BASIC ISOTOPIC HYDROGEN EXCHANGE OF HETEROAROMATIC COMPOUNDS (REVIEW)

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Research on basic isotopic hydrogen exchange of the methyl groups and aromatic ring CH bonds in various classes of five- and six-membered heterocyclic compounds is examined. Principal attention is directed to the problem of the applicability of correlation and quantum-chemical approaches to the establishment of the interrelationship between CH acidity and the peculiarities of the electronic structures of the molecules. The effect of a solvent on the change in the kinetic characteristics of the deuterium exchange of nitrogen-containing heterocycles is discussed.

In the last decade several monographs [1-3] and reviews [4-8] in which the principles of basic isotopic hydrogen exchange and its relationship to the CH acidic properties of organic compounds are examined have been published. The experimental and theoretical study of this area of problems was based chiefly on data pertaining to aliphatic compounds containing strong electron-acceptor substituents and also to aromatic hydrocarbons and their derivatives. Insofar as heterocylic aromatic compounds are concerned, despite the peculiarity of their behavior during basic deuterium exchange and the considerable amount of data on the kinetics of the exchange reaction, there are practically no papers of review character that correlate the data of the available publications.*

The increased interest observed in recent years in the investigation of the exchange capacity of heterocyclic systems has undoubtedly been stimulated by the similarity in the principles of the occurrence of the exchange reaction and many chemical [1, 9-13] and biological [14, 15] processes peculiar to heterocycles. In particular, it has been shown that the manifestations of mutual effects in deuterium exchange of methyl derivatives of heteroaromatic compounds are close in nature to those in reactions involving the condensation of a methyl group with electrophilic reagents or nucleophilic substitution of halogens, which proceeds via an S_N2 mechanism, whereas basic deuterium exchange of the hydrogen atoms of an aromatic ring models processes of the "aryne" and other types.

An attempt is made in the present review to make a systematic examination from a certain single point of view of the chief results of a study of the reactivities of five- and six-membered heteroaromatic compounds by the method of basic deuterium exchange. The results of investigations known from the literature are discussed in connection with data obtained in the isotope laboratory of the State Institute of Applied Chemistry. In the first portion of the review the effect of factors of the electronic structure on the kinetic CH acidity of heterocycles classified according to the type of reaction center is analyzed thoroughly. Moreover, chief attention is directed to research in which the experimental data are discussed from the positions of correlation analysis and quantum chemistry.† The specific effects of intermolecular interaction that frequently mask the effect of structural factors on the change in the CH acidity are discussed briefly in the second portion of this review.

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*Only a brief summary of data on the exchange capacity of heteroaromatic compounds with "active" methyl groups has been published [9].

†In conformity with the task in view, a number of studies, from the results of which only qualitative information can be extracted, are not included; moreover, research involving the deuterium exchange of heterocycles in acidic media is not examined.

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TABLE 1. Isotopic Hydrogen Exchange of Alkyl Groups of Six-Membered Nitrogen Heterocycles in 0.57 N C_2H_5OK in C_2H_5OD

Compound	$-\lg k^*_{25°}$	E, kcal/mole	$\lg A$	ΔE_π, $\lvert\beta\rvert$ units	pK_a^{CH}†
2-Methylpyridine	8,2	24,7	9,8	4,56	(27)
3-Methylpyridine	11,0	31,0	11,7	4,64	(28)
4-Methylpyridine	6,3	20,3	8,7	4,57	(25)
2-Methylpyrazine	5,1	20,6	9,4	4,54	(23)
5-Methylpyrimidine	9,3	25,5	9,2	4,58	(28)
2-Methylquinoline	5,4	20,8	9,8	4,50	(23)
4-Methylquinoline	5,1	18,3	8,3	4,47	22,2
6-Methylquinoline	11,1	27,6	9,1	4,61	(30)
3-Methylquinoline	(9,5)	—	—		(28)
8-Methylquinoline	11,8	31,0	11,0	4,58	(31)
2-Methylquinoxaline	2,7	18,3	9,7	4,48	(20)
α-Naphthoquinaldine	7,4	26,2	11,8	4,51	(26)
β-Naphthoquinaldine	6,4	22,5	10,1	4,52	(25)
9-Methylphenanthridine	5,1	20,9	10,2	4,41	22,8
9-Methylacridine	4,3	17,0	8,1	4,54	21,1
2-Methylpyridine N-oxide	3,5	19,9	11,1	4,41	22,3
3-Methylpyridine N-oxide	7,2	26,2	13,0	4,66	—
4-Methylpyridine N-oxide	3,8	15,8	7,8	4,45	—
2-Methylquinoline N-oxide	1,6	17,6	11,3	4,32	—
4-Methylquinoline N-oxide	(4,1)	—	—	—	21,3
1-Methylisoquinoline	5,7	21,0	9,7	—	25,0
1,2-Dimethylpyridinium iodide	(−2,0)	—	—	—	—
1,4-Dimethylpyridinium iodide	(−1,0)	—	—	—	—
2-Benzylpyridine	4,9	9,5	2,6	—	23,9
3-Benzylpyridine	5,7	16,8	6,3	—	24,9
4-Benzylpyridine	4,7	10,4	2,9	—	23,4
2-Benzylpyridine N-oxide	2,9	16,5	9,2	—	22,0
3-Benzylpyridine N-oxide	3,9	23,5	13,3	—	22,8
4-Benzylpyridine N-oxide	1,8	20,4	13,1	—	22,0
Toluene	(15,9)	—	—	4,64	(36)

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*Here and subsequently, the experimental rate constants in a number of cases are reconverted to standardized reaction conditions.

† The pK_a^{CH} values were determined by a "stepwise" method relative to indicator hydrocarbons (fluorene 20.5, 9-phenylxanthene 24.2, triphenylmethane 27.2, and diphenylmethane 28.6) on the Steiner and Stark scale. A solution of sodium ethoxide in dimethyl sulfoxide containing alcohol was used for the lower portion of the scale of CH acidities, a solution of sodium dimsyl in DMSO was used for the middle portion of the scale, and a solution of sodium amide in liquid ammonia was used for the upper portion of the scale. The pK_a^{CH} values calculated from expression (1) are presented in parentheses.

ELECTRONIC INTERACTIONS IN HETEROAROMATIC COMPOUNDS

1. Basic Deuterium Exchange as a Method for the Study of the CH Acidity of Heteroaromatic Compounds

Although the ability of methyl derivatives of heteroaromatic compounds to undergo deuterium exchange reactions has been known for quite some time [16-19], a systematic study of it on a quantitative basis was begun only in recent years. In a number of cases it has been shown [20-25] that the exchange of a hydrogen of an alkyl group attached to a ring proceeds via a carbanion mechanism, the slow step of which is stripping of a proton by the base, and, consequently, its rate may serve as a measure of the CH acidity of compounds of the type under consideration here:

$$\mathrm{Het-CH_3} \xrightleftharpoons{RO^-} \left[\mathrm{Het-CH_2^-}\right] \xrightleftharpoons{ROD} \mathrm{Het-CH_2D}$$

A direct confirmation of this is the observance of a linear dependence between the logarithms of the deuterium-exchange rate constants and the pK_a^{CH} value, which characterizes the acid–base equilibrium of similarly constructed heteroaromatic and aromatic substrates in protophilic media [26]:

$$\lg k = 14.26 - 0.84\ pK_a^{CH}, \tag{1}$$

TABLE 2. Isotopic Hydrogen Exchange of the Methyl Groups of Five-Membered Heterocycles in 0.57 N C_2H_5OK in C_2H_5OD

Compound	$-\lg k$		E, kcal/mole	$\lg A$	ΔE_π, $\lvert\beta\rvert$ units
	180°	25°			
2-Methylfuran [34]	6,1	—	—	—	4,66
2-Methylthiophene [34]	5,3	—	—	—	4,58
3-Methylthiophene [34]	(10,0)	—	—	—	4,80
2-Methylbenzofuran [34]	2,9	—	29,0	11,2	4,57
2-Methylbenzothiophene [34]	3,8	—	25,4	8,5	4,52
1,2-Dimethylindole (2) [34]	4,4	—	34,4	12,2	4,57
2,5-Dimethylthiazole (2)*	0,6	7,2	25,2	11.5	4,46
4-Methylthiazole*	5,2	10,5	20,9	4,8	4,73
5-Methylthiazole*	3,4	9,4	23,4	7,9	4,59
3-Methylisothiazole†	—	(9,1)	—	—	4,59
4-Methylisothiazole†	—	(13,6)	—	—	4,76
5-Methylisothiazole†	—	(7,4)	—	—	4,48
2,4,5-Trimethyloxazole (2)*	1,3	8,0	27,9	12,2	4,55
2,4,5-Trimethyloxazole (4)*	(8,0)	—	—	—	4,77
2,4,5-Trimethyloxazole (5)*	(5,0)	(12,0)	—	—	—
1,2-Dimethylimidazole (2)*	—	7,5	17,1	5,0	—
1,3,5-Trimethylpyrazole (3)*	(8,0)	—	—	—	—
1,3,5-Trimethylpyrazole (5)*	4,3	—	—	—	4,70
2-Methylbenzothiophene [34]	−1,6	3,2	19,2	10.9	4,46
2-Methylbenzothiazole [34]	−1,0	3,5	18,0	9,7	4,40
2-Methylbenzoselenazole [34]	−2,1	2,8	19,3	11,4	—
1,2-Dimethylbenzimidazole [34]	−0,6	5,6	28,5	15,3	4,50
2-Methyl-Δ^2-thiazoline*	—	4,8	18,5	8,8	4,39
1,2-Dimethyl-Δ^2-imidazoline (2)*	—	4,2	10,4	3,4	4,45
1,3,4-Trimethyl-Δ^2-pyrazoline (3)*	—	6,2	14,6	4,5	4,53
2-Methyl-Δ^2-imidazoline*	—	4,6	21,3	11,0	—

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*According to the data of N. N. Zatsepina, I. F. Tupitsyna, and A. I. Belyashova.

