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Deuterium Exchange of 4-Pyrimidones and 4-Pyrimidthiones (1)

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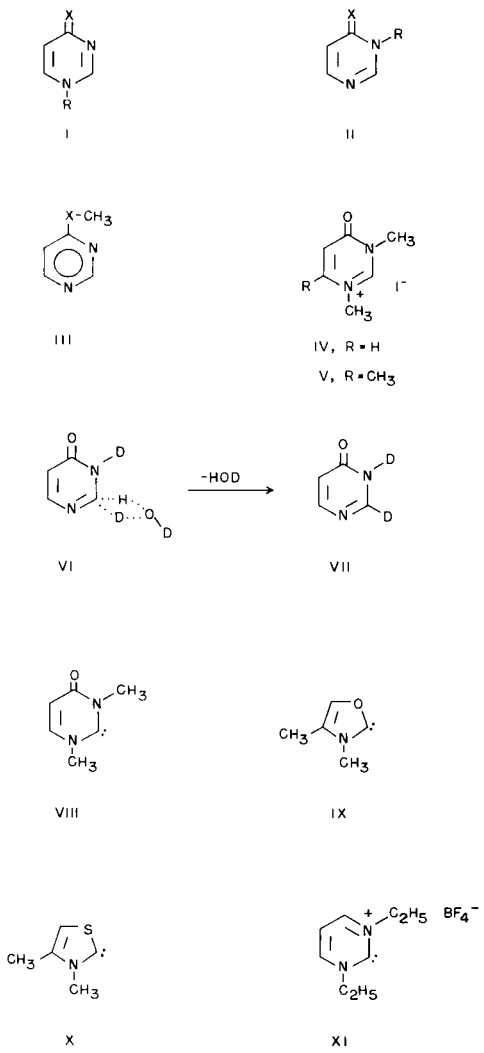
The hydrogen-deuterium exchange of H-2 in 4-pyrimidone, a number of 1- and 3-alkyl-4-pyrimidones and several of their thione analogs in deuterium oxide at moderate temperatures is reported. This reaction is apparently not susceptible to acid or base catalysis. Cations of the 4-pyrimidones were found not to exchange H-2 at all in acid media. Catalytic amounts of bases do not alter the exchange rates whereas more concentrated alkali decompose the pyrimidone. However, 1,4(3,4)-dihydro-1,3-dimethyl-4-oxopyrimidinium iodide (and its 6-methyl analog) exchange H-2 quite rapidly in neutral deuterium oxide, almost instantly when triethylamine is added as a catalyst, and very slowly in dilute solutions of deuterium chloride in deuterium oxide. Mechanisms are proposed to account for these phenomena.

Hydrogen-deuterium exchange of ring protons has been observed in many 5- and 6-membered heteroaromatic systems (2). Most of these exchange reactions are acid or base catalyzed, and frequently different ring protons exchange depending on the catalyst.

Exchange in the Pyridine Series.

At 220° pyridine does not exchange any of the ring protons in deuterium oxide alone, in the presence of one equivalent of hydrochloric acid, or in 96% deuteriosulfuric acid. However, in 10% sodium deuteroxide at 200°, both H-2 and H-6 are exchanged (3). Pyridine 1-oxide, on the other hand, exchanges both H-2 and H-6 in deuterium oxide at 180° and in 5% sodium deuteroxide at reflux (3). From this data it appears that the inductive effect of the *N*-oxide facilitates the exchange. Thus, it is not surprising that when the ring is quaternized, as in 1-methylpyridinium iodide, the α-protons exchange with deuterium oxide at 130° while the base-catalyzed exchange gives the fully deuterated salt (3). Pyridine, the *N*-oxide and the quaternary salt, however, do not undergo exchange in 96% deuteriosulfuric acid at 220° (3,4).

1-Methyl-4-pyridone has been found to undergo base catalyzed exchange of the α-hydrogens in 0.5 *N* sodium deuteroxide at 100°, whereas 1-methyl-4-methoxypyridinium fluoroborate exchanges the α-hydrogens with 0.85 *N* sodium methoxide in deuteriomethanol at room temperature (2). In contrast to the pyridines above, 4-pyridone and 1-methyl-4-pyridone exchange H-3 and H-5 in deuteriosulfuric acid at 170°, ostensibly by electrophilic substitution on the free bases. 4-Methoxypyridine does not exchange the β-hydrogens under these conditions (5).



Exchange in the Pyrimidine Series.

