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Studies on Hydrogen Exchange. XIV.[1] Selective Hydrogen-Deuterium Exchange in Aliphatic Amines and Amino Acids catalyzed by Platinum

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Various classes of aliphatic amines including amino acids were catalytically deuterated in D_2O in the presence of Adams platinum at 30° and 100°. The positions deuterated depended on the chemical structure of the amino nitrogen; α-hydrogens were the most stable in primary amines, while they were the most labile in tertiary amines. The reaction profile of secondary amines seems to be intermediate between those of primary and tertiary amines. Quaternary amines did not react under the reaction condition studied. A tentative reaction mechanism was proposed.

Keywords——catalytic hydrogen exchange; platinum catalyst; aliphatic amines; amino acids; selective deuteration

Catalytic hydrogen exchange of various organic compounds has recently been studied in solution as extensively as in gas phase, using Group VIII transition metals as the catalyst.[3,4] This paper describes a general feature of catalytic hydrogen-deuterium exchange in aliphatic amines, including amino acids, in the presence of Adams platinum. Under the reaction condition chosen in the present study, a marked selectivity was demonstrated in H–D exchange of these amines depending on their chemical structure. Most of the papers so far reported do not discuss the labeled positions in the molecules examined.[3,4]

Experimental

Materials——Most of the amines and amino acids used were commercially available reagents. The amines were used as their hydrochlorides because lower alkylamines were too volatile to be treated and higher ones has too poor a solubility in water. Alkylpiperidines were prepared by the authentic preparative methods.[5,6] Platinum dioxide (PtO_2-$2H_2O$) was purchased from Kawaken Fine Chemicals, Tokyo.

General Procedure for Hydrogen Exchange——Platinum oxide, weighing 20, 50, or 100 mg, was placed in a test tube (10×150 mm) with 1 ml of D_2O and hydrogenated in D_2 gas atmosphere with vigorous mechanical vibration. After hydrogenation of the catalyst was completed (within 2 hr in general), most of the solvent was removed with a small pipette and 1 mmol of an amine-HCl or free amino acid dissolved in 2 ml of D_2O was added. Then the reaction mixture was frozen and degassed up to 10^{-3} Torr. After this procedure was repeated twice more to eliminate molecular hydrogen involved, the reaction tube was sealed under 10^{-3} Torr pressure. The tube was gently shaken in water bath at 30° ± 0.5° or kept standing in boiling water for 40 hr. After the catalyst was eliminated by filtration, the NMR spectrum of the filtrate was measured with a JEOL-3H-60 spectrometer operating at 60 MHz for quantitative analysis of the deuterium incorporated into the respective positions of amine molecule. In all the cases examined, decomposed products were not detected by either thin-layer or gas chromatography.

1) Part XIII: M. Maeda and Y. Kawazoe, *Tetrahedron Lett.*, **1975**, 1643.
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3) A.F. Thomas, "Deuterium Labeling in Organic Chemistry," Appleton-Century-Croft, New York, 1971, pp. 209—338, and literatures cited therein.
4) J.L. Garnett, "The Proceedings of the 2nd International Conference on Methods of Preparing and Storing Labelled Compounds," Brussels, 1966, pp. 709—754.
5) M. Tsuda and Y. Kawazoe, *Chem. Pharm. Bull.* (Tokyo), **18**, 2499 (1970).
6) Y. Kawazoe, M. Tsuda, and T. Horie, *Chem. Pharm. Bull.* (Tokyo), **19**, 429 (1971).

Results

Some significant dependence of H–D exchange on the chemical nature of the hydrogens in the molecule was brought out into relief.

Primary Amines Including Amino Acids

The most characteristic feature observed in this group of amines is that α-hydrogen to the amino function were the most resistant toward catalytic exchange among all the hydrogens in the molecule, as seen from the data summarized in Table I. This feature was true for the

Table I. H–D Exchange of Primary Amines in D_2O in the Presence of Adams Platinum

Compound	Deuteration %[a]					
	at 30°			at 100°		
	α-H	β-H	γ-H (others)	α-H	β-H	γ-H (others)
Ethylamine HCl	0	40		0	40	
Propylamine HCl	0	0	0	0	20	5
Isobutylamine HCl	0	0	0	0	10	0
Isopropylamine HCl	0	10		0	60	
Cyclohexylamine HCl	0	20	0	100	100	(100)
β-Alanine HCl	0	50		0	50	
α-Methylalanine HCl		50			100	
L-Alanine	0	50		40	100	
β-Methylalanine HCl	0	0	0	0	80	90
L-Alanine HCl	0	40				
L-Alanine, sodium	0	50				
L-Alanine, N-formyl	0	0	(formyl, 0)			
L-Alanine, N-acetyl	0	10	(acetyl, 50)			
DL-Alanylalanine	0	50		20	80	
DL-Alanylalanine	0	0		0	40	
L-Valine	0	0	0	20	100	90
L-Leucine	0	0	0(0)	0	70	70(80)
L-Isoleucine	0	0	0(0)	0	100	100(95)

a) H_2N-CHα—CHβ—CHγ—.

