SELECTIVE LABELING OF SOME 4-AMINO PYRIDINES BY HYDROGEN-DEUTERIUM EXCHANGE

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The use of hydrogen labeled molecules is increasingly important in studies to determine reaction mechanisms in chemical and biological systems. A formidable barrier to such investigations is the preparation of molecules labeled at specific positions.

Common methods to achieve selective hydrogen labeling in aromatic systems employ reductive dehalogenation and decarboxylation reactions (1). Labeling by means of acid- and base-catalyzed hydrogen reactions generally lacks specificity (2). A notable exception in a heteroaromatic system is 1-methyl-4-pyridone which was labeled at the α positions in alkali (3) and at the β positions in acid (4).

We report the results of a kinetic study which makes possible the preparation of a variety of selectively labeled 4-substituted pyridines. Our study was carried out over an acidity range which extends from 1 M $DClO_4$ to 3 M NaOD. Reaction conditions have been found to achieve selective hydrogen exchange at either the α or the β positions of 4-amino- (I) and 4-N,N-dimethylaminopyridine (II). Under a third set of conditions exchange can be achieved at all positions of I and II, Fig. 1. Kinetic results point to the existance of several pathways for exchange. One of these is remarkably independent of changes in the basicity of the reaction medium.
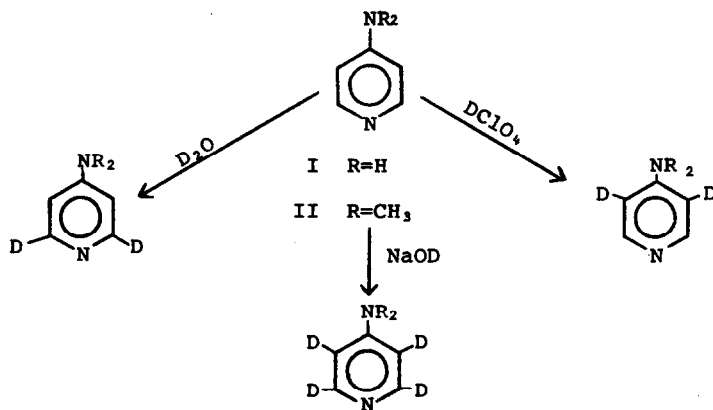
Figure 1

Base-catalyzed hydrogen-deuterium exchange takes place at both the α and β positions of amines I and II. Exchange at the α positions strongly predominates over β exchange in the weakly alkaline solutions made by adding amine to pure D_2O. The rate of exchange at the α positions of both amines is not influenced by changes in basicity up to 3 M NaOD. The rate of exchange at the β positions, however, does increase in progressively more alkaline solutions and eventually surpasses the rate of α exchange. Results are quantitatively expressed by the slopes, k_α/k_β, of the rate plots in Fig. 2. Although the deprotonation rates for the α positions of I and II are almost identical, the β positions of I exchange about five times more rapidly than similar positions in II.

The most likely mechanism for hydrogen exchange at the α positions of I and II involves the formation of an ylid intermediate. An ylid such as III is formed by deuteroxide ion catalyzed deprotonation of an α center in a pyridinium ion. Similar observations regarding ylid formation during H-D exchange at the α positions of pyridine have been reported (5). The region of base-independent exchange for pyridine occurs only in much more dilute alkaline solutions, however. The difference between the amines and pyridine is related to the greater basicity of the former compounds. I is approximately 8000 times (at 25°) more basic than pyridine (6).

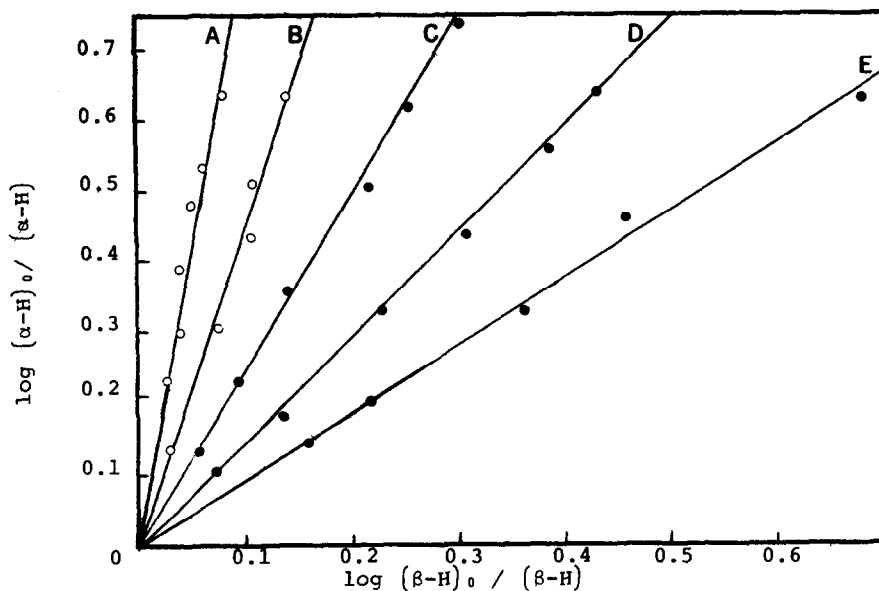The mechanism for exchange at the β positions of II very likely is similar