Few exchanges have been reported in this ring system. It has been shown that, while 1-ethylpyrimidinium fluoroborate does not exchange, 1,3-diethylpyrimidinium difluoroborate exchanges both H-2 and H-5 in deuteriotrifluoroacetic acid at 78.2°. The exchange rates of the two positions, however, are quite different, the rate of exchange of H-2 being the faster (6). 4,6-Pyrimidinediol exchanges H-5 slowly at room temperature with deuterium oxide in dimethyl sulfoxide (7). This reaction was found to be catalyzed by both sodium deuteroxide and deuteriosulfuric acid.

RESULTS

Exchange in Deuterium Oxide.

We have observed the ready hydrogen-deuterium exchange of H-2 in 4-pyrimidones (I, II; X = O, R = H, alkyl) and 4-pyrimidthiones (I, II; X = S, R = H, methyl) at 90° in deuterium oxide. The rates of exchange, as determined by the decrease in relative n.m.r. peak intensity of H-2 with time, of a number of these compounds are presented in Table I. However, when the aromatic analogs of these compounds, 4-methoxy- and 4-methylmercaptopyrimidines (III, X = O, S respectively), were heated in deuterium oxide under the same conditions no measurable exchange occurred. Two quaternary salt derivatives were prepared which did exchange H-2 but at a much greater rate than the free bases. Thus, the rate of exchange of H-2 of 1,4(3,4)-dihydro-1,3-dimethyl-4-oxopyrimidinium iodide (IV) in deuterium oxide at 60° was found to be 9.9×10^{-4} sec^{-1} and that of 1,4(3,4)-dihydro-1,3,6-trimethyl-4-oxopyrimidinium iodide (V), 1.15×10^{-3} sec^{-1}. Furthermore, IV exchanged 50% of H-5 at 95° after 2 hours, which is considerably slower than the exchange of H-2.

TABLE I

Rates of Exchange of H-2 of 4-Pyrimidones and 4-Pyrimidthiones in Deuterium Oxide at 90°

Compound	$k_{90°}$ (x 10^4)	k relative
1-Methyl-4-pyrimidone	5.86	8.45
1-Benzyl-4-pyrimidone	4.92	7.10
1-Methyl-4-pyrimidthione	4.90	7.07
3-Methyl-4-pyrimidone	2.06	2.97
4-Pyrimidone	1.91	2.76
3-Ethyl-4-pyrimidone	1.49	2.15
4-Pyrimidthione	1.21	1.75
3-Methyl-4-pyrimidthione	0.69	1.00

Attempts to Catalyze Exchange.

To obtain an insight into the exchange processes, catalysis by both acids and bases was attempted. The rates of exchange of 3-methyl-4-pyrimidone as a model compound in various media are presented in Table II. The presence of catalytic amounts of bases led to no significant differences in the exchange rate of 3-methyl-4-pyrimidone whereas heating the compound with 0.32 *N* sodium deuteroxide in deuterium oxide caused only a slight increase in the rate while at the same time new n.m.r. signals appeared indicative of decomposition to unidentified products (8). When 3-methyl-4-pyrimidone was heated at 95° in concentrated deuterium chloride for 24 hours, no measurable exchange of H-2 occurred. However, under these conditions, H-5 had exchanged over 60%. This exchange probably involves electrophilic substitution by deuterium ion on the free base. Smaller concentrations of acid, 0.1 *M* and 0.01 *M* deuterium chloride and even 2×10^{-2} *M* acetic acid, tend to retard the exchange.

TABLE II

Rates of Exchange of H-2 of 3-Methyl-4-pyrimidone at 90°

Medium	$k_{90°}$ (x 10^4)
D_2O	2.06
0.32 *M* NaOD in D_2O	2.4 (a)
0.24 *M* $N(C_2H_5)_3$ in D_2O	2.01
10^{-2} *M* $NaHCO_3$ in D_2O	1.92
2×10^{-2} *M* CH_3CO_2H in D_2O	1.83
0.01 *M* DCl in D_2O	1.30
0.1 *M* DCl in D_2O	1.16
38% DCl in D_2O	(no exchange)

(a) This really represents an approximate rate determination. The appearance of a new signal (see reference 8) only 7 c.p.s. downfield from the broad H-2 resonance imparted an uncertainty to the measurement of the rate disappearance of H-2.

Catalysis of the quaternary salts, however, showed somewhat different results. When IV was heated at 60° in 0.1 *M* deuterium chloride in deuterium oxide for 10 hours, no exchange of H-2 had occurred (9). In the presence of a small amount of triethylamine, on the other hand, the rate was too fast to be measured at room temperature.