molecules bearing a carbonyl group at position α or β to the amino group. At 30°, neither α-CH nor CH_2 of the amines was exchanged with deuterium. Even when the reaction temperature was raised to 100°, only a few amines were deuterated at α-position at the smallest rate among all other positions of the molecule. These data also show that β-hydrogens of the amines were more readily exchanged than to more distant hydrogens and that among those at β-position, CH_3 was more reactive than CH_2 or CH. Among primary amines examined, the exchange reactivity of α-amino acids may be of special interest for synthesis of ^2H- and ^3H-labeled amino acid with retention of the optical property of the α-position. β-Methyl hydrogens of L-alanine were readily deuterated in any forms of the free amino acid, hydrochloride, or sodium salt at 30°, whereas α-CH remained intact. No racemization took place in this case. When L-alanine was reacted at 100°, deuteration of α-hydrogen and racemization occurred at the same rate, preceded by deuteration of β-methyl hydrogens. But this is an exceptional case where α-hydrogen was exchanged, and α-position in most of amino acids and their derivatives was not exchanged even at 100°. It is of interest to note that reaction of DL-alanyl-DL-alanine at 30° resulted in ready deuteration of the N-terminal methyl hydrogens but no deuteration took place at the C-terminal methyl hydrogens nor methine hydrogens of both alanyl groups. When this dipeptide was treated at 100°, exchange reactivity was in the descending order of N-terminal CH_3>C-terminal CH_3>N-termi-

nal CH>C-terminal CH, where the last one was extremely inert under this reaction condition. This result suggests that it is possible to racemize the N-terminal moiety selectively, leaving the C-terminal intact. It is of interest that the exchange reactivity remained almost unchanged by modification of the carboxyl group, while it was decreased by modification of the amino group. This tendency was further demonstrated in the reaction of N-acyl derivatives. N-Formylalanine did not undergo the exchange at all even at β-position, while N-acetylalanine underwent the exchange at β-position but to much less extent than alanine itself.

With regard to some other aliphatic amino acids, deuteration did not proceed at all at 30°. At 100°, β- and more distant hydrogens underwent deuteration, while α-methine did not undergo in all the cases examined. The latter was confirmed by the fact that $[\alpha]_D$ values of the reaction products were completely the same as those of the parent amino acids. β-Aminopropionic acid (β-alanine) underwent the exchange to afford a deuterated product which was selectively deuterated at a methylene β to the amino group, *i. e.*, α to carboxyl group.

Tertiary Amines

The data shown in Table II are in contrast to those of primary amines. Deuteration at 30° occurred exclusively at the α-position to the tertiary amino group. Even at 100°, it was at the α-position that deuteration took place in most cases. Another characteristic feature was that, among the α-hydrogens, CH was the most readily exchanged, followed by CH_2. Thus, the reactivity of α-hydrogens was in the descending order of N–CH>N–CH_2>N–CH_3. Exchange of α-CH_3 hydrogens was found only in a few cases at 100°. As already reported in our previous paper,[6] the same trend was found with the deuteration of N-methylpiperidine derivatives, in which only α-hydrogens were exchangeable at 30° and the most reactive ones were α-CH of 1,2-dimethyl- and 1,2,6-trimethylpiperidinium hydrochloride.

Table II. H–D Exchange of Tertiary Amines in D_2O in the Presence of Adams Platinum

Compound[a]	Deuteration %[b] at 30°					at 100°				
	α-H			β-H	γ-H (others)	α-H			β-H	γ-H (others)
	CH	CH_2	CH_3			CH	CH_2	CH_3		
$EtMe_2N$ HCl		0	0	0			70	0	0	
Et_2MeN HCl		20	0	0			60	0	0	
Et_3N HCl		30		0			30		0	
Me_2PrN HCl		0	0	0	0		50	20	0	0
$MePr_2N$ HCl		10	0	0	0		20	0	20	0
Me_2iPrN HCl	90		0	0		100		0	0	
$MeiPr_2N$ HCl	40		0	0						
Me-cyclohexylamine HCl	80		0	0	0(0)	100		50	0	0(0)

a) Et: ethyl; Me: methyl; Pr: propyl; iPr: isopropyl.

b) $N(-CH_\alpha-CH_\beta-CH_\gamma-)_3$.

