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ISOTOPIC HYDROGEN EXCHANGE IN METHYL DERIVATIVES OF FIVE-MEMBERED AROMATIC HETEROCYCLES

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The kinetics of isotopic exchange of the hydrogen atoms of the methyl groups in an alcohol solution of potassium ethoxide were studied for an extensive series of methyl derivatives of azoles and di-, tri-, and tetrazoles. The electronic effect of one or several heteroatoms and substituents on the rate of deuterium exchange of five-membered heterocycles is satisfactorily conveyed by the correlation relationship previously established for a series of substituted toluenes and six-membered heteroaromatic compounds ($\rho_{25°} = 7.6$). The limitations that exist in a number of cases are discussed in connection with the peculiarities of the electron-density distribution in five- and six-membered heterocycles.

In our previous research [1] we established that the trend of the change in the intensity of the bands of C–H stretching vibrations in the IR spectra ($A^{1/2}_{C-H}$) and the chemical shifts of the protons of the methyl group in the PMR spectra (δ^{CH_3}) of methyl derivatives of azoles and di-, tri-, and tetrazoles containing polar substituents in the heteroaromatic ring is determined by the sum of additive contributions made to the $A^{1/2}$ and δ values by one or several heteroatoms and substituents. The possibility of their examination within the framework of a single reaction series with the corresponding methyl derivatives of six-membered aromatic and heteroaromatic compounds was demonstrated, and, in addition, the applicability of a quantum-chemical treatment of the changes in the δ and $A^{1/2}$ values was investigated.

In order to study the possibility of the extension of a similar approach for the description of the electronic effects on the characteristics of the reactivities of five-membered aromatic heterocycles, in the present research we found comparable (with one another) rate constants of basic deuterium exhcnage of an extensive series of methyl derivatives of thiazole, oxazole, isoxazole, pyrazole, imidazole, oxa- and thiadiazoles, triazole, and tetrazole, and we also made a correlation analysis of the experimental data obtained. In a subse-

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TABLE 1. Kinetics of Deuterium Exchange of the Methyl Groups in Five-Membered Aromatic Heterocycles

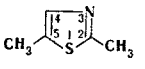
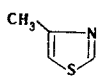
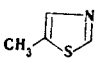
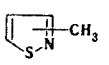
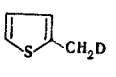
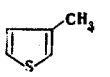
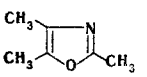
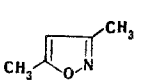
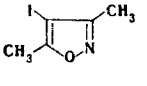
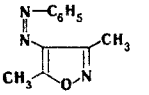
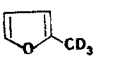
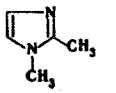
Compound No.	Compound	Position	Medium[a]	t, °C	$k \cdot 10^5$, sec^{-1}	E, kcal/mole	lg A	lg $k_{25°}$[b]	$\Sigma\sigma$ (σ^+)	Synthetic method
1	2	3	4	5	6	7	8	9	10	11
1		2	A(0,57 N)	85 70 55	12.0 2.5 0,46	25.2	11,5	7,0	1,25	13
2		4	A(0,57 N)	180 160 140	0,5[c] 0.2 0.05	20.9	4.8	10.6	0.6	13
3		5	A(0,57 N)	150 135 120	4,6[c] 1.9 0.4	23,4	7.9	9,3	0,9	13
4		3	D	—	—	—	—	(9.1)[d]	0.7	—
5		4						(13.6)[d]	0.2	
6		5						(7,4)[d]	1,1	
7		2	A(0,57 N)	180	0,54[f]	—	—	(14,0)[e]	0,4	—
8		3	B	95	3.0[c,g]	—	—	(17,8)[h]	−0,3	—
9		2	A(0,57 N)	105 95 85	12,0 4,4 1.5	27,9	12,2	8,3	0,9	
10		5	A(0,57 N)	30 20 180	9,9 3,2 1.5	19,9	8,5	(14,5)[e]	0,3	—
			C	110	11,0	—	—			
11		4	A(0,57 N)	180	No exchange				0,5	
12		3	A(0,57 N)	200 180	(11,0)[i] (1,4)[i]	—	—	(10,2)[i]	0,65	14
13		5		160	(0,27)[i]				0,75	
14		3	A(0,57 N)	120 95	15,0 1,9	—	—	8,6	0,92	15
15		5	A(0,57 N)	50 37 25	3,1 1,8 0,83	21,7	11,0	5,1	1,07	
16		3	A(0,57 N)		No exchange				—	—
17		5	A(0,1N)	0	48	—	—	1,4[j]	1,75	16
18		2	A(0,57 N)	180	0,08[f]	—	—	(~15,0)[e]	0,1	—
19		2	A(0,57 N)	135 105 80	5,9 1,3 0,22	17,1	4,9	7,6	0,9	17

