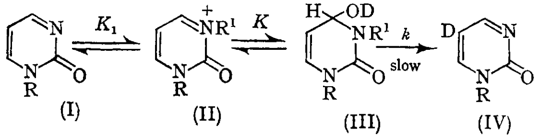
Covalent Hydration in Simple Pyrimidines: Evidence from Kinetics of Hydrogen Exchange

By A. R. KATRITZKY,* M. KINGSLAND, and O. S. TEE
(*School of Chemical Sciences, University of East Anglia, Norwich*)

COVALENT hydration is now a well recognized phenomenon for quinazolines and other polyazanaphthalenes.[1] The only known examples of this phenomenon among pyrimidines were recently discovered for the cations of certain 5-nitro-derivatives,[2] where the electron-withdrawing nitro-group assists the addition reaction. We now present evidence which suggests that many simple pyrimidines may contain appreciable quantities of covalently hydrated species. This may be significant in biochemical reaction mechanisms.

The substitution of an aza-nitrogen atom for a CH-group is expected to decrease the susceptibility of an aromatic ring towards electrophilic substitution. Comparisons of kinetic rates for analogous pyridines and benzenes confirm this:[3] the $\sigma_m{}^+$-constant for an aza "substituent" is *ca.* 0·60.[4] We have now found that the 5-hydrogen of [^{2}H]-pyrimidin-2-one (I; R = D) is unexpectedly exchanged for deuterium *ca.* 10^4 times *faster* than the 3- or 5-hydrogen of pyrid-2-one.[5] This indicates that the former compound must be reacting by a different mechanism. The observed kinetics[6] are compatible with the exchange of the pyrimidine derivative occurring on a small equilibrium proportion of the covalent hydrate[1] (III; R = R^1 = D).



The above mechanism is confirmed by the behaviour of 1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium (II; R = R^1 = Me) salts. The cation (II) itself should resist electrophilic attack at the 5-position, whereas its pseudo-base (III; R = R^1 = Me) might undergo ready exchange, and is a model for the covalent hydrate (III; R = R^1 = D) of pyrimidin-2-one. The equilibrium (II ⇌ III; R= R^1 = Me) was measured ($pK = 7{\cdot}03$), and the exchange was observed for the cation (II; R = R^1 = Me) at a rate ($k_{obs} = 1{\cdot}5 \times 10^{-2}$ hr.$^{-1}$ at pH 1·25 and 107°) comparable to that for pyrimidin-2-one ($k_{obs} = 1{\cdot}75 \times 10^{-1}$ hr.$^{-1}$ at pD = 1·40 and 107°) and for 1-methylpyrimidin-2-one (I; R = Me) ($k_{obs} = 2{\cdot}02 \times 10^{-1}$ hr.$^{-1}$ at pD = 1·65 and 107°). Qualitatively, these similar rates indicate that the rate-determining steps in all the exchanges are of the same type (III → IV), and incidently exclude exchange by a ylid mechanism. Consideration of the equilibrium constant for the covalent hydration of pyrimidin-2-one is made difficult by the unknown quantitative electronic and steric effects of the *N*-methyl groups, but we believe that the proportion of covalent hydrate is in the range 0·1—1%. Other work in progress in this laboratory suggests that pyrimidin-4-one and pyridazin-3-one can also undergo exchange *via* small proportions of covalent hydrates.

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[4] *Cf.* the series "Kinetics and Mechanism of the Electrophilic Substitution of Heteroaromatic Compounds", *J. Chem. Soc.* (*B*).

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