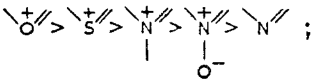
† Found by extrapolation of the data in [35].

Expression (1) holds true over a range of pK_a^{CH} changes of ~15 units. It may be used for an approximate evaluation of the pK_a^{CH} values in those cases in which direct spectrophotometric determination of the equilibrium CH acidity is difficult.

The available data on the equilibrium acidity of aromatic CH bonds in heterocycles are disjointed and frequently contradictory [27, 28]. Although a certain correspondence exists between the measured log k and pK_a^{CH} values, in view of the limited and unsystematic character of the experimental data, the question of the possibility of the use of kinetic data for the evaluation of the equilibrium ionization constants of aromatic heterocycles as CH acids is presently an open one.

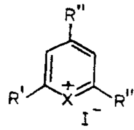
2. Deuterium Exchange of Methyl Derivatives of Five- and Six-Membered Aromatic Heterocycles

Unsubstituted Heterocycles. From a comparison of the literature data on the kinetics of deuterium exchange, a portion of which is presented in Tables 1-3, it follows that, depending on the position of the heteroatom relative to the methyl group undergoing exchange, its effect on the CH acidity changes in the following order: methylpyridines 4>2>3 [24, 29-31], methylpyridine N-oxides 2>4>3 [24, 30, 31], 1-methylpicolinium iodides 2>4>3 [24, 30, 31], methylpyridazines 4>2 [32], methylpyridazine N-oxides 6>5>4>3 [32], methylquinolines 4>2>3>6>8 [28, 29, 33], methylthiophenes 2>3 [34], methylthiazoles and methyloxazoles 2>5>4 (Table 2), and methylisothiazoles and methylisoxazoles 5>3>4 [35, 36].

The activating effect of heteroatomic groups in equivalent positions of the ring decreases in the following order: for six-membered rings [24, 30, 31, 37]  $\overset{+}{O} > \overset{+}{S} > \overset{+}{N}\text{–} > \overset{+}{N}\text{–}O^- > N$; for five-membered rings [25, 34] $-Se- > -O- \gtrless -S- > -NH-$.

On the whole, the observed trend of the change in the CH acidity is in agreement with the concepts of classical electronic theory regarding the character of transmission of electronic effects of heteroatomic substituents through an aromatic ring. The fact that the method of isotopic exchange can be used to evaluate the prototropic activity of such unreactive compounds as 3-methylpyridine, 3-, 6-, and 8-methylquino-

TABLE 3. Isotopic Exchange of the Hydrogen of the Methyl Groups of Pyrylium, Thiopyrylium, and Pyridinium Salts in Methanol*

Compound type	R′	R″	R‴	X	E, kcal/mole	lg *A*	Relative rate constants at 30°C
	C_6H_5	C_6H_5	CD_3	O	20,1	9,64	87
	C_6H_5	C_6H_5	CD_3	S	20,5	9,64	48
	C_6H_5	C_6H_5	CD_3	N—CH_3	27,3	12,87	1
	C_6H_5	CD_3	C_6H_5	O	18,6	9,85	1800
	C_6H_5	CD_3	C_6H_5	S	16,0	7,41	480
	H	H	CH_3	N—CH_3	—	—	0,01

*According to the data in [37]; see also [9, 40, 41] regarding the exchange capacity of pyrylium salts.

line, and methylfuran and its isologs makes it possible to conclude that the concept of "active" and "inactive" methyl groups is a quantitative rather than a qualitative one.

The deuterium exchange of methyl derivatives of mono- and polycyclic heteroaromatic compounds that do not contain polar substituents serves, by virtue of the simplicity of the electronic structure of their molecules, as a convenient model for the quantum-chemical study of reactivities within the framework of different variants of the MO LCAO method.* As a result of investigations of this sort, it was established that within the limits of series of compounds of similar structure (mono- and diazines and their condensed analogs [24, 29, 38, 39], aromatic N-oxides [24], five-membered heterorings containing −O−, −S−, and −NH heteroatoms [34], azoles [35], benzazoles [34], azolines, etc.) the changes in the rate constants can, as a rule, be correlated by the magnitude of the delocalization energy of the π electrons $[\Delta E_\pi = E_\pi(\text{Het-}CH_2^-) - E_\pi(\text{Het-}CH_3)]$ (Tables 1 and 2). The π-electron charge on the carbon atom adjacent to the methyl group $[q_{C(CH_3)}]$ has also been used as a quantum-chemical index of the reactivity [24, 34]. The quality of the correlation deteriorates when attempts are made to unite heterocycles of diverse structure in a single reaction series, but in this case the theory conveys the general tendency of the change in the CH-acid properties (Tables 1 and 2). The conclusion of the possibility of encompassing the kinetic data by means of a single approximation of the $\log k - \Delta E_\pi[q_{C(CH_3)}]$ type cannot yet be applied to compounds containing more than one heteroatom in the heteroatomic grouping (for example, to aromatic N-oxides and also to substituted toluenes in view of the fact that quantum-chemical calculation by means of a small number of reliably determined α_X and β_{CX} parameters cannot be realized for them. The indicated limitations are not a consequence of the inadequacies peculiar only to the Hückel method. A similar difficulty is also present in the case of calculations made within the framework of more rigorous methods. Thus, for example, even the most accurate variant of the semiempirical MO LCAO calculation – calculation by the CNDO/2 method – predicts a carbanion-stabilizing effect not only for electron acceptors but also for such typical electron donors as the p-CH_3 or p-OCH_3 groups [45].

The application of the method of correlation analysis for the quantitative description of electronic interactions detected in changes in the kinetic CH acidity of heteroaromatic compounds is based on the assumption of the possibility of considering the heteroatom or heteroatomic grouping built into the aromatic ring to be a normal polar substituent. Although there are certain difficulties in extending expressions of the Hammett type to heterocyclic systems [46], appreciable progress was recently achieved here owing to the publication of a number of studies [30, 47-57] that substantially refine data on the various forms of σ constants of heteroatomic groups. Sets of σ constants (σ_I, σ_R^0, σ^0, σ^-, and σ^+) that were obtained on the basis of a critical examination of the results of investigations of several independent reaction series and differentially characterize the complex set of electronic effects of heteroatoms are presented in Table 4.

According to [24, 25, 30, 34, 58, 59], the trend of the change in the deuterium-exchange rate constants of an extensive series of substituted toluenes and methyl derivatives of heterocycles correlates with the

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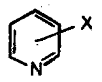
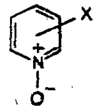
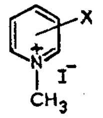
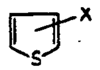
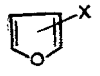
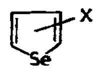
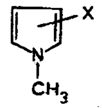
*A large number of the calculations have been made by the Hückel method (the hyperconjugation model for the methyl group) with the aid of a standard set of parameters of heteroatomic α_X and β_{CX} groups [24, 34, 42]. The calculations of the delocalization energies of isomeric methylpyridines carried out by the SCF LCAO method within the Pariser–Parr–Pople (PPP) π-electron approximation [43, 44] and the partial-neglect-of-differential-overlap (PNDO) approximation [44] give different absolute ΔE_π (or ΔE) values but the qualitative character of the results does not change.

