INVESTIGATION OF ACID DEUTERIUM EXCHANGE IN A NUMBER OF ISOQUINOLINE AND 4-HYDROXY-ISOQUINOLINE DERIVATIVES

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The acid deuterium exchange of isoquinoline and 4-hydroxy- and 3-methyl-4-hydroxyisoquinolines at 145°C in 94% D_2SO_4 was investigated by PMR spectroscopy. The sequence of substitution and the rate constants for deuterium exchange of the protons of the isoquinoline ring were determined. The most reactive protons in isoquinoline and 3-methyl-4-hydroxyisoquinoline are those of the benzene ring, while the proton in the 3 position of the β-pyridol ring is the most reactive in 4-hydroxyisoquinoline.

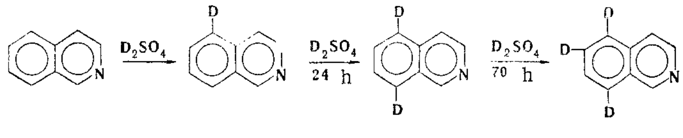
A PMR spectroscopic investigation of the basic deuterium exchange of 3-hydroxyquinoline [1] and 4-hydroxyisoquinoline [1] demonstrated that the introduction of an annelated benzene ring into the 5,6 or 4,5 positions of the β-pyridol ring has a different effect on the sequence of substitution and the reactivity of the heteroring protons. Thus, in contrast to 3-hydroxypyridine [2], the proton in the 4 position was primarily exchanged in the basic deuterium exchange of 3-hydroxyquinoline. On the other hand, the same sequence of substitution as in 3-hydroxypyridine was retained in the case of 4-hydroxyisoquinoline, but the rate of exchange of the ortho proton was higher by a factor of 100.

In connection with the data presented, it seemed of great interest to compare the chemical behavior of 3-hydroxyquinoline, 4-hydroxyisoquinoline, and their derivatives during acid deuterium exchange.

The acid deuterium exchange of isoquinoline and 4-hydroxy- and 3-methyl-4-hydroxyisoquinolines was investigated in the present paper by PMR spectroscopy.

Isoquinoline

The interpretation of the PMR spectrum of isoquinoline is simplified by the fact that there is no difficulty in isolating the signals from the pyridine ring protons from the overall spectrum. Thus the 1-H signal lies in the weakest-field region at 9.41 ppm and is a singlet. The 3-H and 4-H chemical shifts practically coincide (8.34 ppm), and one signal, the intensity of which corresponds to two protons, is observed in the spectrum. The signals from the protons of the benzene ring give a more complex pattern of overlapped multiplets at 7.90-8.40 ppm. On the basis of our experimental results and an analysis of the literature data, the sequence of arrangement of the chemical shifts of these protons varies in the following order: 8-H, 5-H, 7-H, 6-H.



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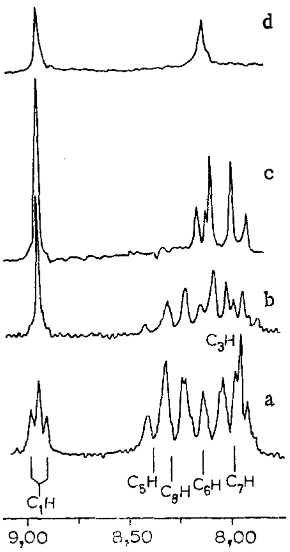

Fig. 1. PMR spectrum of the aromatic protons of 4-hydroxyisoquinoline at 100 MHz as a function of the heating time in 94% D_2SO_4 at 145°: a) without heating; b) after 1 h 20 min; c) after 8 h 10 min; d) after 43 h 50 min.

The order of substitution of the isoquinoline protons in our experiments (94% D_2SO_4, 145°) coincides with the literature data [3] for deuterium exchange in 90% D_2SO_4 at 180°. The 5-H proton initially undergoes exchange, followed by the 8-H proton; the total exchange of 8-H is complete 27 h after the instant the kinetic experiment is set up. Changes accompanied by the appearance of a singlet in the region of the 7-H signal are observed in the portion of the spectrum from the 7- and 6-H protons after heating for 6 h; this is evidence that the 6-H proton enters into deuterium exchange. As heating is continued, the intensity of the singlet increases, and exchange of 6-H is complete after 70 h. Exchange of the protons of the pyridine ring was not observed during the experiments.