DISCUSSION

Since it has been found that the exchange of H-2 of 4-pyrimidones and 4-pyrimidthiones is not acid or base catalyzed, a mechanism must be sought involving only the free base and deuterium oxide. Such a mechanism might involve a four-center transition state, VI [shown for 3-(D)-4-pyrimidone], which upon loss of HOD, forms 4-pyrimidone-d-2, VII. The rates of exchange of 4-pyrimidone were determined at 70°, 80° and 90° and found to be 0.283, 0.90 and 1.91×10^{-4} sec^{-1}, respectively. From these values was calculated an activation energy

TABLE III

N.M.R. Parameters of 4-Pyrimidone Salts in D_2O (from TPS)

Compound	Chemical Shifts (δ)				Coupling Constants (cps)			
	H_2	H_6	H_5	H_{other}	J_{56}	J_{26}	J_{25}	J_{other}
IV	9.62	8.10	6.90	NCH_3:3.99, 3.69	7.5	2.1	-	J_2-NCH_3:0.5
V	9.62		6.90	NCH_3:3.92, 3.68				J_2-NCH_3:0.4
				CH_3:2.52				J_5-CH_3:0.9

$\Delta E_{act.}$ = 23.7 kcal./mole. Calculations using absolute rate theory gave an entropy of activation $\Delta S_{act.}$ = -12.4 cal./deg. Since a highly ordered transition state, such as VI above, is accompanied by a decrease in the entropy of the system, the value of $\Delta S_{act.}$ found is at least consistent with a four-center transition state for the exchange.

It was observed that in 0.01 *M* deuterium chloride the rate of exchange was considerably slower. In this medium a mixture of 3-methyl-4-pyrimidone and its cation would be expected to be present, and one would have to consider the rate of exchange of the cation also. When the concentration of acid was increased the rates decreased, and this diminution can be attributed to either the very slow exchange of the cation or to the decrease in concentration of "free" deuterium oxide available.

The addition of basic catalysts did not affect the rate markedly in direct contrast to the base-catalyzed exchange of the salts, IV and V (see below).

While the differences in the exchange rates of the pyrimidones and pyrimidthiones studied are not great, they do present an interesting trend. The 1-substituted compounds as a group exchange faster than the 3-substituted compounds. The four-center transition state postulated requires a change in hybridization of C-2 from sp^2 to a nearly sp^3 intermediate involving a pair of π electrons from the ring. It has been demonstrated (10) that 3-substituted 4-pyrimidones and thiones possess a greater amount of aromatic character than the 1-substituted analogs. Transition state formation in 3-substituted 4-pyrimidones and thiones, therefore, occurs at the expense of the aromatic resonance to a greater degree than in 1-substituted. Thus, 4-substituted pyrimidines do not exchange at all, the energy barrier being too large. 4-Pyrimidone and thione (mixtures of the 1- and 3-H tautomers) exchange at rates intermediate between the 1- and 3-substituted compounds.

The exchange of H-2 of the two quaternary salts, IV and V, presents a different problem. The exchange is definitely base catalyzed and proceeds at a much faster rate than that of the pyrimidones and thiones themselves. The exchange is also inhibited by acids. The formation of a neutral "ylid" intermediate, VIII, is most probable since H-2 should be quite labile. Similar ylid intermediates have been postulated for the exchange of H-2 of oxazolium and thiazolium salts, *e.g.*, IX and X (11), and for the exchange of H-2 of 1,3-diethylpyrimidinium difluoroborate, XI (6).

N.M.R. SPECTRA OF PYRIMIDONE SALTS

The two quaternary salts studied in this work, IV and V, showed interesting n.m.r. patterns (Table III) in deuterium oxide solution. The n.m.r. spectra of 4-methoxypyrimidine, 4-pyrimidone, 1-methyl- and 3-methyl-4-pyrimidone have been reported in deuterium oxide together with those of their cations (7) and in dimethylsulfoxide solution (10). The chemical shifts of corresponding protons in the quaternary salts exhibit large downfield shifts with respect to 1- and 3-methyl-4-pyrimidones themselves (7) and are on the order of those of the 4-pyrimidone cations (7). This large deshielding is felt most strongly at the 2 and 5 positions, the 6 proton being shifted downfield to a lesser degree. The decrease in electron density of these positions serves to deshield the corresponding protons.

The line width of the ring protons of the pyrimidone cations have also been observed to be smaller than those of the free bases, and a greater amount of structure may be seen in the signals due to H-2. This is due to removal of the interference of the electric quadrupole of the adjacent nitrogens because of the change in their charge distribution. The H-2 signal of IV shows, in fact, twelve distinct lines arising not only from coupling with H-6 and a small amount with H-5, but also from long-range coupling to the *N*-methyl groups. This long-range coupling, which is approximately identical to both methyl groups, is well resolved in the methyl signals also. Compound V also exhibits this coupling through the *N*-methyls as well as coupling of H-5 to the 6-methyl hydrogens. Much less structure is evident in the ring signals of this compound, however, possibly obscured by long-range coupling of H-2 with the 6-methyl hydrogens. Several examples of

coupling through an *N*-methyl group are available from the literature. Thus, the coupling of the formyl proton with the *trans* *N*-methyl protons of dimethylformamide is about 0.6 c.p.s. whereas the coupling to the *cis* *N*-methyl is about 0.3 c.p.s. in the neat state (12). Dimethylthioformamide shows similar couplings, the *trans* being 0.7 c.p.s. while the *cis* is 0.5 c.p.s. in benzene solution (12). The *cis* relationship of H-2 with the *N*-methyl groups of IV and V is consistent with the small values (0.4, 0.5 c.p.s.) of this long-range coupling.

