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A DUAL MECHANISM FOR H → D EXCHANGE IN 1,2,4-TRIAZINES

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Abstract—H-3 of a series of 1,2,4-triazines is subject to base-catalyzed H → D exchange. This exchange appears to occur *via* an anionic intermediate. Under neutral conditions, H-3 → D-3 exchange occurs *via* a covalently hydrated intermediate, in those 1,2,4-triazines where covalent hydration has been shown to take place in acidic media.

Proton-deuterium exchange processes of carbon-bound hydrogen in heteroaromatic systems have been extensively studied. These studies have, by and large, established that the base-catalyzed exchange reactions occur *via* ylide or anionic intermediates.[1] It has also been shown that, in some systems, these exchanges occur by base-independent processes.[2,3,4]

As part of our continuing examination of the chemistry of 1,2,4-triazines,[3] we have examined the susceptibility of this ring system to H-D exchange under varying conditions. Somewhat to our surprise, we found that 1,2,4-triazine, and its 5-methyl, 6-methyl and 5,6-dimethyl derivatives undergo H-3 → D-3 exchange under neutral conditions (see Table 1). These observations appear to represent the first examples of *facile* H → D exchange occurring in a functionally unsubstituted π-deficient heteroaromatic ring system under neutral conditions (H-2 and H-6 of pyridine are reported to exchange extremely slowly in D_2O at 218°[6]).

A comparison of the exchange rate of H-3 of 6-methyl-1,2,4-triazine (13×10^{-5} sec^{-1}) with that of 1,2,4-triazine (14×10^{-5} sec^{-1}) itself demonstrates that a methyl group at the 6-position does not significantly alter the rate of this exchange process. On the other hand, the presence of a methyl group at the 5-position decreases the exchange rate 20-fold, while a phenyl group at this position totally inhibits the reaction.†

One factor, whether directly related to these exchange reactions or not, becomes eminently clear, namely that *only those* 1,2,4-*triazines that undergo covalent hydration are prone to* H3 → D-3 *exchange in neutral* D_2O.

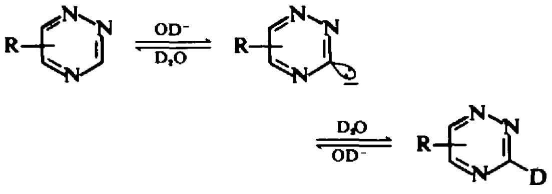
We find that as the pH is decreased, the H-3 → D-3 exchange rate in 1,2,4-triazine rapidly falls to zero (at 0·2 N DCl) while the amount of covalently hydrated compound increases until it is the sole component.[3]

In basic solution, H-3 in 5-phenyl-1,2,4-triazine exchanges considerably more readily than either 6-methyl- or the parent 1,2,4-triazine. Thus, a *reversal* of the relative exchange rates occurs in going from a neutral D_2O solution to an alkaline medium. In fact, under identical conditions the 5-phenyl compound undergoes H-3 → D-3 exchange 15 times faster than does 1,2,4-triazine itself.

A plot of the H-3 → D-3 exchange rates of 1,2,4-triazine *vs* base concentration intercepts the rate axis at 12×10^{-5} sec^{-1}. This value compares well with the experimental exchange rate in neutral D_2O (14×10^{-5}). In a similar plot for 5-phenyl-1,2,4-triazine, the rate goes essentially to zero at zero base concentration.

Thus one is led to the inescapable conclusion that H-3 of the 1,2,4-triazines exchanges by two distinct mechanisms. One, which appears to involve, in some fashion, the propensity of some of the 1,2,4-triazines to undergo covalent hydration across the N-4–C-5 bond, and one which follows the established mechanism for base-catalyzed H → D exchange in π-deficient heteroaromatic systems and which involves a carbanion intermediate.

The base-catalyzed exchange reactions can be represented by the following equilibrium:



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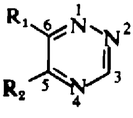
†Because of solubility difficulties with 5-phenyl-1,2,4-triazine, the exchange was studied in DMSO/D_2O mixtures, and the results compared with those of the other 1,2,4-triazines in the same solvent mixtures.

Table 1. Rate constants for H-3 → D-3 exchange at 100° of some 1,2,4-triazines



Compound	Solvent	$k_1 \times 10^{5d}$ (sec^{-1})	$k_2 \times 10^{3d}$ (mole^{-1}sec^{-1})
$R_1 = R_2 = H$	D_2O	$14 \pm 0{\cdot}7$	—
	0·02 N DCl	$14 \pm 0{\cdot}7$	—
	0·2 N DCl	$0^{f,g}$	—
	$DMSO + D_2O^{a}$	$0{\cdot}093 \pm 0{\cdot}005$	—
	$NaOD^{b}/D_2O$	$12^{e} \pm 0{\cdot}6$	1·0
	$NaOD/DMSO + D_2O^{c}$	$0{\cdot}22 \pm 0{\cdot}015$	0·02
$R_1 = H, R_2 = CH_3$	D_2O	$0{\cdot}69 \pm 0{\cdot}04$	—
	$NaOD^{b}/D_2O$	$0{\cdot}64^{e} \pm 0{\cdot}04$	0·20
$R_1 = CH_3, R_2 = H$	D_2O	$13 \pm 0{\cdot}7$	—
$R_1 = R_2 = CH_3$	D_2O	$0{\cdot}90 \pm 0{\cdot}04$	—
$R_1 = H, R_2 = C_6H_5$	$DMSO + D_2O^{a}$	0^{f}	—
	$NaOD/DMSO + D_2O^{c}$	0^{e}	0·30

[a] 0·5 ml DMSO and 0·1 ml D_2O.