TABLE 1 (continued)

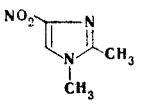
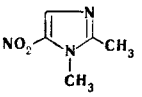
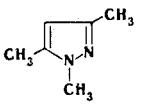
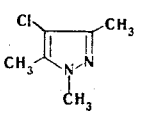
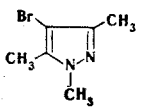
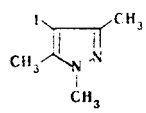
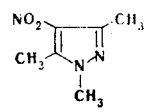
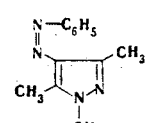
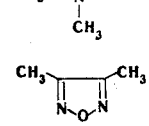
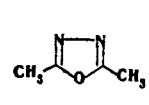
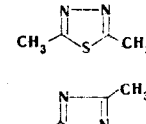
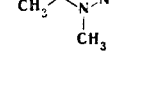
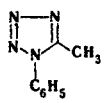
1	2	3	4	5	6	7	8	9	10	11
20		2	A (0,1 N)	25	11,0	—	—	2,4	1,8	18
21		2	A (0,1 N)	25 15 0	11,0 3,5 0,64	18,6	9,6	2,4	1,88	19
22		3	C	150	0,2	—	—	(~14,7)	0,35	
23		5	C	115 95	10,0 2,5	19,7	7,1			—
			A (0,57 N)	180 160	5,2 0,7	—	—	(~12,0)	0,55	
24		3	A (0,57 N)	160	No exchange			—	0,61	20,21
25		5	A (0,57 N)	145 130	3,3 1,2	(22,6)	(7,3)	9,5	0,81	
26		3	A (0,57 N)	160	No exchange			—	0,61	20,22
27		5	A (0,57 N)	145 130 115	4,1 1,3 0,45	23,8	8,0	9,5	0,81	
28		3	A (0,57 N)	160	No exchange			—	0,62	20,22
29		5	A (0,57 N)	145 130 115	4,6 1,6 0,6	22,5	7,5	9,0	0,82	
30		3	A (0,1 N)	110 95 80	5,8 1,3 0,23	29,0	12,3	8,2	1,13	20
31		5	A (0,05 N)	25 10 0	17,0 3,0 0,9	18,6	9,9	2,8	1,82	
32		3	A (0,57 N)	135 120	6,0 1,6	—	—	9,4	1,0	16,20
33		5	A (0,57 N)	40 25	9,4 1,6	—	—	4,8	1,55	
34		3,4	A (0,57 N)	95 80 65	21,0 3,6 0,55	30,0	14,1	7,9	1,15	23
35		2,5	A (0,57 N)	45 35	10,0 4,8	—	—	5,0	1,45	24
36		2,5	A (0,57 N)	35 25 15	13,0 4,2 1,3	20,7	10,8	4,4	1,75	25
37		3	A (0,57 N)	160	0,56	—	—	(~10)	1,25	
38		5	A (0,57 N)	95 80 65	16,9 3,3 0,73	25,5	11,3	5,2	1,55	26

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11
39		2	A (0,1 N)	50 35 25	22,0 3,9 0,93	25,0	13,2	4,3	2,1	—

