Summary

Attempted deoximation of 2-nitro-1-indanone oxime (I) with formalin and hydrochloric acid in acetone gave unexpected compounds, namely, 2-hydroxymethyl-2-nitro-1-indanone oxime (IV), 2-hydroxymethyl-2-nitro-1-indanone (V), and 2-nitro-1-indanone (VI).

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192. Yutaka Kawazoe and Masako Ohnishi : Studies on Hydrogen Exchange. III.*1 Deuterium Exchange of Carbonyl Compounds in Alkaline Media.*2

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Almost all of hydrogens contained in organic compounds can be considered to be acidic since the most atoms bonding to hydrogens are electrically more negative than hydrogen itself. They tend, therefore, to be abstracted away as protons in presence of bases or appropriate catalysts. Namely, any type of hydrogens can be regarded as the so-called active hydrogens under an appropriate circumstance. Therefore, when the reaction medium contains ordinary active hydrogens such as -OH, -NH, etc., intermolecular hydrogen exchange may occur between solute and solvent molecules. It can be expected, as a result, that any types of hydrogens are to be, in principle, deuterated selectively and successively by using deuterium-containing solvent if an appropriate reaction condition could be chosen. It turns out, therefore, that systematic studies on hydrogen-deuterium exchange must be important not only for synthetic purposes of deuterium (or tritium)-containing compounds but also for studies on various types of reactions such as oxidations, reductions, rearrangements, isomerizations, substitutions which are closely related to the exchange reactivity of hydrogens. From the above standpoint we have attempted to classify hydrogens depending on their reactivities toward intermolecular hydrogen exchange. The classification is tentatively made from two different standpoints; one, according to the reaction condition under which the exchange occurs and the other, according to the exchange rate at which it proceeds under a certain given reaction condition. The latter classification can be conveniently done by nuclear magnetic resonance (NMR) technique, all types of hydrogens being classified into three groups, as follows :

Group 1——Those in which chemical exchange proceeds rapidly enough to give only a singlet signal for all species of active hydrogens in the solution. (Theoretical condideration tells us that when two species of hydrogens, whose chemical shift-difference is δ, are under chemical exchange to give a singlet signal for both species of hydrogens,

*1 Part II : This Bulletin, **13**, 1103 (1965).

*2 A preliminary communication of this work appeared in This Bulletin, **12**, 846 (1964). This paper constitutes Part XI of a series entitled by "Nuclear Magnetar Resonance Studies" by T. Okamoto and Y. Kawazoe. Part X : This Bulletin, **12**, 1384 (1964).

*3 Tsukiji, Chuoku, Tokyo (川添 豊, 大西桂子).

the average life times for which they retain at each site can be roughly evaluated as within $1/\delta$ sec.)

Group 2——Those in which chemical exchange proceeds with solute and/or solvent active hydrogens but not so rapidly as to make their respective signals collapse seriously. When one uses the solvent containing active deuterium, these kinds of hydrogens are replaced by deuterium and reaches an exchange equilibrium in a certain period. If a large excess of active deuterium exists in the solution examined, intensity of the signal due to the hydrogens concerned decreases and finely becomes almost zero in a limited period.

Some kinds of hydrogens reach the exchange equilibrium within one second and some reach in a few minutes.

Group 3——Those in which chemical exchange does not take place with any other active hydrogens in the solution in a limited period. These hydrogens can not be replaced by deuterium present in the solvent under the experimental condition chosen.

Now, let us consider, in the first place, the ordinary so-called active hydrogens such as -OH, -NH and so on. In presence of a trace of acidic or basic catalyst, rapid intermolecular hydrogen exchange occurs between these types of active hydrogens to result in signal collapse into one singlet signal. Under these conditions, therefore, these types of hydrogens can be classified in Group 1. Details on these kinds of active hydrogens have previously been reported in a short communication[1] in connection with the quantitative analysis of active hydrogens in complex organic mulecules.

This paper concerns deuterium exchange of the hydrogens adjacent to carbonyl functions such as ketones, carboxylic acid, amides, esters, etc., in alkaline media. They may be the second most active hydrogens and belong to Group 2 under alkaline condition at room temperature. Namely, they can be replaced by deuterium but their reaction rates are not so rapid as to give a singlet signal for all the hydrogens concerned. Importance of these studies might be emphasized in connection with their high reactivities toward a wide variety of reactions in alkaline media, for example, enolization, racemization, condensation, etc., and with quantitative determination of this kind of active hydrogens in the course of the structural studies on natural products. The general features of deuterium exchange of the carbonyl compounds and the simple method for their quantitative analysis by NMR technique will be described in this paper.