Secondary Amines

With secondary amines, it seems difficult to find a clear-cut correlation of the exchange reactivity with the chemical nature of hydrogens (*cf.* Table III). β-Hydrogens were more reactive in some derivatives but α-hydrogens were more than β-ones in some cases. In a type of amines of R–NH–CH_3 (R= alkyls higher than methyl), α-hydrogens in R were not exchanged, regardless of the size of R, *i.e.*, ethyl, propyl, or isopropyl, at 30° and true even

at 100°. A different situation was seen in another type of amines of R_2NH (=alkyls higher than methyl). α-Methylenes in Et_2NH did undergo the exchange although β-methyl was more reactive than those, while α-methines in diisopropylamine were more reactive than the β-methyl hydrogens at both 30° and 100°. It seems that both α- and β-hydrogens were exchangeable and its rate depended on the bulkiness of substituents of the nitrogen.

Table III. H–D Exchange of Secondary Amines in D_2O in the Presence of Adams Platinum

Compound[a]	Deuteration %[b] at 30°					at 100°				
	α-H			β-H	γ-H (others)	α-H			β-H	γ-H (others)
	CH	CH_2	CH_3			CH	CH_2	CH_3		
EtMeNH HCl		0	0	30			0	20	70	
Et_2NH HCl		0		80			0		30	
MePrNH HCl		0	0	0	0		0	0	0	0
MeiPrNH HCl	0		20	20		0		0	40	
iPr_2NH HCl	20			0		100			50	
Me-cyclohexylamine HCl	0		0	0	0(0)	100		50	0	0(0)

a) Et: ethyl; Me: methyl; Pr: propyl; iPr: isopropyl.

b) $NH(-CH_{\alpha}-CH_{\beta}-CH_{\gamma}-)_2$.

Quaternary Ammonium Salts

In contrast to primary, secondary, and tertiary amines, aliphatic hydrogens in quaternary ammonium salts examined were entirely inert even at 100°. The compounds examined were trimethylisopropylammonium iodide, trimethylcyclohexylammonium iodide, and N,N-dimethylpiperidinium iodide. Since aromatic hydrogens of trimethylanilinium iodide were readily exchanged under the same reaction condition, it is not likely that the iodide anion affected the platinum to lose its catalytic activity.[7] However, the final conclusion on exchange reactivity of quaternary salts must be made after their chlorides have been examined.

Discussion

There were some regularities in the hydrogen exchange reaction of aliphatic amines including amino acids catalyzed by Adams platinum. It is worth emphasizing that the reaction took place in specific parts of the molecule as far as the reaction temperature was regulated to 30° or below 100°. Selectivity for this exchange does depend on the chemical structure around the amino nitrogen, *i.e.*, the number and/or bulkiness of the substituent in nitrogen, *etc.*

It appears certain as a general trend that the more crowded the nitrogen is with substituents, the more readily the exchange of α-hydrogens proceeds. Thus, the ease in the exchange of α-hydrogens decreases in the order of $R_3N > R_2NH > RNHMe > RNH_2$ and, among tertiary amines, this order is $-CH-NR_2 > -CH_2-NR_2 > CH_3-NR_2$. With regard to β-hydrogens and

7) In catalytic hydrogenation reactions with platinum, iodide ion does not always decrease the catalytic activity of the catalyst. In general, it is in acidic media that iodide or iodine can be a potent catalytic poison.[5,8,9]

8) A.P. Phillips, *J. Am. Chem. Soc.*, **72**, 1850 (1950).

9) M. Tsuda, N. Uehara, and Y. Kawazoe, to be published.

more distant ones, they were readily exchanged when α-hydrogens were resistant to the exchange (primary amines), whereas they were strongly resistant when α-hydrogens were readily exchanged (tertiary amines).

It appears likely that the reactivity of hydrogens in the amines is essentially related to the specific adsorption of the amino-nitrogen on the surface of the catalyst, followed by dissociative rapture of the C–H bond concerned.[3] Thus, it seems certain that the basic nitrogen is adsorbed on the surface of the catalyst as the first step of the exchange. Then, one can realize that, with regard to tertiary amines, the α-CH group located at the nearest position to the nitrogen has the greatest possibility to be chemisorbed on the catalyst leading to dissociative bond cleavage of the C–H concerned. With respect to primary amines, it may be speculated that the NH_2 group adsorbed on the catalyst is deprotonated to produce a multiple bond-like interaction between the nitrogen and platinum. Hence, the α-CH group may hardly approach the surface of the catalyst. The detailed mechanism should be discussed after more evidence is obtained by further experiments.