Acid Catalysis of Carbon–Hydrogen Bond-breaking in α-Heterocyclic Ketones: A Brönsted Treatment of Catalyst Binding and Reactivity

Alain Argile, A. R. Edwin Carey, Rory A. More O'Ferrall,* Brian A. Murray, and Michael G. Murphy

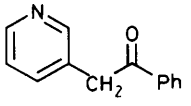
Department of Chemistry, University College, Belfield, Dublin 4, Ireland

The relative effectiveness of O- and N-protonation in catalysing C–H bond-breaking in α-heterocyclic ketones is described by an equation based on rapid binding of catalyst to substrate and a Brönsted–Marcus treatment of the catalytic steps; the equation shows that efficient catalysis reflects strong binding of the catalyst to both the reactant and the product of the uncatalysed reaction.

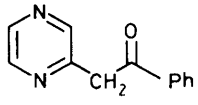
Does acid catalysis of C–H bond-breaking accompanying enolisation of the heterocyclic ketones (**1**)—(**3**) occur with protonation of the oxygen atom of the ketone or the nitrogen atom of the heterocycle? The two possibilities are shown for 2-phenacylpyrazine (**2**) in Scheme 1 where it is seen that N-protonation is followed by a nitrogen-to-oxygen hydrogen shift. Plausibly, N-protonation is favoured by the greater basicity of nitrogen and disfavoured by formation of an enamine (or zwitterion) as additional intermediate.

Experimentally the possibilities are distinguished by comparing observed rate constants (k_H, Table 1) with measurements for related ketones not containing a nitrogen atom. The latter are quite insensitive to the structure of the ketone,[1,2] and for acyclic structures $k_H = 1.0 \times 10^{-5}$ dm^3 moles^{-1} s^{-1} within a factor of 5. On this basis (**1**), (**2**), and (**3**) react respectively 10^6, 10^5, and 200 times faster than expected for O-protonation. Also, Cox[3] has shown that rates of reaction of N-protonated and N-methylated 4-acetylpyridines (**3**) with water are nearly identical (k_{NH^+}/k_{NMe^+} 1.2), and we have found the same for 3-phenacylpyridine (**1**) (k_{NH^+}/k_{NMe^+} 1.3). It follows that all three substrates react *via* the N-protonation pathway.

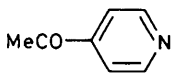
The preference for N-protonation reflects a thermodynamic advantage for this reaction. This is apparent from a Gibbs Free Energy diagram (Figure 1), which shows uncatalysed and O-protonation pathways as full lines and the N-protonation pathway as a dashed line. The uncatalysed transfer of a proton from ketone (K) to base yields an unstable enolate anion (E^-). Under acidic conditions, prior protonation on oxygen yields the more stable enol (OH), but at the expense of



(**1**)



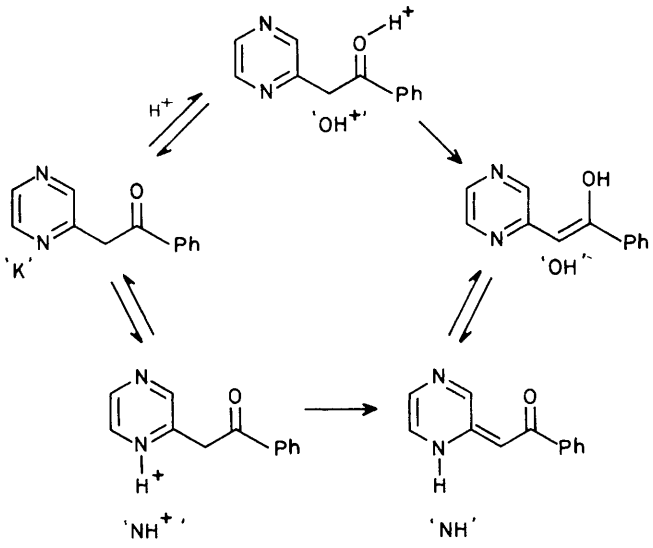
(**2**)



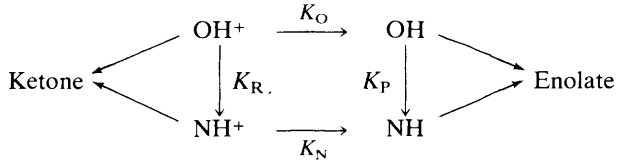
(**3**)

Table 1. Observed protonation rate constants (k_H) and pK_a values.

	(**1**)	(**2**)	(**3**)
$10^2 k_H$/l mol^{-1} s^{-1}	8.1	1.2	0.0014
pK_a	5.03	0.5	3.43



Scheme 1



Scheme 2. Equilibrium constants for reaction pathways of O and N protonation: acid dissociation constants on the wings of the diagrams are $K_a^{OH^+}$ and $K_a^{NH^+}$ (left) and K_a^{OH} and K_a^{NH} (right). The arrows indicate reaction directions referred to by equilibrium constants.

forming an unstable O-protonated ketone intermediate (OH^+). The N-protonation pathway avoids both high energy species (E^- and OH^+) and although the product in this case is an enamine (NH), which is less stable than the enol, this is compensated by the greater stability of the N-protonated (NH^+) over the O-protonated (OH^+) reactant.