Analytical Method

In case where the signals concerned are isolated from other signals on the spectrum, one can determine their areal intensities referring to that of the standard signal which is due to stable hydrogens under the reaction condition chosen. A standard signal can be arbitrarily chosen either from those in the sample molecules or those in an appropriate compound added. It generally happens, however, that the signals concerned are overlapped with others or hidden in a broad hump of signals. In these cases, the quantitative analysis can be made in the same way as previously described[1] for the so-called active hydrogens of Group 1 such as -OH and -NH. Namely, there are involved two processes, that is, deuterium replacement of the active hydrogens and then, measurement of increase in signal intensity of active hydrogens in the solvent caused by liberation of light hydrogens by deuterium replacement. Quantitative analysis of increased amount of active hydrogen can be carried out by comparison of the areal intensity in the examined solution with those in the blank solvent used. The experimental procedure is as follows.

1) Y. Kawazoe, M. Ohnishi : This Bulletin, **12**, 846 (1964).

Preparation of the Solvent

A simple compound containing an arbitrary kind of unexchangeable hydrogen, which is required to give a well-separated signal from others, are exactly weighed out in an appropriate amount (a mg.) and dissolved in an appropriate solvent containing as large excess of active deuterium as possible, such as D_2O, CH_3OD or mixtures of D_2O and organic solvents (dioxane, pyridine, etc.). The signal of the unexchangeable hydrogens contained in the above solution is used for the reference signal for quantitative analysis of areal intensity. To this solution is, then, added a basic catalyst such as sodium hydroxide in an appropriate amount necessary for catalysing deuterium replacement of hydrogens adjacent to the carbonyl function concerned. Then, the intensity ratio (α) of the signal due to the exchanging hydrogens in the solvent to the reference signal is determined by signal integration. The solvent thus prepared is now ready for use for the analysis.

Analysis

The sample to be examined weighing b mg. is dissolved in a difinite volume of the above-prepared solvent exactly containing a mg. of the reference compound. The spectrum of this solution is measured and the signals due to the reference hydrogen and the exchanging active hydrogen are integrated, the areal intensity-ratio *vs.* the reference signal being determined as β. Then, the number (x) of active hydrogens in the sample molecule can be derived by the following equation.*4

$$x=f(\beta-\alpha)naM\mathrm{s}/bM\mathrm{r}$$

Ms : molecular weight of the sample molecule
Mr : molecular weight of the reference molecule
n : number of the reference hydrogens contained in the reference molecule
α : ratio in the signal-intensity of the catalysing exchangeable hydrogen to the unexchangeable reference hydrogen in the blank solvent
β : ratio in the signal-intensity of the exchanging hydrogen to the reference hydrogen in the solution containing the sample examined
f : evaluated as $(1+g)$, g being the ratio in amount of exchangeable hydrogen to the deuterium in the solution measured

The factor f included in the equation is due to the incompleteness of deuterium exchange. When a large excess of active deuterium exists in the solution measured, it can be approximated by an unity.

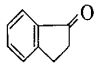
Table I includes some examples of the quantitative analysis at 23°.

Observed values are compatible with the expected ones within a certain but tolerable error. It is of interest that in benzoylacetone, the methylene hydrogens are only exchangeable under the condition described in the table. Enolization or stabilization of carbanion may be one-sided toward the methylene carbon, so that methyl hydrogens may not be activated toward the exchange reaction as illustrated in Chart 1.

In order to confirm the credibility for estimation of factor f, acetone was analysed under such an unfavorable condition that f became near two, namely, that only a half of active hydrogens of acetone were replaced by deuterium even at the exchange equilibrium. The result was satisfactory as shown in Table I. Now, testosterone gave

*4 The accuracy of this method does depend mainly on that of the instruments for the signal integration. One might expect very accurate results if one could completely neglect the saturation phenomenon, drift of the magnetic field and errors in integrating and recording. Although areal intensity is not exactly proportional to the proton-number since it is a function of the relaxation time which is variable for the kind of protons, the proportionality may be utilizable for the present purpose.

