Tetrahedron Vol. 35, pp. 1257 to 1260
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0040-4020/79/0515-1257/$02.00/0

THE CATALYSIS OF PROTON EXCHANGE IN METHYL SUBSTITUTED 2-PYRIMIDONES

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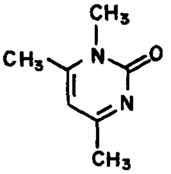
(*Received: in USA 4 August 1978*)

Abstract—The general-acid and general-base catalyzed exchange of the 4- or 6-Me groups in a series of Me substituted 2-pyrimidones has been studied. When the substrate is neutral the 6-Me group is 8–25 times more reactive than the 4-Me group; when the substrate is a cation (either a conjugate acid or a quaternary salt) there is little difference in reactivity. As a consequence the proton activating factor (paf) is larger for the 4-Me group than for the 6-Me group. It is shown that the reaction of hydroxide ion with neutral 1,6-dimethyl-2-pyrimidone is about a thousand times faster than the reaction of water with the compound's conjugate acid; that is, deprotonating the base is more effective at facilitating exchange than protonating the substrate.

We are interested in finding out which molecular features determine the degree to which protonation activates an organic substrate towards bases or nucleophiles.[1] The proton activating factor (paf) is given by eqn (1), where k_{HA} and k_{A^-} are the usual catalytic coefficients and K_{ZH^+} and K_{HA} are, respectively, the equilibrium constants governing the acidities of the conjugate acid of the organic substrate Z and the buffer acid HA.

$$\text{paf} = \frac{k_{ZH^+ + A^-}}{k_{Z+A^-}} = \frac{k_{HA}K_{ZH^+}}{k_{A^-}K_{HA}}. \qquad (1)$$

The present work examines a number of Me substituted 2-pyrimidones, 1–5, two of which are quaternary salts.



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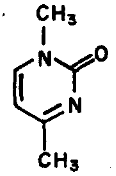

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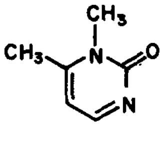

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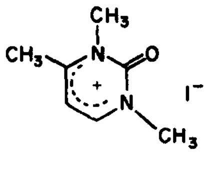

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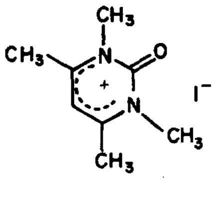

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The reaction studied was the exchange of deuterium for protium in the Me groups at positions 4 and 6 in D_2O solution, brought about by attack of base A^- on the neutral substrates Z or their conjugate acids ZH^+,† or on the latter's quaternary analogues ZQ^+ (as in 4 and 5). The quaternary compounds provide independent checks on the reactivities of the conjugate acids of compounds 1–3, which are presumed intermediates in the general-acid-catalyzed reaction paths of these compounds.

Exchange of the Me hydrogens in 1 and 2 in acidic and basic solution has been previously observed by Batterham, *et al.*[2]

RESULTS AND DISCUSSION

Comparison of positions 4 *and* 6 *in methyl substituted* 2-*pyrimidones*

The reaction of the exchanging Me groups with hydroxide ion was found to be strictly first-order in substrate and first-order in base (see Fig. 1 and 2 for typical results.) The exchange rates of the 4- and 6-Me groups in the trimethyl compound 1 in D_2O–DO^- are given in Table 1. It can be seen that the protons in the 6-Me group are about 25 times more reactive than those of the 4-Me group. The same effect is seen when the isomeric compounds 2 and 3 react with the same base

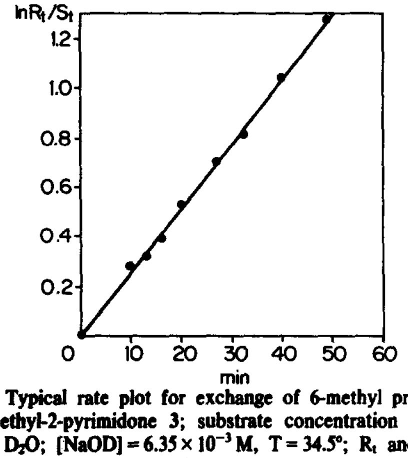

Fig. 1. Typical rate plot for exchange of 6-methyl protons in 1,6-dimethyl-2-pyrimidone 3; substrate concentration 0.1 g. in 1.5 ml. D_2O; [NaOD] = 6.35×10^{-3} M, T = 34.5°; R_t and S_t are areas under N–CH_3 and C–CH_3 signals at time t, respectively.