TABLE 4. Constants of Heteroatomic Substitutents

Compound type	Position of the reaction center	σ−	σ+	σ°	σ_R°	σ_I
	2 3 4	$1{,}0^{30,\,48}$ $0{,}6^{30,\,48}$ $1{,}23^{30}$ $(1{,}17)^{48}$	— — —	$0{,}9^{30,\,47,\,49}$ $0{,}5^{30,\,47,\,49}$ $0{,}7^{30,\,49}$	$0{,}25^{50}$ $(0{,}28)^{51}$	$0{,}45^{1*}$
	2 3 4	$1{,}57^{30,\,48}$ $1{,}18^{30,\,48}$ $1{,}53^{30,\,48}$	$0{,}25^{46}$	$1{,}0^{30,\,47,\,49}$ $0{,}7^{30,\,47,\,49}$ $0{,}7^{30,\,47,\,49}$	$-0{,}20^{51}$	0,9
	2 3 4	$2{,}49^{48}$ — $2{,}32^{48}$	— — —	$2{,}2^{30}$ — $1{,}3^{30}$	$0{,}3^{51}$	1,0
	2 3	$0{,}3\,(0{,}4)^{34}$ $-0{,}3^{4}$**	$-1{,}22^{52}$ $(-0{,}83)^{56,\,57}$ $-0{,}62^{52}$ $(-0{,}48)^{56,\,57}$	$0{,}5^{52}$ $0{,}26^{52}$	$-0{,}14^{51}$ $(-0{,}17)^{2}$†	$0{,}64^{1*}$ $(0{,}9)^{3}$‡
	2 3	$0{,}1^{34}$ —	$-1{,}32^{52}$ $(-0{,}92)^{56,\,57}$ $-0{,}74^{52}$ $(-0{,}45)^{56,\,57}$	$0{,}57^{52}$ $0{,}42^{52}$	$-0{,}13^{51}$ $(-0{,}20)^{2}$†	$0{,}7^{53}$
	2 3	— —	$-1{,}28^{52}$ —	— —	$-0{,}18^{2}$†	$(0{,}7)^{3}$‡
	2 3	— —	— —	— —	$-0{,}23^{2}$†	$0{,}3^{53}$

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* $\sigma_I = \sigma_p^0 - \sigma_R^0$.

† We estimated these values from the intensities of the bands of ring "skeletal" vibrations in the IR spectra.

‡ This value takes into account the contribution of the σ, d effect [53].

** Found from the reaction series of deuterium exchange of methyl derivatives of heterocycles.

nucleophilic σ^- constants. In an alcohol solution of potassium alkoxide the correlation relationship has the form

$$\lg k_{25^\circ} = -15.9 + 7.6\sigma^-. \tag{2}$$

The positive signs and the large value of the ρ constant (the latter is practically equal to the ρ constant in nucleophilic substitution of halogens [48, 60] and more than twice ρ in the ionization of phenols and anilinium ions [54]) attests to the exceptionally high sensitivity of the CH-acid properties to a change in the electronic structure of the molecules and to the high polarity of the carbanion transition state of the exchange reaction.

From the three-parameter correlation dependences established for o- and p-substituted toluenes and heterocycles (t = 180°)

$$\lg k_{\text{para}} = -6.3 + 6.9\sigma_I + 7.0\sigma^\circ_R + 3.0\sigma_R^-, \tag{2a}$$

$$\lg k_{\text{ortho}} = -6.8 + 7.5\sigma_I + 4.1\sigma^\circ_R + 2.5\sigma_R^- \tag{2b}$$

it is apparent that the changes in the free energy of activation of the exchange process of the p-CH_3 group are almost equally sensitive to the inductive and resonance effects of a substituent; the certain increase in the contribution of the inductive component for the ortho position is accompanied by a proportional decrease in the contribution of the resonance component; the overall electronic effects on the rate of the exchange reaction in the case of ortho and para substituents are almost identical.

TABLE 5. Isotopic Hydrogen Exchange of Methyl Groups of Substituted Methylpyridines and Their N-Oxides in 0.57 N Solutions of C_2H_5OK in C_2H_5OD

No.	Compound	$-\lg k_{25°}$		E, kcal/mole	lg A
		exptl.	calc.*		
1	2,6-Dimethylpyridine	9,4	8,6(9,4)	27,7	10,9
2	2,4-Dimethylpyridine (2)†	9,2	8,6(9,4)	27,6	11,0
3	2,4-Dimethylpyridine (4)	7,7	7,2(7,7)	26,3	11,6
4	2,4,6-Trimethylpyridine (2,6)	9,7	9,4(10,0)	28,4	11,1
5	2,4,6-Trimethylpyridine (4)	8,2	7,8(8,2)	26,5	11,2
6	2,6-Dimethyl-4-methoxypyridine	9,2	7,8(9,7)	26,1	9,9
7	2-Amino-4-methylpyridine	8,8	7,6(9,4)	27,9	11,7
8	2-Dimethylamino-4-methylpyridine	9,7	7,3(9,9)	30,1	12,4
9	2,4-Dimethoxy-6-methylpyrimidine	4,5	−3,0(4,8)	—	—
10	2,4-Dimethoxy-5-methylpyrimidine	10,0	8,4(10,7)	19,7	4,3
11	2-Methyl-4-cyanopyridine	4,2	3,6(4,4)	—	—
12	2,6-Dimethyl-3-nitropyridine (2,6)	2,6	−1,8(3,7)	—	—
13	2,6-Dimethyl-4-methoxypyridine N-oxide	4,6	3,0(5,4)	22,1	11,6
14	2-Methyl-4-nitropyridine N-oxide	1,9	−1,3(2,2)	—	—

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* Calculated from Eq. (2) via an additive scheme. The log k values calculated with allowance for "indirect" interactions are indicated in parentheses.

† Position of the methyl group undergoing exchange.

Correlation relationships (2a) and (2b) satisfactorily convey the specific peculiarities of the mechanism of electronic effects in heteroaromatic systems. In particular, it follows from expressions (2a) and (2b) that the sharp increase in the lability of the hydrogen atoms of the methyl group during quaternization of the pyridine nitrogen is caused by an approximately proportional increase in the contributions to the free activation energy of the reaction by the inductive effect and the effect of direct polar conjugation with retention of the approximate constancy of the contribution due to the mesomeric effect of the $\diagdown N \diagup\!\!\!\diagup$ and $\diagdown \underset{|}{\overset{+}{N}} \diagup\!\!\!\diagup$ heteroatoms. The inductive and resonance electronic effect of the N-oxide grouping is manifested almost as strongly as the effect of the $\diagdown \underset{|}{\overset{+}{N}} \diagup\!\!\!\diagup$ heteroatom. However, in view of the "electronic amphoteric character" of the N-oxide group [61], its mesomeric effect ($\sigma_R^0 = -0.2$) acts in a direction opposite to the −I and −C effects, and this is reflected in slowing down of the rate of deuterium exchange of aromatic N-oxides as compared with the corresponding pyridinium salts.

In examining the reasons for the changes in the CH-acid properties of five-membered monocycles one must take into account the effect of two 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. Judging from the magnitudes of the σ_I and σ_R^0 constants of the heteroatoms (Table 4), the competitive interaction of the indicated factors should lead to a relatively strong acidifying effect. In fact, this is not always so. The specific character of the manifestation of the CH-acid properties in a series of five-membered monocycles, which is reflected in reduced values of the nucleophilic σ^- constants ($\sigma^- < \sigma^0$), is probably associated with the fact that in the carbanion transition state, in which two potential donor centers – the heteroatom and the CH_2- group – are present, the electron-donor effect is expressed more strongly than in the starting state. The action of the effect of p, π-conjugation in the 2 position of the thiophene ring ($\sigma^- \simeq \sigma^0$) is evidently masked by the manifestation of the p_π, d_π orbital effect of the sulfur heteroatom, which has the same direction as the −I effect [62, 63]. Estimates of the quantum-chemical reactivity indexes lead to a similar conclusion regarding destabilization of the transition state due to p, π-conjugation. As seen from the ΔE_π values (Table 2), by virtue of their energy overload the transition states of the exchange reaction of methyl derivatives of furan and thiophene are closer to the benzyl anion than to the typical carbanions of methyl derivatives of six-membered nitrogen heterocycles.

For the benzo analogs of five-membered rings, in which the conditions of delocalization of the π-electron density in the transition state of the reaction are more favorable, the changes in the CH-acid properties correspond to a "normal" ($\sigma^- \simeq \sigma^0$) manifestation of the −I and +M effects of the heteroatom ($0 > S > N-CH_3$). The fact that annelation of the benzene ring has a greater effect on the change in the rate constant

TABLE 6. Isotopic Hydrogen Exchange of the Methyl Groups of Substituted Methylquinolines and Their N-Oxides in 0.57 N Solutions of C_2H_5OK in C_2H_5OD [75]

Compound	$-\lg k_{25^\circ}$	E, kcal/mole	lg *A*
2-Methyl-4-methoxyquinoline	6,4	22,8	10,2
2-Methyl-4-chloroquinoline	4,8	20,2	10,0
2-Methyl-4-cyanoquinoline	3,5	18,7	10,2
2-Methyl-5-nitroquinoline	3,7	—	—
2-Methyl-6-methoxyquinoline	7,2	24,1	10,5
2-Methyl-6-fluoroquinoline	5,4	—	—
2-Methyl-6-chloroquinoline	5,2	20,5	9,8
2-Methyl-6-nitroquinoline	2,4	18,1	10,9
2-Methyl-7-chloroquinoline	4,8	20,9	10,5
4-Methyl-6-methoxyquinoline	6,6	23,5	10,6
4-Methyl-6-fluoroquinoline	5,6	19,2	8,5
4-Methyl-6-bromoquinoline	5,2	—	—
4-Methyl-6-chloroquinoline	4,5	21,8	11,5
4-Methyl-6-nitroquinoline	2,2	17,5	10,6
2-Methyl-4-methoxyquinoline N-oxide	2,1	16,1	9,7
2-Methyl-4-chloroquinoline N-oxide	0,6	14,2	9,8
2-Methyl-4-cyanoquinoline N-oxide	0,2	—	—
2-Methyl-6-methoxyquinoline N-oxide	3,7	17,6	9,2
2-Methyl-6-fluoroquinoline N-oxide	2,5	—	—
4-Methyl-6-chloroquinoline N-oxide	3,0	—	—
1-Methylnaphthalene	12,3	31,2	10,5
2-Methylnaphthalene	12,5	29,7	9,3

of deuterium exchange of the methyl group in the furan ring (Δ log k = 3.2) than in the thiophene ring (Δ log k = 1.5), which has greater aromatic character, is also in agreement with the predictions of the MO LCAO theory.