Table I. Quantitative Analyses of Active Hydrogens Adjacent to Carbonyls at 23°

Compound	mg./0.5 ml. solvent	Solvent	Reference	Catalysis	Found	Expected	Factor
$C_6H_5COCH_2COCH_3$	38.8	D_2O	*tert*-BuOH	5%NaOD	1.97	2 or 5	1.00
	53.6	dioxane-D_2O[a]	〃	0.34%NaOD	1.87	2	1.07
$C_6H_5COCH_3$	25.2	〃	〃	〃	3.20	3	1.04
	58.0	〃	〃	〃	4.06	4	1.18
	46.1	〃	〃	〃	4.00	4	1.14
CH_3COCH_3	228.0	D_2O	〃	0.8%NaOD	6.06	6	1.924
Testosterone	35.8	D_2O-CH_3OD[b]	HCOONa	1.2%NaOD	4.00	4 or 5	1.00
〃	51.0	〃	〃	〃	4.08	〃	1.00
〃	52.1	〃	〃	〃	3.98	〃	1.00

a) There contains 8.6 ml. of D_2O in 25 ml. of the solvend for measurement.
b) There contains 1.0 ml. of D_2O in 10 ml. of the solvend for measurement.

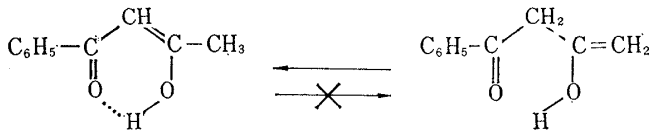


Chart 1.

four of active hydrogens. Two of them were determined as C_4-*H* and 17-O*H* by NMR analysis and other two may be assigned to two C-2 methylene hydrogens but this point is still in question. Malhotra, *et al.*[2] obtained trideuterated derivative from testosterone under the similar alkaline condition. This disagreement is now under investigation.

Next, comparisons were made on the exchange reactivity of α-hydrogens of various ketones. Thus, active hydrogens of ketones are gradually deuterated in very dilute sodium carbonate solutions, ranging from pH 7 to 8, at room temperature. Qualitative comparisons of the exchange rates were carried out by inspection of the NMR spectrum of the solution which contained two compounds to be compared and the following order was deduced of the exchange reactivity (Chart 2).

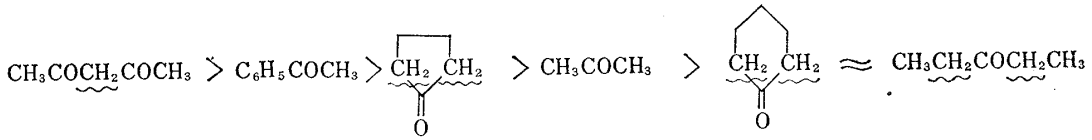


Chart 2.

It is compatible with the theoretical expectation that diethyl ketone was less reactive than acetone probably due to electron donating inductive effect of methyl groups, and that cyclopentanone was more active than cyclohexanone probably due to smaller energy difference between cyclopentane and its dissociated carbanion than the difference for cyclohexane. Further investigations related to the structure-exchange rate relation may be interesting in connection with their pKa values from UV and with the configuration of carbonyl group from IR.

2) S. K. Malhotra, H. J. Ringold : J. Am. Chem. Soc., **86**, 1997 (1964).

Another attempt was made to compare the reactivity of α-hydrogens of carboxylic acids. The hydrogens are much less reactive than those adjacent to the ketone's carbonyls. Compounds were dissolved in 1% NaOD-D_2O solution in NMR sample tubes and reacted at an appropriate temperature. The results are summarized in Table II.

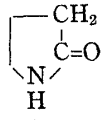
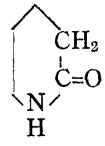
Table II. Deuteration of α-Hydrogens of Sodium Carboxylates in 1.0% NaOD-D_2O Solutions

Compound	Temperature	Time (hr.)	Yield of deuteration (%)
HCOONa	185°	4	0
CH_3COONa	185°	4	90
CH_3CH_2COONa	185°	4	50
$(CH_2COONa)_2$	185°	4	60
$Cl_2CHCOONa$	25°	70	90
C_6H_5-CH_2COONa	100°	2	90
$NaOOCCH=C\begin{matrix}COONa\\CH_2COONa\end{matrix}$	100°	2	90

Decreases in the signal intensities concerned were measured with reference to those due to $(CH_3)_4N^+Br^-$ dissolved together in the solution examined. HCOONa is quite stable under alkaline conditions. One can recognize a considerable deactivating effect of methyl group in propionate on the exchange reactivity compared with those of acetate. On the other hand, substituents such as phenyl and halogen increase the reactivity to a remarkable extent, dichloroacetate starting to be replaced even at room temperature.