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†The kinetic quantity determined herein is actually $k_{ZD^+ + A^-}$. We retain the term paf, however, since the quotients in equation (1) are only slightly affected; the isotope effects on K_{ZH^+} and K_{HA} are comparable and the secondary isotope effect on $k_{ZH^+ + A^-}$ should be small. Likewise, irrelevant exchange processes involving hydrogen atoms at nitrogen sites have been ignored throughout.

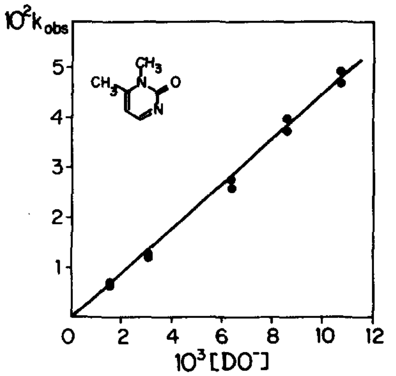
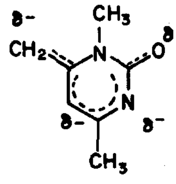


Fig. 2. Rate of exchange of 6-methyl protons in 1,6-dimethyl-2-pyrimidone 3 in D_2O/DO^-.

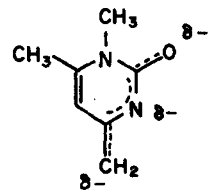
Table 1. Rate constants for the exchange of the C-methyl groups in methyl substituted 2-pyrimidones, 1, 2 and 3 in alkaline D_2O; $k = (-d[Z]/dt)/[Z][DO^-]$

Compound	k, M^{-1} min^{-1} 4-CH_3	k, M^{-1} min^{-1} 6-CH_3	k_{6-CH_3}/k_{4-CH_3}
1	0.076	1.86	24
2	0.22	-	20
3	-	4.45	

(Table 1); the specific rate constant for the reaction of hydroxide ion with the 1,6-dimethylpyrimidone 3 is some 20 times greater than with the 1,4-dimethyl isomer 2. (The half-lives for exchange of the two reactive Me groups in 1 determined by Brown et al.[2] in aqueous base also show the 6-Me group to be the more reactive but in their case the reactivity difference is somewhat less than we observe.) The greater kinetic acidity of the 6-Me group may be a result of the greater degree of charge delocalization in the ion produced by proton loss from this position; compare **Ia** and **Ib**.† With acetate ion as the base the 6-Me group is also the more reactive although the rate difference is now only a factor of 8 for reaction of the neutral substrates 2 and 3 (Table 2).



Ia



Ib

The general-acid-catalyzed path for 1–3 is characterized by a rapid equilibrium protonation of the substrate to give a cation, which upon proton loss from some other position in the molecule, produces an enol or analogous neutral molecule that then undergoes further reaction. Such compounds have been designated Type I compounds to distinguish them from those (Type II) that yield mesoionic intermediates when the cation is deprotonated.[1a] In general, the paf for Type I compounds becomes smaller the greater the rate of reaction of the neutral substrate with base. The reactivity of the isomers 2 and 3 is in line with this generalization since their k_{Z+A^-} values differ substantially and their $k_{ZH^++A^-}$ values only slightly (Table 2).

Comparison of alkylation and protonation as a means of activation.