Figure 2. Plots for the rate of H-D exchange of II (open circles) and I (filled circles) in D_2O-NaOD at 150 ± 1°. The rate of exchange at an α position is plotted against the exchange rate at a β position. Slopes k_α/k_β (M NaOD) are: A 7.0 (1.6M), B 4.5 (2.4M), C 2.6 (0.84M), D 1.5 (1.6M) and E 0.95 (2.9M). The rate constant for exchange at an α position of II is $2.6 \times 10^{-5} sec^{-1}$ and of I is $3.1 \times 10^{-5} sec^{-1}$.
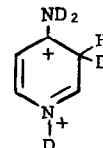
to that for exchange at the β and γ positions of pyridine in alkaline solution

(5). Nucleophilic displacement of hydrogen by base gives rise to a carbanion

such as IV which captures a deuteron from solvent to give labeled product.
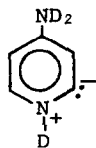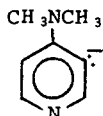
III   IV   VI

Acid-catalyzed H-D exchange was studied using amines I and II and also

1-methyl-4-aminopyridinium chloride (V). Compound V serves as a model for the

conjugate acids of I and II which are protonated predominantly on the annular

nitrogen atom. Exchange takes place preferentially at the β positions of the

three compounds; exchange at the α positions is immeasurably slow in acidic

solution. The kinetic data in Fig. 3 indicate that the relative reactivity for

exchange at the β positions of I, II, and V at 204° is 1.0, 5.0 and 1.9, respec-

tively. The slight increase in reactivity from 1.0 to 1.9 which results upon

replacing a proton on an annular nitrogen by a methyl group has been observed

in similar exchange reactions (7). The similarity of the three compounds in

their rates of exchange and their dependence on acidity strongly suggests that

all react by a common mechanism. This involves addition of a deuteron to the β

carbon of a pyridinium ion to give a dipositive intermediate, VI. That the

amino group is unprotonated and accelerates the rate of exchange is seen from a

comparison of the H-D exchange rate of I and the H-T exchange rate of 2,4,6-

trimethylpyridine. The former is about 10^4 times more reactive than the latter

in one molar acid at 204°. The trimethylpyridine is known to exchange by way of
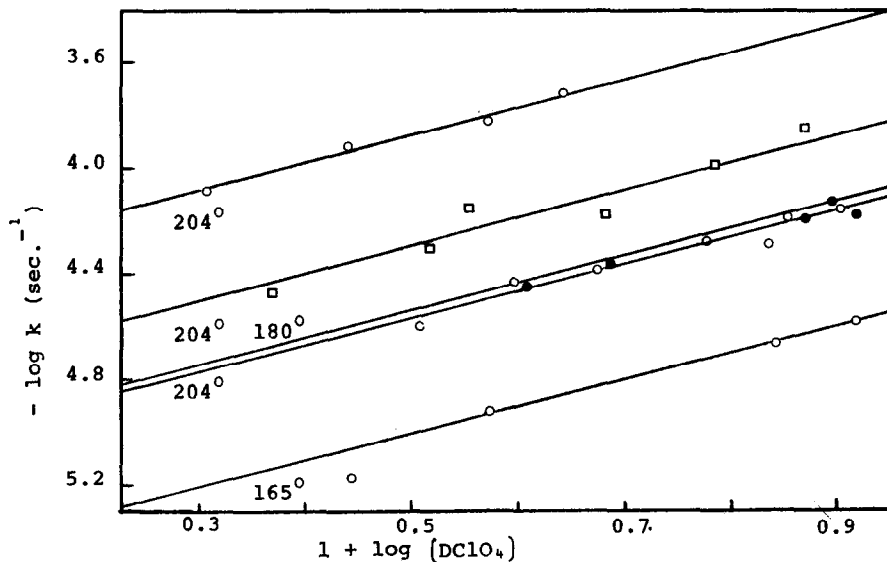
its conjugate acid (7).

Figure 3. Plots for the rate of H-D exchange at the β positions of I (filled
circle), II (open circles) and V (squares) in $DClO_4$. Lines are drawn with a
slope of one.

The H-D exchange kinetic studies were carried out using standard NMR techniques and suitable internal standards (5,8). The NMR spectra of I and II have been reported (9). Since the signals from the α positions of the free amine are broad, aliquots, taken from basic mixtures in a Monel bomb, were acidified prior to analysis. Concentrations are corrected for the thermal expansion of the solvent(11). Deuterated amines were isolated in high yield.

For the deuteration of I on a preparative scale we suggest that the conditions given in Table I be employed. These conditions which use a single exposure to the deuterating medium are designed to introduce approximately 90% D when a 1 M solution of I is employed. $DClO_4$ is made by mixing 70% $HClO_4$ and D_2O. The amine may be recovered by filtration from a cold alkaline solution.

TABLE I

Reaction Conditions for the Preparative Deuteration of I

Position	T, °C	Hours	Medium
α	150	28	D_2O
β	204	11	1 M $DClO_4$
α + β	150	28	3 M NaOD

This work demonstrates that for 4-aminopyridines "cross-over" of positional rates occurs. The directing and rate enhancing effects of the amino group make hydrogen exchange possible at the β positions in acidic solutions. The annular nitrogen serves to direct deprotonation to the α positions in dilute alkaline solutions and to the α and β positions in strongly basic solutions. Further, a wide selection of 4-substituted pyridines labeled selectively at either the α or the β positions may be synthesized. Following the exchange reaction, the amino substituent may be replaced by a variety of groups (10).

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