4-Hydroxyisoquinoline

The signal from the $\overset{+}{N}H$ proton is in the weakest-field region at 12.6 ppm. The signal of the 1-H proton (8.95 ppm) (see Fig. 1) is a singlet, upon which is superimposed a doublet caused by spin–spin coupling (J = 8.0 Hz) with the $\overset{+}{N}H$ proton. The $\overset{+}{N}H$ signal vanishes on even slight heating because of complete exchange by deuterium, and the 1-H signal is converted to a singlet. A group of signals of the remaining ring protons is situated at stronger field at 7.80-8.50 ppm, and there is no difficulty in isolating the 3-H singlet signal at 7.95 ppm. Since the assignment of the benzene ring signals is obvious, there is a possibility for the direct observation of deuterium exchange. The multiplet of the 8-H proton, which is due to coupling with 7- and 6-H, lies at 8.30 ppm. The multiplet of the 5-H proton, which couples with 6-H and 7-H, is partially superimposed on it. The 7- and 6-H protons give signals at 7.99 and 8.14 ppm, and their multiplicity is due to coupling with 8-, 6-, and 5-H and 5-, 7-, and 8-H, respectively. The 3-H proton is practically completely exchanged even after heating for 15 min. In addition, there are changes in the 5-H region of the spectrum. Further heating leads to a change in the spectrum both in the region of the 5- and 8-H protons and that of the 7- and 6-H protons, as evidenced by the development of doublets from the latter protons as 5- and 8-H are substituted (curve b). Heating for 8 h sharply changes the spectral pattern (curve c). Exchange of 5-H and 8-H is complete by this time, and the degree of substitution of 6-H is sufficient to be reflected in the character of the spectrum. In fact, in addition to the two doublets from 7-H and 6-H, a singlet in the 7-H region from a structure with a substituted 6 position is clearly seen. The intensity of the singlet increases on further heating, while the intensity of the 6-H doublet falls, and 6-H exchange is complete after 45 h (curve d). The rates of exchange of the protons that participate in the reaction were estimated from the change in the ratio of the areas of the 1-H signal (which does not undergo exchange) and the signal of the proton under consideration. We made a detailed examination of the calculation of the exchange rate constants in a previous communication [4]. The rate constants calculated in this way were as follows: $k_3 = 1.3 \cdot 10^{-2}$, $k_5 = 1.0 \cdot 10^{-2}$, $k_8 = 2 \cdot 10^{-3}$, and $k_6 = 2.1 \cdot 10^{-4}\ \mathrm{min}^{-1}$. In this case, the 1-H and 7-H protons do not participate in the exchange. Thus the introduction of a hydroxyl group into the pyridine ring of isoquinoline activates the 5, 6, and 8 positions of the ring. In addition, in the case of 4-hydroxyisoquinoline, the α proton of the β-pyridol ring is the first to undergo exchange; this was not the case in isoquinoline itself or in 3-hydroxyquinoline. A comparison of the experimental data on the acid exchange of 3-hydroxypyridine and 4-hydroxyisoquinoline attests to the fact that the introduction of an annelated benzene ring into the 4,5 positions of the β-pyridol ring considerably increases the reactivity of the proton in the ortho position relative to the hydroxyl group. An analysis of the results of the acid and basic deuterium exchange of 4-hydroxyisoquinoline indicates a different sequence of substitution and different reactivities of the protons of the isoquinoline ring for these two cases. Thus, in the case of basic exchange, both positions of the β-pyridol ring are most reactive, and the protons of the benzene portion of the molecule do not participate in the exchange. However, in acid exchange, the 5-, 8-, and 6-H protons of the benzene ring participate along with the 3-H proton of the β-pyridol ring.

3-Methyl-4-hydroxyisoquinoline

The $\overset{+}{N}H$ signal is found at 12.1 ppm in an unheated sample. The 1-H signal, the multiplicity of which is due to the same reasons as in the case of 4-hydroxyisoquinoline, lies at 8.91 ppm. The partially overlapped multiplets of the spectrum of the benzene ring protons are situated at 7.80-8.40 ppm. The order of arrangement of these signals is in agreement with the data for 4-hydroxyisoquinoline (8-H, 5-H, 7-H, 6-H). The signal of the protons of the methyl group lies at 2.79 ppm. Heating for 15 min leads to very appreciable 5-H and 8-H exchange, a consequence of which is the development of two doublets in the region of the spectra of the 7-H and 6-H protons. Practically complete exchange of the 5-H proton is observed after 35 min (compared with 1 h 50 min for practically complete 8-H exchange), and the spectrum of the protons of the benzene ring is simplified as a result of the exchange. The presence of a singlet in the region of the 7-H proton is evidence for 6-H exchange. The intensity of the 7-H singlet increases on further heating, and only three signals from the 1-H, 7-H, and CH_3 group protons are present in the spectrum after 13 h. Heating for 50 h did not lead to an appreciable change in the intensity of these signals; this indicates the absence of substitution of the indicated protons by deuterium. The rate constants were estimated from the ratio of the integral area of the 1-H or 7-H signals and the area of the signal from the proton under consideration and were as follows: $k_5 = 6.3 \cdot 10^{-2}$, $k_8 = 1.6 \cdot 10^{-2}$, and $k_6 = 1.7 \cdot 10^{-3}$ min^{-1}. Thus, as in the case of 3-hydroxyquinoline, the presence of methyl groups in the β-pyridol ring increases the rate of exchange of the protons of the benzene portion of the 4-hydroxyisoquinoline molecule. In addition, in contrast to 2-methyl-3-hydroxypyridine, substitution of the proton in the para position relative to the hydroxyl group does not occur even on heating for 70 h.

The energies and entropies of activation of the exchange reaction for the 5-H, 8-H, and 6-H protons were estimated by an investigation of the dependence of the rate constants of exchange of the protons of 3-methyl-4-hydroxyisoquinoline on the temperature at which the deuterium exchange was carried out. In this case, the dependence of the corresponding k_5, k_8, and k_6 constants on temperature was in the form of the Arrhenius equation. The ΔE_a and ΔS_a values obtained in this way were as follows: $\Delta E_5 = 30.0$, $\Delta E_8 = 35.6$, $\Delta E_6 = 37.5$ kcal/mole; $\Delta S_5 = -5.5$, $\Delta S_8 = -8.22$, and $\Delta S_6 = -12.6$ eu.

EXPERIMENTAL

The methods for the performance of the kinetic experiments, treatment of the PMR spectra, and estimation of the deuterium exchange rate constants were described in [4]. The duration of the kinetic experiments with 94% D_2SO_4 at 145° was 70-75 h. In estimating the energies of activation, measurements were made at four different temperatures from 110 to 145° for each of the protons examined. The accuracy in the estimation of ΔE_a was ± 0.5 kcal/mole.

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