Tetrahedron Letters No. 46, pp 4375 - 4378, 1971. Pergamon Press. Printed in Great Britain

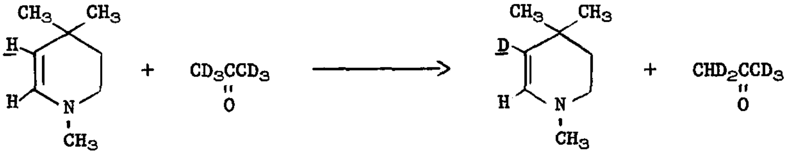
DEUTERIUM EXCHANGE BETWEEN ENAMINES AND HEXADEUTEROACETONE

W.H. Daly, J.G. Underwood and Su C. Kuo
Louisiana State University, Baton Rouge, Louisiana 70803

(Received in USA 1 August 1971; received in UK for publication 11 October 1971)

We have observed that enamines undergo deuterium exchange reactions with acetone-d_6. The exchange occurs primarily with protons bound to carbon atoms β to the nitrogen. The rate of exchange is a function of the enamine structure and represents a new technique for measuring the relative reactivities of a series of enamines. Correlation of the exchange rates with the relative reactivities of a series of enamines were made using this technique and the results correlate well with similar studies by Opitz[1] and by Kuehne[2].

The reaction was characterized by studying the exchange of 1,4,4-trimethyl-Δ^2-tetrahydropyridine(I) with excess acetone-d_6 in benzene. The rate of exchange was determined by monitoring the disappearance of olefinic protons at the 3-position in the nmr spectra as the reaction proceeded. A concommitant increase in the protonated acetone product was observed.



I II

The reversibility of the exchange reaction was tested by preparing 1,4,4-trimethyl-3-deutero-Δ^2-tetrahydropyridine and measuring the exchange rate of this enamine with acetone. A significant kinetic isotope effect was found as indicated by a k_H/k_D ratio of 2.5 at 60°, and 4.06 at 80°.

The exchange was confirmed by a mass spectrometral comparison of the starting enamine and the product isolated by evaporating the deuteroacetone and benzene. The initial spectra of the exchange product contained a strong [M+1] ion which was rapidly converted to an [M] ion by exchange reactions within the sample probe. This exchange precluded a quantitative measure of the extent of deuteration.

Evaluation of the nmr data obtained by multiple integrations of spectra with time indicated that the reaction was pseudo-first order under the conditions observed. The concentration of I was established by comparison of the integrated area at 4.32 δ (β-olefinic H, designated H_v) with an internal standard such as the α-olefinic proton at 5.63 δ (designated

H_R). A plot of the log (H_R/H_V) vs time yielded a straight line with a slope of k/2.303, where k is the pseudo-first order rate constant. Similar rate constants could be obtained by using the combined integrated areas of the methylene peak and the N-methyl peak at 2.66 δ and 2.33 δ, respectively, as the standard. In this case, the rate equation becomes

$$kt = 2.303 \log (H_{CH_2} + H_{CH_3N}/5H_V) \qquad (1)$$

Typical experimental plots of equation 1 are shown in Figure 1, and the rate constants obtained by least squares analysis of the data are compiled in Table 1. The temperature dependence of the rate constants yields a linear Arrhenius plot with a slope corresponding to an energy of activation of 13.8 kcal/mole.

TABLE I

Summary of Data

Temp C°	Acetone-d_6/1,4,4-Amine molar ratio	$k_1 \times 10^6$ sec^{-1}	$t_{\frac{1}{2}}$ min.
Temperature variation			
40°	4.61[a]	6.44	1790.
60°	4.61[a]	45.9	252.
80°	4.61[a]	96.8	199.
100°	4.61[a]	277.	41.7
120°	4.61[a]	467.	24.7
Variation in acetone concentration			
40°	0.211[b]	24.0	482.
40°	0.427[b]	51.0	227.
40°	0.631[b]	74.7	155.
Variation in enamine concentration			
40°	8.72[c]	96.6	120
40°	4.48[c]	151.	76.5
40°	3.14[c]	178.	65.0

a. Benzene/1,4,4-Amine molar ratio ≈ 8.34, about .250cc of Benzene used as solvent. 1,4,4-Amine contained slight impurity according to nmr spectra, which reduced reactivity.
b. Benzene/1,4,4-Amine molar ratio ≈ 2.15.
c. Benzene/Acetone-d_6 molar ratio ≈ 1.80.