With regard to the α-hydrogens of amides, they were made to react with sodium methoxide in absolute methanol in order to avoid hydrolysis, the results being shown in Table III.

Table III. Deuteration of α-Hydrogens of Amides in 1 *M* Sodium Methoxide in Methanol

Compound	Temperature (°C)	Compound	Temperature (°C)
CH_3CH_2COONa	150~180		90
$CH_3CH_2CONH_2$	90		
$CH_3CH_2CON(C_2H_5)_2$	90		
CH_3CH_2CONH-C_6H_5	90		90
$CH_3CH_2CONHCH_2$-C_6H_5	90		

The temperatures indicate those at which the exchange started.

It is concluded that substituents on the amide nitrogen do not affect the reactivity and that five- and six-membered lactams have the same exchange reactivity as that of aliphatic amides. It is worth noting that, when they were treated in aqueous solution, deuteration did not occur in advance of hydrolysis.

Various esters derived from propionic acid were also treated with 1 molar methanol solution of sodium methoxide but deuteration did not occur at below 150°. Acetonitrile underwent the exchange gradually at room temperature accompanied by hydrolysis.

Experimental

Compounds

The compounds used were purchased from Tokyo Kasei Co.

NMR Measurements

The spectra were obtained by a JNM-3H-60 spectrometer of Japan Electron Optics Lab. Co. operating at 60 Mcps. Signal integrations were carried out with a JES-1D integrator attached to our NMR spectrometer.

We are greatly indebted to Dr. Waro Nakahara, Director of National Cancer Center Research Institute, and Professor Toshihiko Okamoto of University of Tokyo for their encouragement and useful discussions throughout this work.

Summary

It was demonstrated that the quantitative analysis of various kinds of active hydrogens was conveniently carried out by nuclear magnetic resonance technique. The exchange reactivities of α-hydrogens adjacent to carbonyl functions were compared with each other by this technique.

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193. Sadao Oida, Masaaki Kurabayashi, and Eiji Ohki : Fragmentation Reaction of Azabicyclic Compounds.*1

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In a recent paper[1] from this laboratory, it was shown that the treatment of 3-methyl-3-azabicyclo[3.3.1]nonan-9-one with phenylmagnesium bromide a 3-methyl-9α-hydroxy-9β-phenyl-3-azabicyclo[3.3.1]nonane (Ia) and its 9β-hydroxy epimer*3 (IIa) and that the former was earily epimerized to the latter on refluxing in 10% aqueous hydrochloric acid. Recently House, *et al.*[2] established the stereochemistry of some 3-azabicyclic compounds including Ia and IIa, as shown below by esterification study and nuclear magnetic resonance (NMR) analysis; they also suggested that as to the transformation process of Ia to IIa the ammonium ion (III) derived from IIa, which is stabilized by an intramolecular hydrogen bond, promotes the Ia~IIa equilibrium to a IIa-rich mixture.

In the course of our recent study on these potential analgesics, interesting observations were made on the chemical nature of 3-azabicyclo-[3.3.1]nonane and -[3.2.1] octane compounds, which form the subject of this paper.

Either the 9α-hydroxy (Ia) or the 9β-hydroxy (IIa) compound was refluxed in methanol, ethanol, or *n*-propanol in place of the aqueous condition in the presence of mineral acid to give the corresponding same ether*3 as a major product. Presumably

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*1 Presented at the Meeting of the Pharmaceutical Society of Japan in Tokyo (May 1966, Tokyo).

*2 Hiromachi, Shinagawa-ku, Tokyo (老田貞夫, 倉林正明, 大木英二).

*3 These derivatives were found to be promissing as new analgesics; and pharmaceutical study on them will be announced in another paper.

1) I. Iwai, B. Shimizu : Jap. Pat. 18,038 (1964) (March 14, 1961); Cf. Brit. Pat. 952,137 (1964) to Sankyo Co., Ltd. (Chem. Abstr., **61**, 5614 (1964)).

2) H. O. House, W. M. Bryant III : J. Org. Chem., **30**, 3634 (1965).