The values of $k_{ZD^++A^-}$ shown in Table 2 for the reaction of the conjugate acids of 2 and 3 with acetate ion was obtained from an analysis of the data for the general-acid-catalyzed reaction in acetate buffers. The quaternary salt 4 provides us with a model for the conjugate acids of these two compounds, both of which are protonated at the digonal N atom to give the structures shown in Table 3. The rates of reaction of the three cations with the same base are there compared. It can be seen that the trimethyl cation 4 reacts at a rate not greatly different from those of the dimethyl cations $2H^+$

Table 2. Reaction of 1,4-dimethyl-2-pyrimidone 2 and 1,6-dimethyl-2-pyrimidone 3 in aqueous buffer

Compound	pK_{ZD^+}	k_{DA} $M^{-1}min^{-1}$	k_{A^-} $M^{-1}min^{-1}$	$k_{ZD^+ + A^-}$ $M^{-1}min^{-1}$	paf	buffer[a]
2	3.66[b]	0.080	1.0×10^{-3}	3.3	3300	acetate
3	3.91[c]	0.30	7.9×10^{-3}	6.9	870	acetate
		1.06	2.5×10^{-3}	2.1	850	formate

[a] The pK_{DA} values in D_2O of acetic acid and formic acid are 5.27 (ref. 14a) and 4.21 (ref. 14b), respectively.

[b] pK_{ZH^+} = 3.21 (ref. 6).

[c] pK_{ZH^+} = 3.38 (ref. 7).

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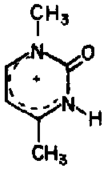
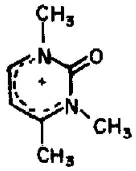
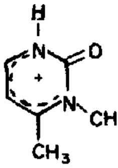
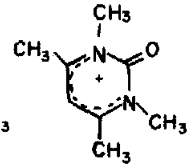
†It is curious that the analogous compounds to 2 and 3 with amino groups instead of methyl groups at the 4 and 6 positions show the same order of acid strength. These compounds, 1-methylcytosine and 3-methylcytosine, are isoelectronic with 2 and 3 and have pK_{HA} values for the amino groups of 16.7 and 13.4,[3] respectively, corresponding to a difference in equilibrium acidity of $2 \times 10.^3$ This rather large effect has been attributed principally to the difference in stability, not of the anions, but of the neutral molecules.[3]

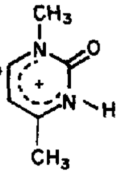
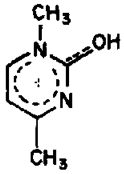
Table 3. Rate constants for reaction of the C-methyl groups of various cations with acetate ion in D_2O at 34.5°

	 **2H**$^+$	 **4**	 **3H**$^+$	 **5**
k, M^{-1} min^{-1}	3.3	5.1	6.9	4.7 (per C-methyl group)

and **3H**$^+$. Replacing an H atom with a Me group causes a small decrease in rate in one case and a small increase in rate in the other. In formate buffer similar results are obtained for **3H**$^+$ and **4**: $k_{ZH^+ + A^-} = 2.1\ M^{-1}\ min^{-1}$, and $k_{ZQ^+ + A^-} = 1.5\ M^{-1}\ min^{-1}$, respectively. Effects of comparable magnitude and variable direction were previously observed for creatinine when that compound's N atoms were protonated or alkylated.[4]

In the quaternary compound **5** the 4- and 6-Me groups are equivalent and, of course, undergo exchange at identical rates. The specific rate constant per Me group for the reaction of the cation with acetate ion is very near that for the reaction of **4** with the same base (Table 3), again showing that the effect of Me substitution is slight.

A vexing question sometimes arises when the mechanism of general acid catalysis is considered for substrates with more than one site of protonation. Does the reaction take place via the principal conjugate acid or via a minor, more reactive, form? In the present case the similarity in rates between the conjugate acids and their quaternary analogues suggests that the reaction does indeed take place via the ordinary N-protonated conjugate acid, e.g. **2H**$^+$, and not via minor tautomers, such as the O-protonated ion **6**.

2H$^+$  **6** 

In the absence of buffer but in the presence of traces of acid to repress reaction with hydroxide ion,† the quaternary salt **4** underwent exchange quite slowly. The pH of these reaction mixtures was, not surprisingly, difficult to control and was found to be between 2.5 and 4.0 in the several experiments that were conducted. The rate of exchange of the C-Me group under these conditions was $k = 5 \times 10^{-3}\ min^{-1}$ at 34.5° and was independent of pH, meaning that catalysis by water contributed only slightly (less than 5%) to the reactions in acetate buffer.[8]

Comparison of **paf** *and* **dpf**. An interesting comparison can be made of the activation that results from (a) protonating the substrate (**paf**) and (b) deprotonating the attacking base. The term deprotonating factor (**dpf**) has been suggested for the latter quantity.[1a] Scheme 1 shows the two catalytic routes for conversion of compound **3** to exchanging intermediates, with the reaction of neutral substrate with water being considered the uncatalyzed reaction for purpose of comparison.