[a]The following symbols were adopted: A is $C_2H_5OK + C_2H_5OD$ (the concentration of the base is indicated in parentheses); B is 0.4 N tert-C_4H_9OK + d_6-DMSO; C is 0.1 N $C_2H_5OK + C_2H_5OD$ + d_6-DMSO; D is NaOD + d_6-DMSO + D_2O (90:10).
[b]In 0.57 N $C_2H_5OK + C_2H_5OD$.
[c]A correction for deuterium exchange in the ring 2 and 5 positions prior to exchange of the hydrogen of the CH_3 groups were introduced.
[d]Obtained by extrapolation of the data in [2].
[e]Estimated by comparison with the CH acidity of 2,5-dimethylthiazole (No. 1) with allowance for a correction for the decrease in the sensitivity of the rate constants to the electronic effect as the temperature rises.
[f]Measured in 0.57 N $C_2H_5OK + C_2H_5OH$ [5].
[g]The measurements were made jointly with Yu. L. Kaminskii.
[h]Estimated by comparison with the CH acidity of toluene: the rate constants (in medium B) at 25, 50, and 95°C are, respectively, $1.6 \cdot 10^{-5}$, $1.2 \cdot 10^{-4}$, and $2.6 \cdot 10^{-3}$ sec^{-1}; in medium A (0.57 N) at 25°C log k = −15.9 [7].
[i]This is the average value of the rate constant for the 3 and 5 positions.
[j]Estimated by comparison with the rate of deuterium exchange of 1,3,5-trimethyl-4-nitropyrazole (No. 30).

quent communication [2] the relative rate constants were compared with the quantum-chemical indices of CH acidity.

The data in the literature on the lability of the hydrogen atoms of methyl groups in five-membered one-ring systems are limited to disconnected measurements of the rate of deuterium exchange of isomeric methylisothiazoles [3], 5-methylisoxazole [4], and 2-methylfuran and 2-methylthiophene [5, 6].

We made most of the kinetic measurements in an alcohol solution of potassium ethoxide; solutions of the ethoxide in alcohol containing d_6-dimethyl sulfoxide (d_6-DMSO) and potassium tert-butoxide in d_6-DMSO were used as the exchange medium in individual cases. The results of the kinetic investigation are presented in Table 1.

It follows from the data obtained that depending on the mutual orientation of the heteroatoms and the methyl group undergoing exchange, the CH acid properties of the latter change in the order 2 > 5 > 4 for methylthiazoles and methyloxazoles, 5 > 3 for methylisothiazoles and methylisoxazoles, and 5 > 3 for 1,2,4-trimethyltriazole. The lability of the hydrogen of the methyl groups in the 1,2,3-oxadiazole ring is lower than in its 1,3,4-isomer. The activating effect of the heteroatomic groups in equivalent ring positions decreases in the order S > O > N(CH_3).

If one takes into account some of the below-noted specific (for five-membered rings) peculiarities of the mechanism of transmission of electronic effects, it is seen from Fig. 1 that the trend of the change in the kinetic acidity of the overwhelming majority of the investigated compounds is satisfactorily described by the same correlation expression (1), which was previously established as applied to the basic deuterium exchange of the methyl groups of substituted toluenes and their nitrogen-containing analogs [6, 7]:

$$\lg k_{25^\circ} = -15.9 + 7.6\Sigma\sigma^-. \quad (1)$$

Analysis of the conditions that determine the applicability of expression (1) to the CH acidity of five-membered heterocycles makes it possible to point out the following distinguishing features of the latter.

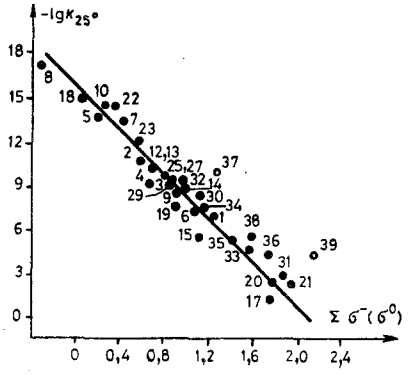


Fig. 1. Correlation of the rate of basic deuterium exchange of the methyl derivatives of five-membered heterocycles by means of Eq. (1) (the numbering of the points corresponds to that in Table 1).

1. As a rule, the electronic effects of the $-O-$, $-S-$, and $-N(CH_3)-$ heteroatoms in azoles and diazoles make additive contributions to the change in the free energy of activation of the exchange process and can be correlated by the effective values of the σ^- constants [6] ($\sigma^-_{2\text{-}S} = 0.4$, $\sigma^-_{3\text{-}S} = -0.3$, $\sigma^-_{2\text{-}O} = 0.1$, $\sigma^-_{3\text{-}O}$, $\sigma^-_{2\text{-}N(CH_3)} = -0.1$, $\sigma^-_{3\text{-}N(CH_3)} = -0.6$, $\sigma^-_{2\text{-}N} = 1.0$, $\sigma^-_{3\text{-}N} = 0.6$, and $\sigma^-_{4\text{-}N} = 1.23$).