Azoles and Benzazoles. The results of a study of the kinetics of deuterium exchange of methyl derivatives of thiazole, isothiazole, oxazole, and benzazoles (Table 2) in conjunction with the above-examined data on the exchange capacity of the corresponding rings with one heteroatom attest to approximately an additive character of the electronic effects of two heteroatoms in such systems. Deviations from the additive character occur only during deuterium exchange of a methyl group in the 5 position of isothiazole and in the 4 position of the thiazole ring, where the experimental rate constants are correlated by Eq. (2) when $(\sigma_S^- + \sigma_N^0)$ is contrasted with their sum in place of $(\sigma_S^- + \sigma_N^-)$. The reason for the observed disruption of the additive character may be the markedly nonequivalent character of the π bonds in five-membered rings,* as a consequence of which the resonance effect of the nitrogen heteroatom is transmitted through the 3–4 bond less intensively than through the 2–3 bond. The situation is to a certain degree analogous to that observed for nucleophilic substitution of halothiophenes [67].

As seen from Table 2, passing from 2-methylazoles to their partially hydrogenated analogs is accompanied, against the background of the overall acceleration of the exchange reaction, by reversal of the sequence of changes in the rate constants (CH_3–N > O > S). The noted disparity is apparently associated with additional stabilization of the transition state of the deuterium exchange of 2-methylazolines due to the effect of specific solvation, which arises as a consequence of the appreciable increase in their basicity ($\Delta pK_a^{NH} \simeq 5$ [68]). The considerable increase in the negative entropy of activation of the deuterium exchange of azolines as compared with azoles constitutes evidence in favor of this assumption.

Substituted Heterocycles. Judging from the data obtained for a series of substituted methylbenzenes and six-membered heterocycles [58], the electronic effect of several substituents on the exchange capacity of toluene derivatives is usually subject to the additivity principle, whereas for many of their nitrogen-containing heteroanalogs the experimental values of the rate constants differ appreciably from the values calculated from the additive scheme (Table 5).† Let us point out the following principal sources of the additive character of the electronic effects in six-membered heterocycles.

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*Calculations of the electronic structures of thiophene [64, 65], furan [66], thiazole [64], and other azoles by the semiempirical MO LCAO method with self-consistency confirm that the 2–3 and 4–5 bonds have increased π orders ($p_{2,3} = 0.8$–0.9), whereas the 3–4 bond is markedly weakened ($p_{3,4} = 0.3$–0.5).

†The practically complete absence of experimental data makes it impossible as yet to define concretely the form of the dependence of the free activation energy of deuterium exchange of methyl groups in five-membered rings on the electronic nature of polar substituents occupying nonequivalent positions in the heteroaromatic ring.

TABLE 7. σ Constants in Two-Ring Systems (according to Charton) [74]

Reaction center	Substituent position							
	1	2	3	4	5	6	7	8
α	—	$\sigma_p^0(\sigma_p^-)$*	$\sigma_{\text{м}}^0$	$\sigma_p^0(\sigma_{\text{м}}^-)$*	$\sigma_{\text{м}}^0$	$\sigma_{\text{м}}^0$	$\sigma_{\text{м}}^0$	—
β	$\sigma_p^0(\sigma_p^-)$*	—	—	$\sigma_{\text{м}}^0$	$\sigma_{\text{м}}^0$	σ_p^0	$\sigma_{\text{м}}^0$	$\sigma_{\text{м}}^0$

---

* In the case of correlation treatment of the data with respect to deuterium exchange [75].

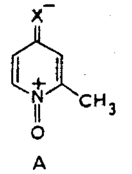
1. If there is a + M substituent in the meta position relative to the reaction center but in the ortho or para position relative to the nitrogen heteroatom, the measured rate constant, as a rule, proved to be less than the value calculated from Eq. (2). This may be interpreted as a consequence of the strong resonance interaction between the + M substituent and the heteroatom, which causes a proportional decrease in the electron-acceptor effect of the latter. This is confirmed by the possibility of a satisfactory description of the trend of the change in the rate constant of deuterium exchange of the group of compounds under consideration by means of Eq. (2) with the use of sum $(\sigma_{p\text{-}X}^0 + \sigma_N^-)$ in place of $(\sigma_{m\text{-}X} + \sigma_N^-)$. The fact that similar although not identical changes in the rate constants are observed also in some of the usual chemical reactions of nitrogen-containing heterocycles [69-71] constitutes evidence for the rather general character of the mechanism of indirect resonance interactions.

The fundamental possibility of the description of polysubstituted heterocycles and toluenes by a single dependence [Eq. (2)] is in agreement with the concept of almost identical capacities of the pyridine and benzene rings to transmit substituent electronic effects [69].

The available data are inadequate for a solution of the problem of the extent to which the conclusions drawn above are valid for substituted aromatic N-oxides. However, judging from the fact that the 4-OCH_3 substituent decreases the rate of deuterium exchange of the CH_3 group in the 2 and 6 positions (No. 13 in Table 5), it can be assumed that the peculiarities of the mechanism of the electronic interactions of a + M substituent with a heteroatom in the carbanion transition state of the exchange reaction of nitrogen heterocycles are also retained (probably in a less sharply expressed form) in the case of their N-oxides.

2. The changes in the electron-density distribution, which are a consequence of the manifestation of the effect of specific solvation, apparently lie at the basis of the nonadditive character of the magnitude of log k during the deuterium exchange of methyl derivatives of nitrogen heterocycles containing a strong − M substituent in the ring. An appreciable decrease in the basicity of the heteroaromatic substrate $(\Delta pK_a^{NH} \simeq 5)$ in this case leads to weakening of the solvating effect of the solvent, on which, as is well known, the degree of manifestation of the − C effect of a heteroatomic substituent depends [72].

3. In the case of the data obtained for 4-nitropicoline N-oxide it is apparent that the experimental rate constant also proves to be lower than the expected value (Δ log k = 3.6) when a − M substituent is introduced into the para position of the N-oxide ring and follows expression (2) only when sum $(\sigma_{p\text{-}NO}^0 + \sigma_{NO}^0)$ is used in place of $(\sigma_{m\text{-}NO_2}^0 + \sigma_{NO^-})$. One of the possible explanations for this consists in the fact that the capacity of the electronic system of the N-oxide ring for type A polarization is reinforced under the influence of a − M substituent [61] and, as a consequence of this, its electron-donor effect on the reaction center increases.



A

Substituted Methylquinolines and Their N-Oxides. Up until now there has been no unified opinion regarding the optimum variant of the σ, ρ analysis of substituted two-membered rings [73, 74]. Recently [75], in the case of methyl derivatives of naphthalene, quinoline, and its N-oxide containing a variable substituent in various positions of the aromatic ring (Table 6) the applicability for description of the kinetic CH-acidity of two-membered ring compounds of two correlation approaches — different variants of the traditional approach of Dewar and Grisadle [76] in which the effect of a substituent from each nonequivalent position of a two-ring system is characterized by the eigenvalue of the σ_{ij} constant, and a modified Charton method

TABLE 8. Isotopic Exchange of α-Hydrogen Atoms of Trans-Stilbazoles and Similar Compounds in 0.6 N Solutions of CH_3OK in CH_3OD*

No.	Compound	$-\lg k_{25°}$	E, kcal/mole	lg A
1	2-Styrylpyridine	10,6	27,0	9,2
2	4-Styrylpyridine	8,7	21,6	7,2
3	2-Styrylquinoline	8,3	22,9	8,5
4	4-Styrylquinoline	7,6	23,6	9,7
5	1-Styrylisoquinoline	8,1	18,8	5,7
6	2-Styryl-6-methoxyquinoline	10,5	29,3	11,0
7	2-Styryl-5,6-benzoquinoline	9,8	19,7	5,6
8	9-Styrylphenanthridine	7,4	17,1	5,2
9	2-Styrylbenzothiazole	5,9	18,3	7,5
10	2-Styrylbenzoxazole	5,4	18,9	8,5
11	2-Nitrostilbene	8,2	24,0	9,4
12	2-Styrylquinoline N-oxide	4,2	15,7	7,3
13	4-Styrylpyridine N-oxide	7,1	21,3	8,5
14	2-Styrylpyridine N-oxide	6,1	19,7	8,3
15	2-(4-Methoxystyryl)pyridine N-oxide	6,5	21,0	8,9
16	2-(2-Methoxystyryl)pyridine N-oxide	6,4	18,4	7,1
17	2-(4-Dimethylaminostyryl)pyridine N-oxide	7,2	20,8	8,0
18	2-(4-Iodostyryl)pyridine N-oxide	5,2	14,4	5,4
19	2-(2-Fluorostyryl)pyridine N-oxide	5,5	20,5	9,5
20	2-(3-Fluorostyryl)pyridine N-oxide	5,1	15,8	6,5
21	2-(2-Chlorostyryl)pyridine N-oxide	5,4	17,9	7,7
22	2-(3-Chlorostyryl)pyridine N-oxide	5,2	17,8	7,9

*According to the data of N. N. Zatsepina, I. F. Tupitsyn, and A. I. Belyashova.