Assuming, as seems reasonable from the results given in the preceding section, that a quaternary ion is a suitable surrogate for a conjugate acid one can compare rate constants for the competing rate-controlling steps leading to exchange. These are designated $k_{ZH^+ + H_2O}$ and $k_{Z + HO^-}$ in Scheme 1. The former has a value of approximately $5 \times 10^{-3}\ M^{-1}\ min^{-1}$ and the latter a value of approximately $5\ M^{-1}\ min^{-1}$ at 34.5°. Thus, removing a proton from the base, water, is roughly a thousand times more effective than adding a proton to the neutral substrate. This is in line with our general experience[1a] that the proton activating factor, **paf**, will be less than the deprotonating factor, **dpf**, *when the latter refers to proton loss from the basic centre itself.*

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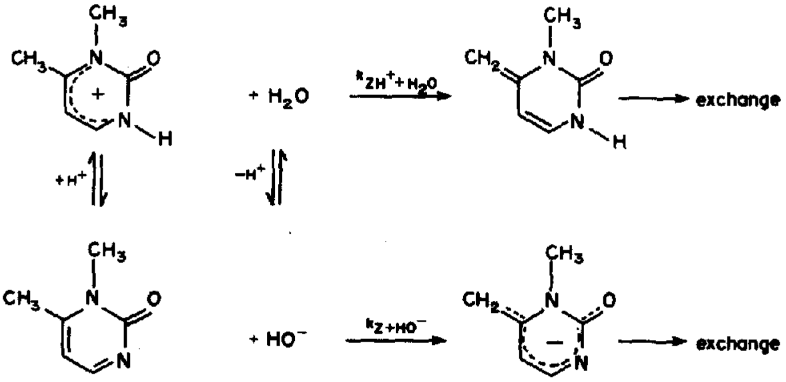
†Katritzky *et al.* have shown that quaternary salts such as **4** react with hydroxide ion to form covalent adducts.[5]



Scheme 1.

EXPERIMENTAL

Compound 1 was prepared by the method of Hale[9a] and recrystallized from benzene, m.p. 61–62°, lit. 63°. Alkylation with MeI gave the quaternary salt 5, which was recrystallized from EtOH-EtOAc, m.p. 192–194°, lit. 194.[9b]

Compound 2 was prepared by the method of Brown and Foster[10] and recrystallized from benzene-petroleum ether, m.p. 159–160°, lit. 156–157°.[10]

Compound 3 was prepared by the method of Brown and Paddon-Row,[11] m.p. 89–90°, lit. 89–90°. Compound 4 was prepared by dissolving 1.0 g of 3 in a mixture of 10 ml acetone and 7 ml MeI and stirring the soln at room temp. overnight. The salt crystallized from soln and could be recrystallized from EtOH, m.p. 139–140°. (Found: C, 31.55; H, 4.31; N, 10.47. Calc. for $C_7H_{11}N_2OI$: C, 31.60; H, 4.17; N, 10.53).

The exchange experiments were conducted in D_2O soln using a T-60 NMR spectrometer, essentially as previously described.[12] The rate of replacement of protium by deuterium in the exchanging C-Me groups was followed by using the non-exchanging N-Me absorption as reference. The quantity R_t/S_t is the ratio of the areas of the two peaks at time t.

The concentration of DO^- in alkaline soln was determined by titration with standard acid. In less basic media glass electrode measurements were used. Standard aqueous buffers were used for the calibration and pD values obtained from the relationship, pD = "pH reading" +0.40.[13]

The pK_{ZD^+} values of 2 and 3 in D_2O were determined spectrophotometrically by using the absorption maxima at 309 nm and 310 nm, respectively.

Acknowledgements—The financial assistance of the National Research Council of Canada is gratefully acknowledged.

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