[b] The following base concentrations were used: 0·016 N, 0·041 N, 0·067 N, 0·098 N, and 0·157 N.

[c] The following base-concentrations were used: 0·016 N, 0·041 N, 0·067 N.

[d] k_1 refers to the pseudo-unimolecular rate constants observed in neutral solutions, while k_2 refers to the second-order rate constants obtained from the base-catalyzed exchange reactions.

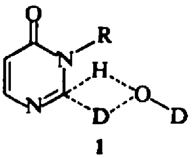
[e] Obtained by extrapolating a base-concn. *vs* rate plot to zero base concentration.

[f] "Zero" rate refers to the reaction, under the conditions cited, where *no* exchange was detectable, by the PMR method, after 150 h.

[g] At acidities significantly greater than 0·02 N DCl, substantial decomposition of the 1,2,4-triazine occurs at 100°. In 0·2 N DCl, after 150 hours at 100° only 44% of the 1,2,4-triazine could be recovered. However, no deuterium incorporation was evident from its PMR and mass spectra.

It now remains to consider a possible exchange mechanism to account for the neutral exchange process. This seems to find as a possible precedent, the neutral H-2 → D-2 exchange in 4-pyrimidones. The analogy between this system and the 1,2,4-triazines might be considered to lie in the electron withdrawing power of the carbonyl group in the pyrimidones and that of the sp^2-hybridized N-1 in the 1,2,4-triazines.

Because the pyrimidone exchange shows a negative entropy of activation (−12·4 cal/deg) in addition to being neither acid- nor base-catalyzed, it has been suggested[4] that a highly ordered transition state such as might be represented by structure 1 is involved in this process.



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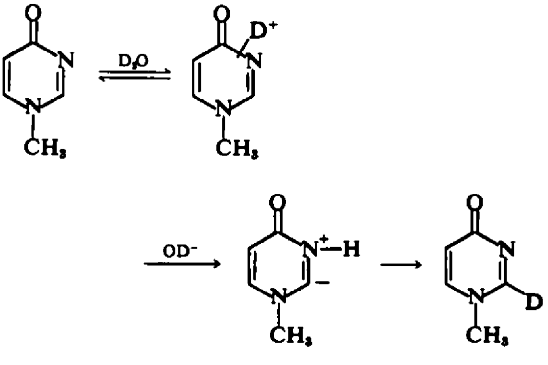
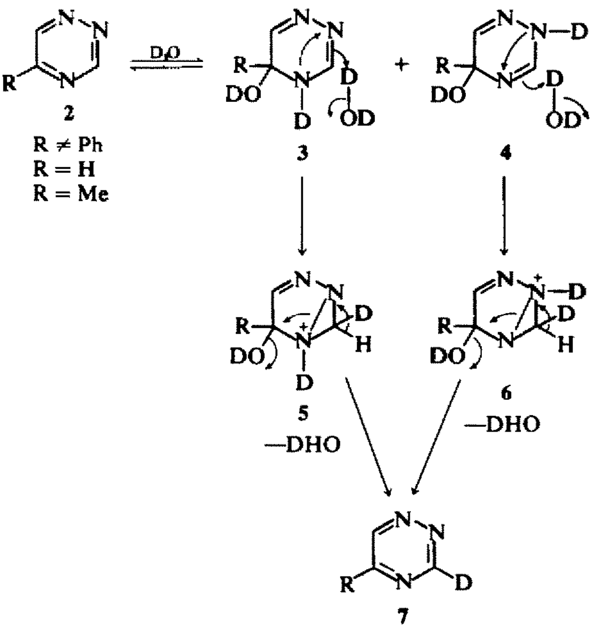
On the other hand, it has recently been proposed[5] that the following sequence more adequately accounts for this type of reaction:



However, the rate constants for the neutral 1,2,4-triazine exchange clearly show the involvement of the C-5 substituents in this reaction. Thus, neither of these mechanistic proposals is applicable to the 1,2,4-triazine system.

One is, consequently, left with the suggestion that the exchange may occur *via* covalently hydrated intermediates. Since the exchanges do not occur under conditions (acidic) where protonated covalently hydrated species are present, we must be dealing with *non*-protonated covalently hydrated intermediates.

Thus, we suggest that the following sequence may well account for these exchange processes:



This sequence, which depends upon the presence of a small amount of the covalently hydrated neutral species (3 and/or 4), also accounts for the observation that a protonated, and thus positively charged, covalently hydrated species is inert to H-3 → D-3 exchange. The proposed intermediacy of the protonated 1,2-diaziridinium ions 5 and 6, finds precedent in our earlier observations describing ring-contraction in some 1,2,4-triazines.[3] The examination of other compounds in this series and of related heteroaromatic compounds, in an attempt to establish either the generality or uniqueness of this behavior, and to delineate the factors which prevent H-5 and H-6 from exchanging under base catalysis, are in progress.

EXPERIMENTAL

Preparation of the various 1,2,4-*triazines*. The compounds were prepared by the procedures described in reference 3 and their purities were established by tlc (alumina plates, developing solvents varied from benzene to benzene-ethyl acetate mixtures), mass spectrometry, and melting points.

Determination of rate constants. The appropriate 1,2,4-triazine was weighed into an NMR tube and 0·4 ml of D_2O, or the appropriate $NaOD/D_2O$ solution, was added. An initial spectrum and integration was then obtained. The NMR tube was then heated at 100° for variable periods of time and the cooled (ice-water) samples were examined by means of PMR spectroscopy. The averaged values of 8 integrations afforded the percentage of exchange of H-3 (Table 1). In all of the compounds, 10–15 points covering at least two-half lives, were obtained.

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