[74], which recommends the usual σ_m and σ_p constants, the choice between which is determined only by the relative orientations of the substituents and the reaction center, as the characteristic of the electronic effect of substituents – was investigated. As shown in [75], the application of the Dewar–Grisdale method in its usual form does not give a satisfactory correlation. The dependence of log k on σ_{ij} becomes linear only in the case of introduction into the σ_{ij} constant of the contribution due to the effect of direct polar conjugation. Replacement of the 14 σ_{ij} constants of the Dewar–Grisdale method by two σ_m and σ_p (σ_p^-) constants does not reduce the accuracy of the correlation calculation. In the case of the selection of σ constants indicated in Table 7 and with allowance for the possibility of transmission of the electronic effect of the +M substituents via a mechanism involving indirect resonance interactions (see above), the rate constants of deuterium exchange of aromatic and heteroaromatic two-ring systems generally follow the same correlation dependence as methyl derivatives of monocycles; the electronic effect of the naphthyl grouping is described by the value $\Delta\sigma = 0.3$. The noted similarities in the mechanism of electronic interaction for one-ring and two-ring systems is not specific for basic deuterium exchange but is also observed for a number of other reaction series [75, 77].

3. Deuterium Exchange of Trans-Stilbazoles and Similar Compounds

A considerable similarity to the corresponding methyl derivatives of aromatic heterocycles is observed with respect to the acidifying effect of structural factors on the α-hydrogen atom of trans-stilbazoles that differ with respect to the structure of the heteroaromatic fragment of the molecule (compare Tables 1 and 8).

$$\lg k_{\alpha\text{-CH}} = -2.8 + \lg k_{CH_3}. \qquad (3)$$

The observed similarity in the manifestation of the electronic effects provides a basis for the conclusion that in the vinyl anions of the type under consideration the degree of delocalization of charge over the aromatic ring, which is accompanied by progressive stabilization of the transition state as the acceptor properties of the heteroatomic grouping increase (–I, –M, and –C effects) is comparable to that observed during aromatization of the sp^3 hybrid carbon atom in anions of the benzyl type.*

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*In terms of the method of valence schemes, the stabilization of the transition state of deuterium exchange of stilbazoles via a conjugation mechanism is described as an increase in the weight of the linear structure of the allene in the resonance hybrid of the anions [78].

TABLE 9. Isotopic Hydrogen Exchange of Aromatic CH Bonds of Six-Membered Nitrogen Heterocycles in 0.6 N Solutions of CH_3OK in CH_3OD

No.	Compound	Atoms undergoing change	$-\lg k_{140^\circ}$	E, kcal/mole	lg A
1	Pyridine	2	6,7	—	—
		3	6,3	—	—
		4	6,1	20,3	4,6
2	3-Aminopyridine	4	5,7	28,6	9,4
3	3-Fluoropyridine*	4	2,9	15,3	5,2
4	3-Bromopyridine	4	4,4	18,7	5,5
5	3-Methoxypyridine	4	4,5	34,0	13,5
6	3-Nitropyridine*	2		No exchange	
		4	3,4	23,2	8,9
7	4-Methoxypyridine	3, 5	5,2	31,6	11,5
8	2-Methoxypyridine	3	5,3	—	—
9	4-Dimethylaminopyridine	2, 6	6,0	—	—
		3, 5	5,7	—	—
10	Pyrazine	2, 3, 5, 6	5,0	21,9	6,6
			$(4,7)^{88}$		
11	Pyrimidine	2	$(5,1)^{88}$		
		4, 6	$(4,5)^{88}$		
		5	4,0	—	—
			$(3,5)^{88}$		
12	Pyridazine	3, 6	$(4,1)^{88}$		
		4, 5	$(2,9)^{88}$		
13	2-Amino-5-nitropyridine	4	3,9	—	—
14	3,5-Dibromopyridine*	4	1,7	25,7	14,1
15	3,5-Dimethoxypyridine*	4	2,9	—	—
16	3,6-Dimethoxypyridazine	4, 5	2,6	14,8	4,5
17	2,4-Dimethoxypyrimidine	5	3,9	24,0	8,8
18	2,4,6-Trimethoxypyrimidine	5	3,1	30,2	12,9
19	Quinoline	2	6,3	—	—
			5,8	—	—
20	Isoquinoline	1	6,0	—	—
		4	5,2	—	—
21	Quinoxaline	2, 3	5,0	20,4	5,8

* In a 0.1 N solution of CH_3OK in CH_3OD.

The effect of substituents from a benzene ring that is not directly connected with the reaction center (Nos. 15-22 in Table 8) is determined by their inductive and mesomeric effects. The electronic effects in this case are transmitted more weakly by a factor of almost three than from the heteroaromatic portion of the molecule ($\rho^0 = 2.7$ and $\rho^- = 8.1$, respectively).

4. Deuterium Exchange of Aromatic CH Bonds

Six-Membered Heterocycles. A large amount of research [13, 72, 79-98] has been devoted to the study of electronic interactions in the isotopic hydrogen exchange of the aromatic ring in substituted benzenes and heterocycles, but the problem of the quantitative evaluation of the effect of various factors on the rate of the exchange process to this very day remains inadequately explained. In the case of several relatively narrow reaction series it has been shown [72, 76-84, 86] that in many cases the electronic effect of ortho substituents in monosubstituted benzenes can be described by means of σ_I induction constants, whereas the effect of meta and para substituents can be explained by means of $\sigma_m{}^0$ and $\sigma_p{}^0$ constants. The appropriate correlation equation for deuterium exchange in alcohol solutions of potassium ethoxide has the form [86]

$$\lg k_{140^0} = -9{,}1 + 7{,}2\sigma_I^{\mathrm{ortho}} + 4{,}8\sigma_{\text{м},\mathrm{p}}^0. \tag{4}$$

For deuterium exchange in a solution of $NH_2^- + NH_8$ (liq), $\rho_I = 11$ [80], and $\rho_{m,p}{}^0 = 4.4$ [72].

In addition, substantial discrepancies between the rate constants measured experimentally and those calculated from one-parameter correlation dependences are observed for some substituted benzenes and, in particular, for nitrogen-containing heterocycles [86, 96]. An extended correlation analysis of the kinetic data pertaining to a large series of substituted benzenes [86] and six-membered nitrogen heterocycles and their N-oxides (Tables 9 and 10) was made recently in order to ascertain the reason for the observed deviations. From a comparison of the parameters of the multiplicity correlations (t = 140°)

$$\lg k_{\mathrm{ortho}} = (-9.4 \pm 0.2) + (7{,}3 \pm 0{,}2)\sigma_I + (0.6 \pm 0.2)\sigma_R^- + (0.6 \pm 0.6)\sigma^\circ_R, \tag{5a}$$

$$\lg k_{\mathrm{meta}} = (-9.4 \pm 0.2) + (4.3 \pm 0.4)\sigma_I + (1.6 \pm 0.4)\sigma_R^- + (-0.3 \pm 0.3)\sigma^\circ_R, \tag{5b}$$

$$\lg k_{\mathrm{para}} = (-9.4 \pm 0.2) + (2.9 \pm 0.6)\sigma_I + (2.8 \pm 0.6)\sigma_R^- + (0.03 \pm 0.3)\sigma^\circ_R \tag{5c}$$

TABLE 10. Isotopic Hydrogen Exchange of Aromatic CH Bonds of Substituted N-Oxides in 0.1 N Solutions of CH_3OK in CH_3OD [84-86]

Compound	Atoms undergoing exchange	$-\lg k_{50°}$	E, kcal/mole	$\lg A$
Pyridine N-oxide	2	5,3	—	—
	3	7,3	18,6	5,3
	4	8,0	24,0	7,6
3-Fluoropyridine N-oxide	2	0,3	22,0	14,6
3-Bromopyridine N-oxide	2	2,0	23,0	13,6
3-Nitropyridine N-oxide	2	−0,3	14,3	8,9
2-Methoxypyridine N-oxide	6	5,2	—	—
3-Methoxypyridine N-oxide	2	3,9	23,7	12,2
4-Methoxypyridine N-oxide	2, 6	5,2	—	—
	3, 5	5,8	—	—
4-Chloropyridine N-oxide	2, 6	4,3	—	—
	3	4,5	—	—
4-Dimethylaminopyridine N-oxide	2, 6	6,5	26,3	11,2
	3	8,5	—	—
3,5-Dibromopyridine N-oxide*	2, 6	1,3	19,6	10,9
	4	2,3	26,2	14,4
3,5-Dimethoxypyridine N-oxide	4	5,7	27,9	13,2
Pyrazine N-oxide†	2, 6	3,2		12,2
	3, 5	7,4	23,0	9,5
Pyrimidine N-oxide†	2	2,4	20,5	11,7
	4	7,4	—	—
	6	3,8	21,6	10,7
Quinoline N-oxide	2	5,5	—	—
Isoquinoline N-oxide	1	4,2	—	—
	3	6,1	—	—
Quinoxaline N,N'-dioxide	2, 3	3,5	—	—

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* In a 0.01 N solution of CH_3OK in CH_3OD.