Data for determining the order of the reaction with respect to the two reactants, enamine I and acetone-d_6, is also presented in Table I. In the case of the reactant, acetone-d_6, the increase in the initial rate constants was directly proportional to the increase in the initial concentration of the acetone-d_6, and a constant value of 117 x 10^{-6} sec^{-1} for the initial rate constant is obtained by dividing the initial rate constants of the individual runs by the initial acetone-d_6 concentration. Increases in the initial concentration of I likewise produced an increase in the initial rate constant of the deuterium exchange reaction, but the increase in the rate constants are not directly proportional to the increases in the concentration of I. The data failed to fit a second order kinetic equation. Attempts to determine the order of reaction by other standard procedures were not conclusive, but such attempts indicated that the over all kinetic expression is probably a complex expression involving an equilibrium expression which takes into consideration the concentration of the partially protonated acetone-d_6 products. Although the over all kinetic expression for the deuterium exchange is not known, the initial rate appears to follow a pseudo first order plot, and such data can be used as a measure of the relative reactivity of enamines.

TABLE II

Pseudo-First Order Rate Constants of Some Cyclic Enamines[a]

Enamine	Mole Ratio Conc. Enamine:Benzene:Acetone	$t_{\frac{1}{2}}$ min	kx10^4 min^{-1}	Relative Reactivity[b]
1-N-Hexamethyl-enimino-1-cyclopentene	1:7.2:5.4	58.1	119.0	5.95
1-N-Hexamethyl-enimino-1-cycloheptene	1:8.1:5.5	176.	39.5	1.98
1-N-Morpholino-1-cyclopentene	1:7.6:5.6	347.	20.0	1
1-N-Piperidino-cyclohexene	1:8.3:6.6	2790.	2.48	.12
1,4,4-Trimethyl-Δ^2-tetrahydro-pyridine(I)	1:8.3:5.0	252.0	27.5	1.37

a. Measured at 60° and corrected for the presence of three exchangable protons.

b. Kuehne reports the relative reactivity ratio of 1-N-piperidinocyclohexene to 1-N-morpholino-1-cyclopentene to be 0.67 in the alkylation reaction with benzylbromide.

We have applied the exchange technique to the measurement of the relative reactivity of a series of enamines derived from cyclic ketones. The results for a few representative enamines are given in Table II. These results combined with further preliminary data indicate that enamines prepared from a given secondary amine will exhibit the following reactivity with respect to the ketone substrate: cyclopentanone > cycloheptanone > cyclohexanone. A similar series of measurements with a constant ketone substrate yielded the relative influence of the amino substituent: pyrrolidine > hexamethyleneimine > piperidine > morpholine > dimethylamine. These results correlate well with the studies by Opitz[1] on the nucleophilicity of enamines and studies by Kuehne[2] on the alkylation of enamines. We hope that further refinement of the data will yield a quantitative measurement of the enamine reactivities as well as a more comprehensive picture of the factors influencing enamine reactivity. Our preliminary results confirm the feasibility of study and represent a new method for characterizing the structure of enamines.

References

1. G. Opitz and A. Griesinger, *Liebigs Ann. Chem.*, **665**, 101 (1963).
2. M.E. Kuehne and T. Barbacik, *J. Org. Chem.*, **35**, 1555 (1970).
3. E.M. Kosower and T.S. Sorensen, J. Org. Chem., 27, 3764 (1962).

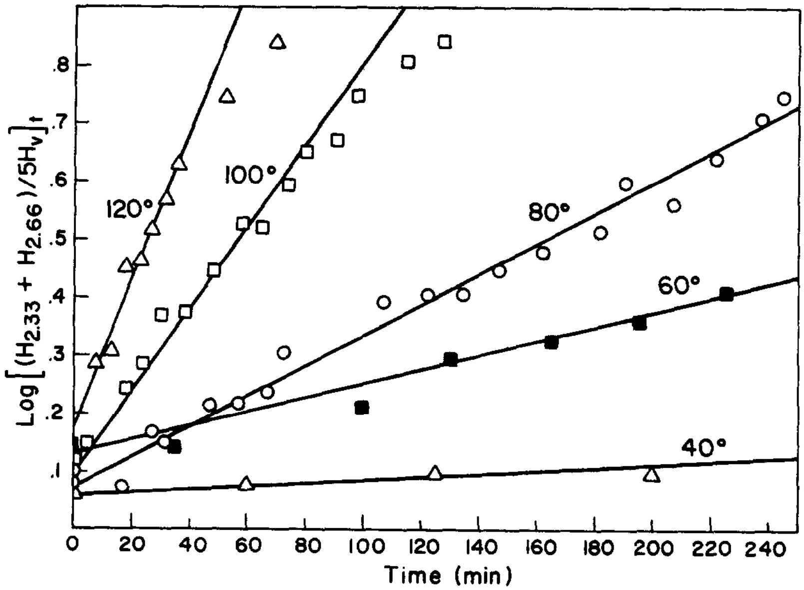


Figure 1. DEUTERIUM EXCHANGE RATE of I with $CD_3\underset{\overset{\|}{O}}{C}CD_3$