In conformity with the adopted concepts, the electronic effect of the examined heteroatomic groups on the C type reaction center is determined by two principal factors: the possibility of activation of the exchange process due to the $-I$ effect, and its deactivation due to the electron-donor effect of the heteroatom via a p,π-conjugation mechanism [5, 6, 8-10]. Proceeding from this, in the case one should have expected correlation of the electronic effects of the heteroatoms with the σ^0 constants ($\sigma \simeq \sigma^0$). The specific character of the manifestation of the CH acid properties in the series of the investigated compounds, which is reflected in the decreased nucleophilic σ^- constants ($\sigma^- < \sigma^0$), indicates that the electron-donor effect of the heteroatomic groups is expressed more strongly in the carbanion transition state of the five-membered heterocycles than in the starting state. The effect of p,π conjugation in the 2 position of the thiophene ring ($\sigma^- \simeq \sigma^0$) is apparently partially masked by the manifestation of the effect of $p_\pi - d_\pi$ conjugation of the sulfur heteroatom, which is in the same direction of the $-I$ effect [5, 6, 9, 10]. Judging from the σ^- constants, the electron-donor effect of p,π conjugation of the $-O-$, $-S-$, and $-N(CH_3)-$ heteroatoms with the aromatic ring is manifested more strongly in the 3 position than in the 2 position.

2. The nonequivalent character of the π bonds in the five-membered rings has little effect on the mechanism of transmission of the inductive and mesomeric effects of the substituents but has a substantial effect on the intensity of the interaction of the reaction center with the electron acceptors and tertiary nigrogen heteroatom ($-N=$) built into the ring via a mechanism of direct polar conjugation (the $-C$ effect). According to the data obtained, transmission of the $-C$ effect along the 2-3 (or 4-5) bond occurs just as effectively as in the benzene ring, while the 3-4 bond blocks it practically completely. A consequence of this is the necessity for the application of σ^- constants in the first case and σ^0 constants in the second case for the correlation of the electronic effects of the $-C$ substituents with Eq. (1). The situation is to a certain degree analogous to that which is observed for nucleophilic substitution of halogens in the thiophene derivatives containing a nitro group as a substituent [11].

3. As seen from Fig. 1, the experimental values of the rate constants for deuterium exchange of the methyl derivatives of triazole (No. 37) and tetrazole (No. 39) are four to five orders of magnitude lower than those expected from correlation expression (1). At present it does not seem possible to give an unambiguous interpretation of the origin of the observed effects, and one can only state that violation of the principle of additivity of the electronic effects in compounds of this type is not specific for the process that we studied. A similar result was noted during a study of the piperidine debromination of tri- and tetrazoles [12].

EXPERIMENTAL

The bulk of the starting compounds were synthesized by known methods (the citations to the selected method of synthesis are given in Table 1). The method used to carry out the exchange reaction has been previously described [27]. The deuterium content in the molecules was determined by the usual method of low-voltage mass spectrometry. An IR spectroscopic method based on measurement of the integral absorption of

* The σ^0 constants of the heteroatomic groups in the five-membered rings are, respectively: $\sigma^0_{2\text{-}O} = 0.57$, $\sigma^0_{3\text{-}O} = 0.42$, $\sigma^0_{2\text{-}S} = 0.50$, $\sigma^0_{3\text{-}S} = 0.26$, $\sigma^0_{2\text{-}N} = 0.9$, $\sigma^0_{3\text{-}N} = 0.5$, and $\sigma^0_{4\text{-}N} = 0.7$.

the band of the deformation vibration at 1090 cm^{-1} (for a 0.5 M solution in chloroform and a layer thickness of 100 μm) was used for the isotopic analysis of 1-phenyl-2-methyltetrazole (No. 39). The positions of the exchanged hydrogen atoms in the molecules were established by analysis of the PMR spectra of solutions of the deuterated substances.

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