† See [93, 94] for the exchange capacity of substituted pyrazine N-oxides.

it follows that although the inductive effect of the substituents dominates in all of the investigated compounds, the electromeric resonance component plays a definite role during deuterium exchange of the meta and, in particular, the para positions of the aromatic ring; as a rule, the contribution of the mesomeric effect proves to be negligibly small. The physical significance of the latter consists most likely in the fact that the electron pair of the aromatic CH bond lies in the nodal plane of the π system, and the possibility of transmission of the effect of a substituent (heteroatom) to the reaction center via a π-electron mechanism is for this reason almost excluded in the static state of the molecule. However, this representation is not a satisfactory approximation of the actual picture of the electronic interactions in the transition state of the reaction: as in other "charged" organic systems, in a carbanion transition state of the phenide type the capacity for interaction between the σ framework of the molecule, including the reacting aromatic CH bond, and the π electrons of the benzene ring should increase. In terms of correlation analysis, this general result of quantum chemistry is expressed in the fact that the ρ_I and ρ_R^- constants become comparable in magnitude. Inasmuch as low σ_R^- values are characteristic for most substituents, the contribution of $\Delta\Delta G_{R^-}^{\#}$ to the change in free energy $\Delta\Delta G^{\#}$ is, as a rule, much less than the contribution of $\Delta\Delta G_I^{\#}$. It is evidently for this reason that the electronic effect of all such substituents is satisfactorily transmitted by correlation relationships that disregard the contribution of the $-C$ effect. The $\Delta\Delta G_{R^-}^{\#}$ term takes on substantial value only in the case of heteroatomic groupings ($\backslash N /\!\!/$, $\backslash \overset{+}{N} /\!\!/ - O^{-}$) or strong $-C$ substituents.

An examination of the possibility of the extension of expression (5) to compounds with three or more substituents (heteroatoms) in the aromatic ring showed that it satisfactorily describes the trend of the change in the rate constants in those cases in which the relative orientation and type of substituent exclude interaction between them via a resonance mechanism. At the same time, the total electronic effect for compounds containing substituents of opposite polarities in interconjugated positions of the heteroaromatic ring (Nos. 13 and 16-18 in Table 9) does not correspond to the effect expected from the additive scheme. The result confirms that disruption of the additivity of the electronic effects in deuterium exchange of aromatic CH bonds is also associated primarily with the peculiarities of the mechanism of transmission of the resonance effect.

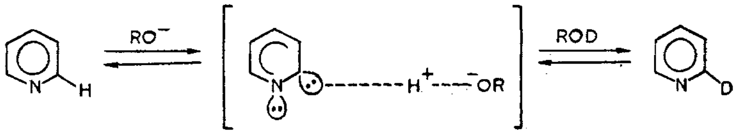
Moreover, the correlation expression does not provide a possibility for a quantitative description of the electronic effect of a nitrogen heteroatom on the rate of deuterium exchange of adjacent CH bonds in molecules of nitrogen heterocycles. This circumstance and the unusual order of change in the labilities of the hydrogen atoms in the heteroaromatic ring that is characteristic for pyridine and its derivatives (4 >

TABLE 11. Isotopic Hydrogen Exchange of Aromatic CH Bonds of Five-Membered Heterocycles in 0.57 N Solutions of C_2H_5OK in C_2H_5OD [25, 102]

Compound	Atoms undergoing exchange	$-\lg k_{140°}$	E, kcal/mole	lg A
Furan	2, 5	3,6	38,4	16,7
	3, 4	—	—	—
Thiophene	2, 5	1,9	29,7	13,8
	3, 4	—	—	—
1-Methylpyrrole	2, 5	6,0	29,1	9,4
	3, 4	No exchange at 180°		
Selenophene	2, 5	5,9	29,0	9,4
Benzofuran	2	2,1	29,4	13,4
	3	4,5	28,9	11,3
Thionaphthene	2	1,6	26,5	12,4
	3	4,6	37,1	15,0
1-Methylindole	2	4,6	21,9	7,0
	3	No exchange at 180°		
3-Methylthionaphthene	2	5,4	—	—
1-Methylimidazole	2	4,7*	21,8	10,0
1-Methylbenzimidazole	2	4,2*	25,7	13,2
Benzothiazole	2	2,1*	18,7	10,5
Benzoselenazole	2	1,8*	—	—
Benzoxazole	2	1,3*	18,2	11,0

$* - \log k_{50°}$.

3>2) [13, 83, 98] serve as a reflection of the complications in the mechanism of electronic interactions, which are associated with the relative retardation of the rate of deuterium exchange in the ortho positions caused by superimposition of an oppositely directed "α effect" of the unshared pair of the nitrogen heteroatom on the electron-acceptor −I and −C effects [83, 86, 88, 92].* The unshared pair of nitrogen is located in the plane of the aromatic ring in direct proximity to the electron pair of the adjacent CH bond that is cleaved during the reaction:



The orbital of the unshared pair of the nitrogen heteroatom is sufficiently diffuse that the effect of mutual repulsion between it and the electrons of the reaction center can effectively oppose the tendency to separation of the positive and negative charges of the CH bond caused by the high electron-acceptor capacity of the $\diagdown N /\!\!/$ heteroatom. In good agreement with the proposed interpretation is the fact that the formation of a semipolar $\diagdown\overset{+}{N}\!\!-\!O^-$ bond in the pyridine N-oxide molecule, which causes a shift of the unshared pair of nitrogen toward the oxygen atom or quaternization of nitrogen, leads to disappearance of the indicated anomaly. The same reason is the basis for the distinctly expressed dependence of the magnitude of the "α effect" on the solvating capacity of the solvent. According to [86], the influence of the "α effect" is relatively small ($\sigma_I^{eff} \simeq 0.3$) when deuterium exchange is carried out in hydroxyl-containing solvents ($CH_3OD + CH_3O^-$), in which specific solvation of the heteroaromatic substrate occurs and reaches a maximum value ($\sigma_I^{eff} \simeq 0$) when protophilic solvents [NH_3 (liq) + NH_2^-, DMSO + tert-C_4H_9OK] are used as the exchange medium.

At the conclusion of this section, it should be noted that the information set forth above regarding the mechanism of electronic interactions was obtained by σ, ρ analysis. The latter is today one of the principal working instruments by means of which a sufficiently large amount of experimental material on deuterium exchange of aromatic CH bonds can be treated. Insofar as quantum-chemical calculations, particularly those made within the π-electron approximation, are concerned, they are poorly adapted for modeling

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*See [50, 99–101] for the manifestation of an "α effect" in the chemical reactivity and spectroscopic characteristics.

TABLE 12. Factors of the Partial Rate of Deuterium Exchange of Five-Membered Rings* in Solutions of DMSO+tert-$C_4H_9O^-$ (25°C) [128]

Compound	f_2	f_3
2D-thiophene	1	—
Thieno[2,3-b]-2D-thiophene	10	—
Thieno[3,2-b]-2D-thiophene	9	—
Benzo-2D-thiophene	4	—
3D-thiophene	$(3\cdot10^{-6})$	1
Thieno[2,3-b]-3D-thiophene	$(3\cdot10^{-4})$	94
Benzo-3D-thiophene	$(2\cdot10^{-4})$	65
Thieno[3,2-b]-3D-thiophene	0,036	—
2D-furan [103]	$(2\cdot10^{-3})$	—
3D-furan [103]	$(3\cdot10^{-6})$	1
2D-selenophene [103, 104, 125]	1,5	—
3D-selenophene [103, 104]	—	8

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*Relative to the rate constants of deuterium exchange in the 2 and 3 positions of thiophene (f_2, f_3).

the changes in the free energy of activation of an exchange reaction in view of considerable polarization of the σ framework in the transition state and the associated peculiarities of the manifestation of the resonance effect [45, 85, 102].

Five-Membered Rings. An interesting and diversified area of study of the CH-acidity of aromatic five-membered rings commenced with the research of A. I. Shatenshtein and co-workers, who measured the rate of basic deuterium exchange in the furan ring and in its isologs [103, 106]. The results of investigations of the exchange capacity of aromatic CH bonds of five-membered rings with one heteroatom [102-106], mono-, di-, and tetrazoles [107-115], benzazoles [25, 115-117], azolium cations and similar compounds [15, 118-123], substituted furans, thiophenes, and selenophenes [104, 124-127], thienothiophene [128], and polyazaindenes [129, 130] have been published.

According to the results obtained (Tables 11 and 12), all of the hydrogen atoms in the furan, thiophene, selenophene, and N-methylpyrrole rings undergo exchange reactions at higher rates than in the case of benzene. The lability of the hydrogen atom in the α position is higher than that of the hydrogen in the β position, whereas the activating effect of the heteroatom changes in the order $Se \simeq S > O > N-CH_3$ for the α position and $O > S > N-CH_3$ for the β position. The introduction into the aromatic ring of two or more heteroatoms, particularly a nitrogen heteroatom with a positive charge, causes a sharp increase in the rate of the exchange process (Tables 13 and 14).

