The difference is apparently explained by the fact that the authors of [20] used an acidity function H_A during calculation of pK_a of furazane while for calculation of the pK_a of other weak bases, tetrazole and oxazole, the acidity function H_0 was used. Conversion of the pK_a values using this function shows that their values lie between −7.62 to −8.45, which agrees well with our calculations.

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