

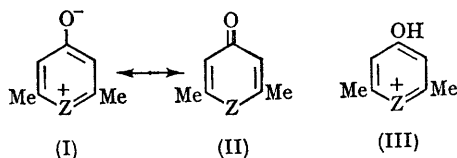
Acid-catalysed Hydrogen Exchange of 2,6-Dimethyl-4-pyridone, -pyrone, and -thiapyrone: Relative Effects of Heterocyclic Sulphur, Oxygen, and Nitrogen on Electrophilic Substitution Rates¹

By P. BELLINGHAM, C. D. JOHNSON, and A. R. KATRITZKY*

(School of Chemical Sciences, University of East Anglia, Norwich NOR 85C)

PREVIOUS studies have shown that the :NH^+ group in pyridinium ions has a very large deactivating effect towards electrophilic substitution, *e.g.*, nitration² and acid-catalysed hydrogen exchange.³ We now report the first quantitative study of the effects of :O^+ and :S^+ poles within a heterocyclic ring: they have an even greater deactivating effect than :NH^+ .

Because of the expected instability of unsubstituted or alkyl-pyrylium and -thiapyrylium salts under the vigorous conditions required for electrophilic substitution, we chose to study 2,6-dimethyl-4-pyrone and -thiapyrone. As their free bases (I \leftrightarrow II; a and b), these compounds are isoelectronic with the anion of 3,5-dimethylphenol (I \leftrightarrow II, d), whereas the corresponding heterocyclic conjugate acids (III; a and b) are isoelectronic with the free phenol (III d). The methyl groups serve both to activate the 3- and 5-positions in the heterocycles towards electrophilic substitution and to stabilise the ring against nucleophilic opening at the 2- and 6-positions.



a, Z=O; b, Z=S; c, Z=NH; d, Z=CH-

The heterocycles smoothly exchange the 3- and 5-hydrogen atoms for deuterium in D_2SO_4 , D_2O and

the rates were followed by the n.m.r. technique already described.¹ Rate profiles are shown in the Figure. The slight negative slopes of the corresponding rate profiles show that 2,6-dimethyl-4-pyrone and -thiapyrone undergo exchange as the free base under all the conditions examined. Although the pyridone analogue also reacts as free base at low acidities, it changes over to reaction on the conjugate acid at $H_0 < -3$ as shown by the rate profile slope of 0.35. 3,5-Xylenol exchanges as the anion (I \leftrightarrow II, d) at $\text{pD} \geq 3.5$ and as the neutral molecule (III d) at higher acidities.

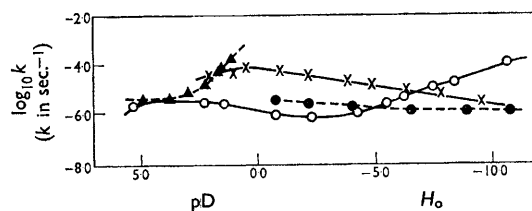


FIGURE. Rate profiles for hydrogen exchange for: 3,5-xylenol at 100° (\blacktriangle), 2,6-dimethyl-4-pyrone at 148° (\times), 2,6-dimethyl-4-thiapyrone at 148° (\bullet) and 2,6-dimethyl-4-pyridone at 108° (\circ).

The rate constants in the Table are all corrected to 100°, measurements on the pyrone and thiapyrone were made over the range 130–160°. Corrections for the concentration of free base were made assuming the $\text{p}K_a$ in D_2O at 20° to be 0.5 units higher than the known value in H_2O .⁴ No correction was made for variation in $\text{p}K_a$ or acidity with temperature.

TABLE
Kinetic data at 100° at $H_0 = 0$

	pK_a^a	Reaction on free base		Reaction on conjugate acid	
		$\log k^b$	k_{rel}	$\log k^b$	k_{rel}
2,6-Dimethyl-4-pyrone	-0.23 ^c	-6.1	$10^{-11.4}$	≤ -12	$< 10^{-8.7}$
„ -4-thiapyrone	0.56 ^c	-6.7	$10^{-12.0}$	≤ -12	$< 10^{-8.7}$
„ -4-pyridone	4.13 ^c	-1.5	$10^{-6.8}$	-7.5	$10^{-4.2}$
3,5-Xylenol anion	10^{-15}^d	+5.3	1	-3.5	1

^a At 20° in H_2O .

^b k in sec^{-1} .

^c Spectrophotometric measurements.

^d A. Albert and E. P. Serjeant, "Ionisation Constants of Acids and Bases," Methuen, London, 1962.

The relative k values show that in this series, whereas the substitution of ring CH by NH^+ lowers the reactivity at the *meta*-position by *ca.* 10^7 , substitution by O^+ and S^+ both deactivate by *ca.* 10^{12} . Comparison with our earlier data¹ for phenol and 4-pyridone shows that the two methyl groups activate xylenol and its anion by factors of *ca.* 10 , 2,6-dimethyl-4-pyridone by *ca.* 10^3 , and the 2,6-dimethyl-4-pyridone conjugate acid by *ca.* 10^4 . The corresponding activations for the pyrone free bases and conjugate acids are probably greater, perhaps *ca.* 10^5 and 10^6 , respectively.

The relative effects of NH^+ , O^+ , and S^+ in this six-membered-ring series show an interesting

parallelism with those of NH , O , and S in five-membered heteroaromatic compounds. Marino and his co-workers⁵ have shown that the relative rates are *ca.* $1:10^2:10^8$ for thiophen, furan, and pyrrole for trifluoroacetylation and molecular bromination in the α -position. Similar results, pyrrole \gg thiophen \gg furan, were reported by Mayer *et al.* for acid-catalysed hydrogen exchange in sulphuric acid.⁶

A value⁷ of 1.85 for σ_m^+ of $:NH^+$ implies $\rho = 3.78$ for the reaction which gives σ_m^+ for $:O^+$ and $:S^+$ as 3.0 and 3.2, respectively; these are the largest σ_m^+ values known.

(Received, August 21st, 1967; Com. 896.)

¹ For previous Paper, see P. Bellingham, C. D. Johnson, and A. R. Katritzky, *J. Chem. Soc. (B)*, 1967, in the press.

² C. D. Johnson, A. R. Katritzky, B. J. Ridgewell and M. Viney, *J. Chem. Soc. (B)*, 1967, in the press.

³ A. R. Katritzky and B. J. Ridgewell, *J. Chem. Soc.*, 1963, 3753.

⁴ E. Högfeldt and J. Bigeleisen, *J. Amer. Chem. Soc.*, 1960, **82**, 15.

⁵ S. Clementi, F. Genel and G. Marino, *Chem. Comm.*, 1967, 498; P. Linda and G. Marino, *ibid.*, p. 499.

⁶ K. Schwetlick, K. Unverferth, and R. Mayer, *Z. Chem.*, 1967, **7**, 58.

⁷ G. P. Bean and A. R. Katritzky, *J. Chem. Soc. (B)*, 1967, in the press.