From the kinetic data presented in Table 11 for benzofuran, benzothiophene, and N-methylindole, it follows that the general character of the activating effect of heteroatomic groups is identical in one-ring and two-ring systems, but the lability of the hydrogen atoms in the 2 and 3 positions of two-ring systems is higher than in the corresponding one-ring systems.

The trend of the change in the rate constants of deuterium exchange in one-ring compounds is satisfactorily described by equations obtained for substituted benzenes and six-membered heterocycles; this confirms the correctness of the concept of the dominant role of the inductive effect of heteroatoms during basic deuterium exchange in the α position of five-membered rings and regarding the appreciable manifestation of a positive effect of p, π conjugation during deuterium exchange of aromatic CH bonds in the β position. The applicability of the same relationships to data on the exchange capacity of three- and five-substituted thiophenes [124] and azoles (except for the positions adjacent to the nitrogen heteroatom, the exchange in which is complicated by the above examined "α effect" of the unshared pair) [124] attest to the approximately identical abilities of the thiophene and benzene (pyridine) rings to transmit electronic effects in deuterium exchange and, in addition, to the additivity of the effects of the substituent and heteroatom (or two heteratoms) in the investigated series of compounds.

It follows from the results of comparative studies [125, 126, 128, 131-134] of the rate of basic (protophilic) and acidic (electrophilic) deuterium exchange of furan, thiophene, and selenophene that, as a rule, the exchange capacity of aromatic CH bonds in both reaction series changes in the same order. This sort of specific character in the manifestation of electronic effects in five-membered rings is associated with the fact that the O, S, and Se heteroatoms are a rare example of substituents that have simultaneously large positive σ^0 values and large negative σ^+ constants (Table 3). For the indicated reason, they considerably

TABLE 13. Isotopic Hydrogen Exchange of Aromatic CH Bonds in Thiazole and Similar Compounds at 31° [107]

Compound	Reaction center	$k_2 \cdot 10^5$, liter · mole^{-1} · sec^{-1}		Relative rate
		$CH_3O^- + CH_3OD$	$OD^- + D_2O$	
Thiazole	2	5,6	5,8	1
	4	No exchange		10^{-6}
	5	5,1	4,3	0,8
Isothiazole	3	No exchange		10^{-7}
	5	39	—	7
4-Methylisothiazole	3	No exchange		10^{-7}
	5	9,7	9,7	1,7
5-Methylisothiazole	5	13	—	2,3
4-Phenylisothiazole	4	No exchange		10^{-7}
	5	59	—	10,5
1,3,4-Thiadiazole	2	—	$3,6 \cdot 10^4$	$6,2 \cdot 10^3$
1,2,3-Thiadiazole	4	No exchange		
	5		$4,8 \cdot 10^6$	$(3,1 \cdot 10^4)$
3-Phenyl-1,2,4-oxadiazole	5	—	—	$(3,5 \cdot 10^4)$*
2-Phenyl-1,3,4-oxadiazole	5	—	—	$(1,24 \cdot 10^4)$*
1-Ethyl-1,2,3,4-tetrazole	5	—	—	$(1,95 \cdot 10^4)$*

* Estimated from data on the rate of deuterium exchange with a 0.4 N solution of piperidine in CH_3OD.

accelerate both reactions that are promoted by electron-donor substituents ($\rho < 0$) and reactions that are promoted by electron-acceptor substituents ($\rho > 0$) (see [52] for more details).

The problem of the role of the d-orbital effect in the activation of the exchange process of positions adjacent to sulfur and selenium is deserving of special discussion.

The mechanism of filling of the vacant d orbitals of S and Se heteroatoms by electrons during deuterium exchange of aromatic CH bonds – the σ,d effect [15, 63, 102] – differs from the usual mechanism of p,d conjugation realized in systems in which the sulfur (selenium) atom and the electron-donor grouping are not adjacent and interect only through the conjugated system. The essence of the σ,d effect consists in "lateral" overlapping between the 3d orbital of suitable symmetry and the p component of the unshared pair of electrons of the adjacent atom. Considering the different trends of the change in the rate constants of deuterium exchange of oxazolium, thiazolium, and imidazolium cations and the spin–spin coupling constants that record the change in the s character of the CH bond in the α positions of the ring [121], it can be concluded that the σ,d effect is manifested mainly in the transition state of the reaction. The concept of the possible reinforcement of the inductive effect of a heteroatom by the effect of d-orbital stabilization has been used to explain the increased electron-acceptor effect of sulfur (selenium) during deuterium exchange of thiophene, selenophene [102, 106], azoles [107], and azolium salts [15, 118, 121]. The influence of the σ,d effect is responsible, in particular, for the considerably stronger stabilization of the negative charge arising at the instant of the exchange reaction in the β positions of the thiophene (selenophene) ring as compared with the furan ring. On passing to the β positions, where the σ,d effect is not substantial, the activating effect of a sulfur (selenium) heteroatom is smaller than in the case of oxygen.

If the magnitude of the k_S/k_O ratio is taken as an approximate measure of the participation of the d levels of sulfur in an exchange reaction, it follows from the data presented in [102] that the d-orbital interactions in the heteroaromatic carbanions under consideration play a lesser role than in carbanions in which the heteroatom is included in the composition of the aliphatic fragment of the molecule ($k_S/k_O = 10^2$–10^{-2} and 10^5–10^7, respectively). The probable reasons for this are the great s character of the unshared pair of electrons of the carbanion carbon atom, the possibility of its delocalization via a mechanism of σ, d interaction, and the geometrical factor, which reduces the effectiveness of σ,d-overlapping in the heteroaromatic ring [102].

EFFECT OF A SOLVENT ON THE KINETIC CH-ACIDITIES OF HETEROAROMATIC COMPOUNDS

The problem of the effect of a solvent on the CH acid properties of organic compounds in general and heteroaromatic compounds in particular has been the subject of intensive investigations [1, 6, 135-142].

TABLE 14. Isotopic Hydrogen Exchange of Aromatic CH Bonds in Salts of Azoles at 31° [118]

Compound	Atom undergoing exchange	k_2, liter · mole^{-1} · sec^{-1}	pD*	Relative rate
3-Ethylthiazolium iodide	2	$9{,}8 \cdot 10^5$	5,07	1
	4	—	—	$1 \cdot 10^{-4}$
	5	—	8—10	$1 \cdot 10^{-4}$
2-Methylisothiazolium iodide	3	—	10	—
	5	$7{,}3 \cdot 10^2$	8,20	$7 \cdot 10^{-4}$
3-Ethyl-1,3,4-thiadiazolium chloride	2	$2{,}6 \cdot 10^9$	1,66	$3 \cdot 10^3$
	5	$1{,}8 \cdot 10^5$	5,81	$2 \cdot 10^{-1}$
3-Ethyl-1,2,3-thiadiazolium tetrafluoroborate	4	$4{,}2 \cdot 10^3$	7,44	$4 \cdot 10^{-3}$
	5	$4{,}6 \cdot 10^5$	5,40	$5 \cdot 10^{-1}$

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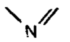
* When $\tau_{1/2} = 10$ min.

Within the framework of this paper, it does not seem possible to illuminate the various aspects of this complex problem. We will dwell briefly only on the specific character of the interaction of a heteroaromatic substrate with the medium, which is responsible for the ambiguous nature of nitrogen-containing heterocycles. It is well known that the latter display a capacity to react as bases of medium strength as well as CH-acid properties. This determines the possibility of the participation of heterocycles in deuterium exchange in the form of neutral molecules, cations, or anions formed during the reaction of the solvent with the  or -NH- groupings.

1. Investigation of the Solvation Interactions by Analysis of the Activation Parameters

The role of the solvation interaction, which is concealed during an analysis of the changes in the rate, shows up more distinctly during an examination of the activation parameters of an exchange reaction. It has been shown [143] that the exchange process is a type of reaction series in which correlations of the Hammett type are satisfied, but changes in the $\Delta H^{\#}$ and $\Delta S^{\#}$ values are not correlated by the isokinetic expression. A compensation dependence occurs only for the "external" activation parameters.*

The general tendencies of the change in the $\delta\Delta H_{ext}^{\#}$ and $\delta\Delta S^{\#}$ values depend substantially on the peculiarities of the electronic structure of the substrate. The decrease in the $\delta\Delta H_{ext}^{\#}$ and $\delta\Delta S^{\#}$ values for a series of substituted benzenes and nitrogen-containing heterocycles occurs in conformity with the increase in the electron-acceptor strength of the substituents in the heteroaromtic or benzene ring. Reinforcement of the degree of solvation of the transition state, which causes a decrease in both the entropy and the enthalpy of activation, is reflected in the observed relationship between the external activation parameters.

