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Abstract

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Hydrogen Isotope Exchange and the Capacity of Methyl Derivatives of Nitrogen-Containing Heterocycles for Condensation Reactions

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Nitrogen-containing heterocycles with a methyl substituent located in the α- or γ-position relative to the heteroatom, and their quaternary salts, enter into condensation reactions with aldehydes, nitroso compounds, diazo compounds, nitroolefins (1), etc. These transformations usually proceed in alkaline medium. On the basis of a large amount of qualitative data, the compounds under consideration may be arranged according to their activity in the following series:

[structural formulas] $<$ [structural formulas] $<$ [structural formulas] $<$ [structural formulas] $<$ (1)

It is widely believed (see, for example, (2)) that the rate of condensation reactions, and the very possibility of their occurrence, are determined by the ease with which protons are split off from methyl substituents. Since the immediate quantitative characteristic of the ease of proton removal is the rate of hydrogen isotope exchange in alkaline medium, it was of interest to compare the rate of hydrogen exchange of the compounds under consideration with their tendency to undergo condensation reactions. Such a study is also important for elucidating the factors that determine the mobility of hydrogen in the methyl group as a function of structure.

In the present work, hydrogen exchange was investigated between compounds of series (1) and methyl alcohols CH_3OD in the presence of triethylamine. In experiments with bases, the ratios of substance, alcohol, and catalyst were approximately constant and equal, respectively, to $0.007 : 0.03 : 0.001$ mol. Exchange in salts was studied in solutions 15–30 times more dilute. After exchange, the substances were isolated: for the bases, by vacuum distillation; for the salts, by crystallization from their solutions in CH_3OD upon cooling. The refractions and melting points of the isolated compounds in all cases agreed with literature data. Water obtained by combustion of these compounds was subjected to isotope analysis by the flotation method. In Fig. 1, the experimental data obtained are presented as the dependence of the quantities $-\ln(1-z)$ on time

Fig. 1. Kinetics of exchange in the methyl residue of nitrogen-containing heterocycles.

Figure 1: Fig. 1. Kinetics of exchange in the methyl residue of nitrogen-containing heterocycles.

t (z is the fraction of exchange calculated for the three exchanging hydrogen atoms of the methyl substituent).

The experimental points satisfactorily fall on straight lines for first-order reaction kinetics. The mean values of the rate constants K, given in Table 1, were found from the slopes of these straight lines.

Under the conditions of our experiments, exchange involves only the hydrogen of methyl substituents located in the α- or γ-position relative to the heteroatom (not counting the hydrogen of the N—H bonds). This conclusion is confirmed by the first order of the exchange kinetics, indicating the equivalence of all exchanging atoms, and by the cessation of the reaction observed by us after exchange

3H and with the data of Shatenstein and Zvyagintseva ([3,4]) on the exchange of α-picoline and quinaldine with ND_3 and $C_2H_5OD + C_2H_5O^-$. As for the hydrogen of methyl residues bonded to nitrogen in quaternary salts, it is known that it

Fig. 1. Kinetics of exchange in the methyl residue of nitrogen-containing heterocycles.
a: 1 —α-picoline, 180°; 2 —2-methylbenzothiazole, 180°; 3 —2-methylbenzoxazole, 180°;
b: 1 —5-(6-)nitro-2-methylbenzimidazole, 130°; 2 —quinaldine, 150°; 3 —2-methylbenzimidazole, 130°; 4 —9-methylacridine, 70°.

does not exchange under conditions much more severe than those of our experiments ([5]). Consequently, the sequence we found in the rates of exchange reflects differences in the ease of detachment of protons from the methyl residues.

Table 1

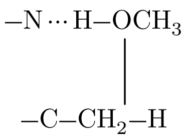
Rates of hydrogen isotope exchange in methyl derivatives of nitrogen-containing heterocycles

Substance	Exchange conditions, °C	Rate constant, $sec.^{-1} \cdot 10^5$	Percent exchange	Substance	Exchange conditions, °C	Rate constant, $sec.^{-1} \cdot 10^5$	Percent exchange
α-Picoline	180	1.7		2-Methylbenzimidazole	130	3.6	

Substance	Exchange conditions, °C	Rate constant, sec.$^{-1}$ · 10^5	Percent exchange	Substance	Exchange conditions, °C	Rate constant, sec.$^{-1}$ · 10^5	Percent exchange
2-Methylbenzothiazole	180	2.1		9-Methylacridine	70	5.2	
2-Methylbenzoxazole	180	5.0		1,2-Dimethylpyridinium iodide	18 (8 min)		43
Quinaldine	150	3.8		1,2,3-Trimethylbenzimidazolium iodide	18 (8 min)		72
5-(6-)Nitro-2-methylbenzimidazole	130	2.9		1,9-Dimethylacridinium iodide	18 (8 min)		79

Comparison of series (1) with the data of Table 1 shows that the activity in condensation reactions is not in correspondence with the tendency toward abstraction of protons from methyl residues and that, consequently, ionization of hydrogen does not serve—at least in many cases—as the limiting stage of condensation reactions.