The kinetic advantage of N-protonation may be expressed thermodynamically using Brönsted's or Marcus's equation[4] to convert rate constants to equilibrium constants. Then the relative effectiveness of N- and O-protonation is given by equation (**1**), in which K_N and K_O are equilibrium constants for carbon–hydrogen bond-breaking, and $K_a^{OH^+}$ and $K_a^{NH^+}$ are ionisation constants, for O- and N-protonated substrates respectively. The Brönsted equation refers to the carbon acids OH^+ and NH^+ and $\bar{\alpha}$ is the Brönsted exponent or, in Marcus's equation (in which α is variable), the average of Brönsted exponents, for the two reactions. If we recognise that the ionisation constants correspond to (inverse) proton binding constants, we see that the catalysis is treated as a binding step, followed by a catalytic step in which the bound catalyst acts as a substituent upon the rate and equilibrium constants of the uncatalysed reaction.

Using the normal relationship between substituent and equilibrium constants[5] we may replace K_N/K_O by the ratio of equilibrium constants K_R/K_P for OH to NH tautomerisation of protonated reactants and products (Scheme 2) which in turn corresponds to ratios of proton binding (or ionisation) constants in reactants and products ($K_R = K_a^{OH^+}/K_a^{NH^+}$ and $K_P = K_a^{OH}/K_a^{NH}$). These relationships are intuitively obvious

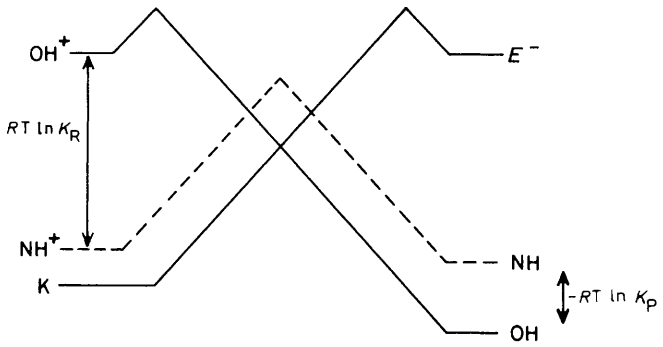


Figure 1. Gibbs free energy–reaction co-ordinate diagram for enolisation of a heterocyclic ketone, K. NH^+ and OH^+ denote N- and O-protonated ketone, respectively, and NH, OH, and E^-, enamine (or zwitterion), enol and enolate anion. Kinetic barriers to proton transfer between O and N atoms are assumed to be small. (——) Uncatalysed and O-protonation pathways; (– – –) N-protonation pathway.

and are formally implied by the thermodynamic cycle of Scheme 2. They allow us to rewrite equation (1) as equation (2)

$$k_{NH}/k_{OH} = (K_a^{OH^+}/K_a^{NH^+})(K_N/K_O)^{\bar{\alpha}} \quad (1)$$

$$k_{NH}/k_{OH} = K_P^{\bar{\alpha}}\, K_R^{(1-\bar{\alpha})} \quad (2)$$

Bearing in mind the interpretations of K_R and K_P in terms of proton binding, equation (2) shows that efficient catalysis reflects strong binding of the catalyst to both reactants and products of the uncatalysed reaction, with the balance of reactant and product contributions controlled by the Brönsted exponent. We commonly speak of a good catalyst binding strongly to the transition state; equation (2) translates 'binding to a transition state' into reactant and product contributions.

Equation (**2**) is useful for analysing examples of catalysis and for assessing deviations from normal (or 'ideal')[5] behaviour. For semi-quantitative analysis, a simple but often effective approximation (*e.g.* see ref. 6) is to take $\alpha = 0.5$. Then for 3-phenylacylpyridine (**1**), combining the pK_a values of 8.8, 8.4, and 5.03, for enol, zwitterion, and N-protonated ketone, respectively, with an assumed pK_a of −6 for O-protonated ketone, leads to the prediction that N-protonation will be favoured over O-protonation by a factor of $10^{(10.63/2)} \simeq 10^5$, which is in satisfactory agreement with the value of 10^6 deduced above. On the other hand, attempting to predict relative rates for (**1**), (**2**), and (**3**) (assuming equal rates for the O-protonation pathways) leads to the incorrect order (**1**) > (**3**) > (**2**), and quantitative values (1: 0.006: 3×10^{-2}) in poor agreement with the observed rates ($1 : 0.12 : 2 \times 10^{-4}$; *cf.* k_H values above).

Thus the equation underestimates the reactivity of phenacylpyrazine (**2**) and overestimates that of 4-acetylpyridine (**3**). Interestingly, this is the expected result of neglecting variations in (Marcus's) intrinsic kinetic barrier, arising from 'imbalance' of charge development at the transition state.[6] Ionisations of ketones are known to show weaker delocalisation of charge from the α-carbon atom to keto oxygen atom in the transition state than in enolate product,[7] and this leads to an enhanced effect of substituents on reactivity at the

α-carbon [(**2**) compared with (**1**)], and an attenuated effect at the carbonyl group [(**3**) compared with (**1**)], as observed here.

Received, 6th May, 1987; Com. 614

References

1 J. Toullec, *Adv. Phys. Org. Chem.*, 1982, **18**, 1.
2 A. R. E. Carey, B. Murray, R. A. More O'Ferrall, and M. G. Murphy, to be published.
3 B. G. Cox, *J. Am. Chem. Soc.*, 1974, **96**, 6823.
4 R. A. Marcus, *J. Phys. Chem.*, 1968, **72**, 891.
5 A. Argile, A. R. E. Carey, G. Fukata, M. Harcourt, R. A. More O'Ferrall, and M. G. Murphy, *Isr. J. Chem.*, 1985, **26**, 303.
6 C. F. Bernasconi, *Tetrahedron*, 1985, **41**, 3219; W. P. Jencks, *Chem. Rev.*, 1985, **85**, 511.
7 R. P. Bell and S. Grainger, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1367.