In a series of aromatic N-oxides the trend of the change in the external activation parameters is the direct opposite of this: reinforcement of the acceptor properties of the substituents in the ring is accompanied by an increase in the $\delta\Delta H_{ext}^{\#}$ and $\delta\Delta S^{\#}$ values. Judging from the fact that for N-oxides containing the electron-acceptor substituents the total $\delta\Delta H^{\#}$ value is almost equal to the $\delta\Delta H_{int}^{\#}$ value, solvation stabilization of the carbanions plays a secondary role in this case.

An explanation of the observed changes in the solvation effects can be given on the basis of the assumption that the measurable activation entropy is the algebraic sum of two principal contributions: 1) a negative contribution due to the more polar structure of the carbanion transition state as a whole as compared with the starting structure; 2) a positive contribution arising from dissipation of the charge of the transition state on transfer of a proton from the carbo acid to the CH_3O^- ion. Inasmuch as the alkoxide ion is solvated to a much greater extent than the considerably bulkier aromatic carbanions, its neutralization during the exchange process is accompanied by a positive entropy change. Moreover, the greater ease with which the charge is delocalized from the reaction center due to the "internal" stabilization of the intermediate carbanion by electron-acceptor substituents, the higher the degree of the indicated effect of disruption of the solvate shell of the CH_3O^- ion.

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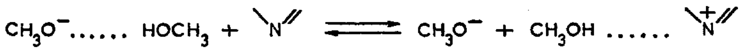
*According to [144], $\delta\Delta H_{ext}^{\#} = \delta\Delta H^{\#} + 2.3RT\rho\sigma$ and $\delta\Delta S_{ext}^{\#} = \delta\Delta S^{\#}$, where the symbol δ indicates an increment caused by the substituent effect.

It follows from the material presented above that the first factor — the effect of "ordering" of the solvent molecules about the transition state — makes the principal contribution to the entropy change during deuterium exchange of compounds of the first group. On the other hand, predominance of a disordering effect over an ordering effect is peculiar to exchange reactions of compounds of the second group. This difference may be the result of both the weaker resonance stabilization of the carbanion of unoxidized nitrogen heterocycles as compared with the carbanions of the corresponding N-oxides, for which this sort of stabilization is extremely considerable, and also to the greater capacity of the nitrogen heteroatom for association with solvent molecules, which is responsible for the distinctly expressed basic properties of nitrogen heterocycles.

2. Changes in the Rate of Isotopic Exchange Caused by Variation of the Composition of the Alcohol Medium

Effect of the Alkoxide Ion on the State of a Heteroaromatic Substrate in Solution. A general feature of the exchange process of nitrogen heterocycles is the fact that the activation energy in "pure" alcohol is 3-10 kcal/mole lower than in an alcohol solution of potassium alkoxide, although the exchange rate in the latter case is two to five orders of magnitude greater [140, 141]. This constitutes evidence for complications in the mechanism of deuterium exchange, which can be explained by assuming that the addition of potassium alkoxide to alcohol leads to the development in solution of two types of hydrogen bonds:



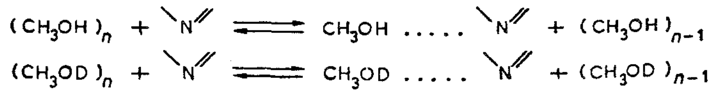
The possibility of the participation of the heteroaromatic molecule in the exchange process in the "free" or partially protonated (more exchangeable) form depends on the position of this equilibrium. Protonation of nitrogen-containing heterocycles promotes labilization of the CH bond, which involves a decrease in the magnitude of E. Inasmuch as the ease of protonation is determined by the basicity of the heterocycle, the observed similar trend of the pK_a^{NH} and log k values for deuterium exchange of heterocycles in "pure" alcohol (for example, 1-methylimidazole > 1-methylbenzimidazole > 2-methylbenzothiazole > 2-methylbenzoxazole) becomes understandable [25]. Judging from the fact that "correct" tendencies in the changes in the activation parameters ($E^{ROD} > D^{RO^- + ROD}$) are observed for N-oxides, the N-oxide group is inclined to a much lesser degree to specific interactions with alcohol molecules. The latter conclusion is in agreement with the fact of the sharp decrease in the basic properties of aromatic N-oxides as compared with the corresponding unoxidized heterocycles ($\Delta pK_a^{NH} \simeq 5$).

Studies of the dependence of the rate of deuterium exchange of thiazole [108], benzimidazole [116], imidazole [113], etc. on the pH of the medium confirm the presence of two mechanisms of deuterium exchange of nitrogen heterocycles in hydroxyl-containing solvents. According to the results obtained, a mechanism in which the heteroaromatic substrate acts as a free base in the exchange reaction is realized for pH values ≥ 11, as a rule. A mechanism including pre-equilibrium protonation is characteristic for solutions with low and intermediate pH values.

Effect of an Aprotic Dipolar Solvent on the Rate of Deuterium Exchange. The addition of dimethylformamide (DMFA) — a solvent with a clearly expressed capacity for the formation of a hydrogen bond with hydroxyl-containing solvents and a low solvating capaicty with respect to anions — to an alcohol solution of potassium alkoxide has a distinct differentiating effect on the rate of exchange reactions of nitrogen-containing heteroaromatic substrates [141]. The latter is due to the fact that desolvation of both the alkoxide ion and the heterocycle molecule occurs in the presence of DMFA:

Moreover, whereas desolvation of the alkoxide ion increases its nucleophilicity and thereby the reaction rate, desolvation of the substrate leads to opposite results. The role of the first equilibrium is more substantial, the higher the basicity of the substrate, and the accelerating effect of DMFA is therefore minimal for the most basic compounds (nitrogen heterocycles with $pK_a^{NH} \simeq 5$) and maximal for the least basic compounds (substituted benzenes and five-membered heterocycles that do not contain a nitrogen heteroatom); in this sense, aromatic N-oxides ($pK_a \leq 1.5$) and benzazoles ($pK_a \leq 3$) occupy an intermediate position.

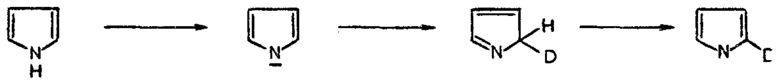
Solvent Secondary Isotope Effect (SSIE). According to [141], a distinct relationship between the kinetic characteristics of an exchange process and the SSIE (determined as the k_{CH_3OD}/k_{CH_3OH} ratio) is not observed, although the latter also displays a tendency to increase as the CH acidity of nitrogen containing heterocycles increases. Thus, for example, the SSIE values during the exchange of 2-methylpyridine ($pK_a^{CH}=27$), 2-methylquinoline ($pK_a^{CH}=23$), and 2-methylquinoxaline ($pK_a^{CH}=20$) are, respectively, 2.0, 6.7, and 7.3. The SSIE changes over a considerably narrow interval during exchange of aromatic N-oxides and substituted benzenes: a variation in the deuterium content in alcohol from 20 to 95 atomic % increases the rate constants of deuterium exchange by a factor of 1.5 to 3. The detected changes in the SSIE are apparently associated with differences in the mechanism of solvation of comparable heteroaromatic molecules. In the deuterium exchange of aromatic N-oxides, in which desolvation of the RO^- ion makes the principal contribution to the interaction of the medium with the substrate, the isotopic difference in the energies of conversion of the associated alcohol molecules that solvate the RO^- ion (the starting state) to ROD or ROH molecules (the transition state) is responsible for acceleration of the exchange process in "heavy" alcohol. In the case of exchange of nitrogen heterocycles that manifest an increased tendency to specific solvation, attack of the reagent (ROH or ROD) on the nitrogen heteroatom requires additional cleavage of the hydrogen bonds in chain associates:



Inasmuch as the energy of cleavage of $O-H\ldots{}^-O-$ bonds in "light" alcohol is greater than the energy of cleavage of $O-D\ldots{}^-O-$ bonds in "heavy" alcohol, deuterium enrichment of the solvent favors specific solvation of the substrate, thereby promoting acceleration of the exchange process. The solvation interaction thus makes an additional contribution to the measureable SSIE.

3. Peculiarities of the Exchange of Heterocyclic Compounds Containing a Secondary Nitrogen Atom

A comparison of the rate of deuterium exchange of pyrrole, indole, and their N-methyl derivatives shows [102, 145] that in alkaline media the N-methyl analogs undergo exchange more slowly by a factor of 10^3-10^5. Moreover, whereas substitution of hydrogen by deuterium in N-methyl derivatives is directed exclusively to the 2 position, the exchange of compounds containing an NH group occurs in the 3 position (indole and its 2,5,6-substituted derivatives) or 2 and 3 positions (pyrrole). These facts serve as an indication of the change in the mechanism of the exchange process. The reasons for the change may be explained if one takes into account the "acidic" character of the NH group of pyrrole and indole ($pK_a \simeq 17$), which is responsible for the presence in solution of appreciable amounts of anions capable of undergoing exchange via an electrophilic mechanism with greater ease than the neutral molecules:



In conformity with the electrophilic nature of the exchange process, electron-donor substituents increase whereas electron-acceptor substituents decrease the rate of deuterium exchange of the heteroaromatic ring of indole and its derivatives [145-148].

It has been shown [146-148] that an electrophilic mechanism is also realized during basic deuterium exchange of hydroxy derivatives of pyridine, quinoline, and isoquinoline.

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