Since long-range coupling of H-2 with *N*-methyl hydrogens had not been observed in the spectra of 1- and 3-methyl-4-pyrimidones themselves (7,10), their spectra were taken in concentrated deuterium chloride in deuterium oxide. The *N*-methyl signals of these cations did indeed show small long-range couplings (1-methyl-4-pyrimidone deuterochloride, J_2-NCH_3 = 0.3 c.p.s.; 3-methyl-4-pyrimidone deuterochloride, J_2-NCH_3 = 0.4 c.p.s.). Probably this coupling in the free bases is obscured by the quadrupole broadening due to the ring nitrogens.

EXPERIMENTAL (13)

The n.m.r. spectra were determined with a Varian A-60 spectrometer equipped with a variable temperature probe. Chemical shifts are recorded in parts per million (δ) downfield from sodium 3-(trimethylsilyl)propanesulfonate (TPS) as internal reference. The infrared spectra were taken on a Perkin-Elmer Model 337 instrument.

Kinetic data were obtained by following the decrease with time of the n.m.r. integral of the exchangeable proton with respect to a non-exchanging ring proton. A preweighed amount of sample was dissolved in a measured amount of solvent at the temperature of the run (solutions were approximately 1.7 *M* in pyrimidone). Three or four integration curves were obtained at each time interval and the logarithm of the average "ratio unexchanged" plotted against time.

That exchange had occurred at position 2 was evident from the n.m.r. spectra of the deuterated compounds. The downfield signal (H-2) had disappeared leaving the H-5 and H-6 signals as doublets (*ortho* $J_{5,6}$). Upon evaporation of deuterium oxide from a solution of 1-methyl-4-pyrimidone-d-2 and dissolution of the solid in ordinary water, heating gave the original spectrum of 1-methyl-4-pyrimidone. The infrared spectra (in chloroform) of 3-methyl-4-pyrimidone and 3-methyl-4-pyrimidone-d-2 were compared, a C-D stretching band being evident at 2275 cm^{-1} in the spectrum of the latter.

The syntheses of the materials used in this study are described in a previous publication (10) with the exception of the following compounds.

1,4(3,4)-Dihydro-1,3-dimethyl-4-oxopyrimidinium Iodide.

4-Pyrimidone (4.8 g., 0.05 mole) and methyl iodide (34.5 g., 0.25 mole) were dissolved in 75 ml. of methanol and the solution stored at room temperature. After 17 days yellow crystals had separated (1.6 g.), m.p. 200-210°. A solution of this salt in water was passed through a column of Amberlite (IR-4B, 20 g., previously equilibrated with 2 *M* ammonium hydroxide) and the salt eluted with water (150 ml.). Evaporation of the effluent *in vacuo* and subsequent crystallization from ethanol gave light yellow needles (1.1 g., 8.7%), m.p. 204-210°, lit. (13) m.p. 205-206°.

1,4(3,4)-Dihydro-1,3,6-trimethyl-4-oxopyrimidinium Iodide.

To a solution of 6-methyl-4-pyrimidone (14) (9.6 g., 0.087 mole) in 75 ml. of methanol was added methyl iodide (34.5 g., 0.25 mole) and the solution allowed to stand at room temperature for three weeks. The solid which had precipitated was filtered and washed with methanol to give 4.35 g. (19%) of colorless solid, m.p. 280-284°. This solid (1 g.) was placed on a column of Amberlite identical to that above. Elution with water (200 ml.), evaporated *in vacuo* and crystallization from ethanol (200 ml.) gave colorless needles, m.p. 283-285°.

Anal. (15) Calcd. for $C_7H_{11}IN_2O$: C, 31.59; H, 4.16; N, 10.53. Found: C, 31.88; H, 4.44; N, 10.38.

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(9) A freshly prepared sample of IV had an anomalously slow rate of exchange in deuterium oxide. The solution was found to be quite acidic. This was undoubtedly due to residual HI present in the sample after crystallization. Therefore, IV and V were passed through ion-exchange columns before determining their exchange rates.

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