For understanding the dependence of the ease of isotopic exchange on structure, it is important that the nitrogen of the bases we studied forms hydrogen bonds with the solvent in alcoholic solutions. In such complexes:



$$\begin{array}{l} -\mathrm{N}\cdots\mathrm{H}-\mathrm{OCH_3} \\ \qquad\quad | \\ -\mathrm{C}-\mathrm{CH_2}-\mathrm{H} \end{array}$$

as Shatenshtein and Zvyagintseva have recently shown$^{(3)}$, ionization and exchange are considerably facilitated, since in them the electrophilicity of nitrogen is increased, which promotes the σ-π conjugation shown in the scheme. Obviously, the concentration of complexes (2) is the higher, the more basic the heterocycle.

However, the basicity series compiled on the basis of direct data on the values of pK_A (given in parentheses) and chemical data:

methylbenzoxazole < methylbenzothiazole < nitromethylbenzimidazole < methylquinoline < methylbenzimida

– – (4.3)(6) 5.42(7) 5.7(6) 5.97(8) (> 5.7)(9

does not coincide with the sequence in ease of exchange. It follows from this that conjugation of type (2) is not the only cause of exchange. Another cause is apparently conjugation with the aromatic rings in the ion $-N = C'-CH_2^-$, which increases the stability of this ion and, consequently, facilitates ionization. Such conjugation should be favored by an increase in the number of rings and by electrophilic substituents. These considerations explain why 9-methylacridine exchanges more rapidly than quinaldine, and the latter more rapidly than α-picoline. Substances with the same number of rings in the molecule are arranged, according to the rate of exchange, in the series:

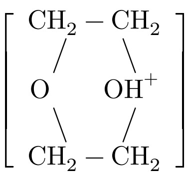
methylbenzothiazole < methylbenzoxazole < methylquinoline < nitromethylbenzimidazole < methylbenzimida

which coincides with series (3), with the exception of nitromethylbenzimidazole and methylbenzoxazole, which is readily explained by conjugation with the nitro group and by the inductive influence of the oxygen of the oxazole nucleus.

The very great acceleration of exchange on passing from bases to quaternary salts is of considerable interest. It is explained by the fact that the positive charge on the nitrogen of the salt greatly enhances σ-π conjugation analogous to (2), and thereby facilitates ionization. It is interesting that in this case as well the proximity of an aromatic ring facilitates hydrogen ionization and exchange, as is seen when the salt of picoline is compared with the salts of quinaldine and 2,3-dimethylbenzimidazole.

In the works of Kursanov, Setkina, and Bykova(5), it was shown, using the examples

$[(CH_3)_4N^+]\,CH_3SO_4^-$,



HSO_4^- and others,

that the inductive influence of N^+ or O^+ does not lead to significant labilization of the hydrogen of C—H bonds. We believe that only certain types of

conjugation: a) of the σ-π type,

$$-\overset{+}{N} = C - CH_2 - H$$

as found in the present work; b) the so-called σ-d conjugation, consisting in the displacement of electrons of C—H bonds to vacant d-levels, causing rapid exchange in onium salts of phosphorus, sulfur, selenium, arsenic, etc.:

$$(\mathrm{CH_3})_3\overset{+}{\mathrm{X}} - \mathrm{CH_2} - \mathrm{H}$$

and, finally, c) analogous conjugation leading to exchange in carbonium ions (^{10}):

$$> \overset{+}{\mathrm{C}} - \mathrm{CH_2} - \mathrm{H}$$

In the light of the data of this work, the hydrogen exchange between concentrated acids and the α-positions of molecules of ketones and carboxylic acids, found by Kursanov and co-workers, should be explained not by the formation of carbonium salts:

$$\left[\begin{matrix}\mathrm{R}\\ \mathrm{R_1}\end{matrix} > \overset{+}{\mathrm{C}} - \mathrm{OH}\right]\mathrm{HSO_4^-}, \qquad \left[\mathrm{R} - \overset{+}{\mathrm{C}}\begin{matrix}\mathrm{OH}\\ \mathrm{OH}\end{matrix}\right]\mathrm{HSO_4^-}$$

and labilization of their hydrogen under the influence of $\mathrm{C^+}$ (^{11}), but by the formation of oxonium compounds

$$\left[\begin{matrix}\mathrm{R}\\ \mathrm{R_1}\end{matrix} > \mathrm{C} = \overset{+}{\mathrm{O}}\mathrm{H}\right]\mathrm{HSO_4^-}, \qquad \left[\mathrm{R} - \mathrm{C}\begin{matrix}\overset{+}{\mathrm{O}}\mathrm{H}\\ \mathrm{OH}\end{matrix}\right]\mathrm{HSO_4^-},$$

containing the grouping of atoms

$$-\overset{+}{\mathrm{O}} = \mathrm{C} - \mathrm{C} - \mathrm{H},$$

analogous to the grouping

$$-\overset{+}{\mathrm{N}} = \mathrm{C} - \mathrm{C} - \mathrm{H}$$

in the ammonium salts studied by us, and likewise labilizing hydrogen. Such an interpretation has the advantage that the oxonium structure of the salts considered is considerably more probable than the carbonium structure.

It may be supposed that compounds possessing the grouping of atoms

$$-\overset{+}{\mathrm{X}} = \mathrm{C} - \mathrm{C} - \mathrm{H}$$

all more or less readily exchange their hydrogen for deuterium, especially in an alkaline medium. We intend to verify this on salts of amidines, salts of imido ethers, and dimethylglyoxime complexes of metals, and also to ascertain the possibility of carrying out condensation reactions with these substances in alkaline media.

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Note: Figure translations are in progress. See original paper for figures.