Mechanistic Studies in the Chemistry of Urea. Part I. Reaction with Pentane-2,4-dione (Acetylacetone)

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Urea, methylurea, and *NN'*-dimethylurea react with pentane-2,4-dione in acidic solution to give hydroxypyrimidines (pyrimidones). Kinetic and spectral evidence suggests that the mechanism of reaction is acid-catalysed attack of urea on the keto–enol form of pentane-2,4-dione followed by cyclisation. This is confirmed by examination of the reactions of 1,1,1-trifluoro- and 1,1,1,5,5,5-hexafluoro-pentane-2,4-dione with methylurea. Absence of an enolizable hydrogen at the 3-position in pentane-2,4-dione completely changes the course of the reaction.

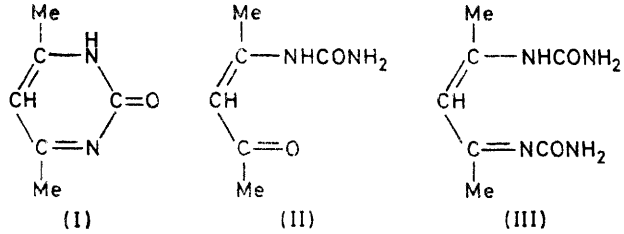
UREA has a unique place in the history of organic chemistry and there has recently been a full examination of the mechanism of its formation from cyanic acid.[1] However, there have been few other mechanistic studies of its reactions apart from hydrolysis. Urea may be looked upon as an amide and, like other amides, it is resistant to nonenzymatic hydrolysis.[2] On the other hand, it is hardly a typical amide and its lack of reactivity has been ascribed to a type of aromaticity.[3] In some circumstances urea shows a surprising readiness to react, as with pentane-2,4-dione. Here it appears to behave more like hydrazine or hydroxylamine than an amide, although the similarity is more apparent than real. This study is concerned with the mechanism of this reaction.

RESULTS AND DISCUSSION

In the presence of acid the reaction of urea and pentane-2,4-dione yields what has been called 2-hydroxy-4,6-dimethylpyrimidine,[4] although it exists predominantly in the oxo-form (I).[5] Two other products are possible, (II) and (III), and their formation will be discussed later. For a study of the kinetics of this reaction in aqueous solution urea and hydrochloric acid were present in large excess. The spectral changes accompanying the reaction are shown in Figure 1 and the final spectrum is

[1] A. Williams and W. P. Jencks, *J.C.S. Perkin II*, 1974, 1753.
[2] W. H. R. Shaw and D. G. Walker, *J. Amer. Chem. Soc.*, 1956, **78**, 5769; G. Travagli, *Gazzetta*, 1952, **82**, 528.
[3] P. Gund, *J. Chem. Educ.*, 1972, **49**, 100.
[4] P. N. Evans, *J. prakt. Chem.*, 1892, **46**, 352; O. Stark, *Ber.*, 1909, **42**, 699.
[5] J. R. Marshall and J. Walker, *J. Chem. Soc.*, 1951, 1004.

identical with that of the salt of (I). Formation of (I) must occur in two major steps: reaction of urea with one



carbonyl group of the diketone to give (II), followed by cyclisation to give (I). The tight isosbestic points at 240 and 275 nm, shown in Figure 1, indicate that there is only one slow step in the overall process. The absorbance due to pentane-2,4-dione disappears as that due to (I) appears. Therefore, the mechanism cannot be rapid formation of (II) followed by slow cyclisation. With the

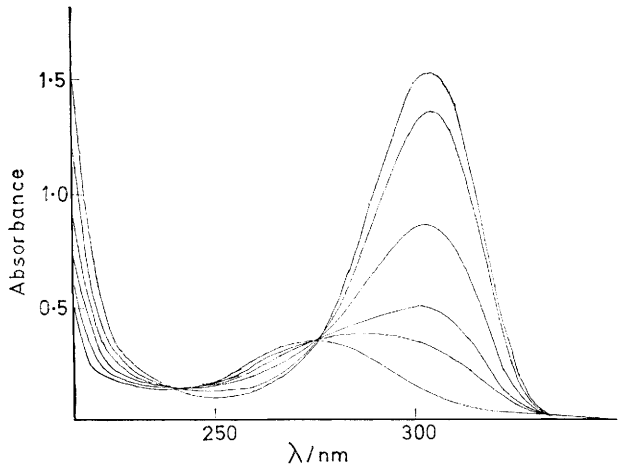
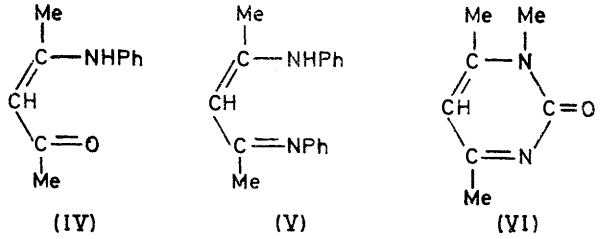


FIGURE 1 Spectral changes occurring after *ca.* 1, 15, 30, 70, and 240 min during the reaction of urea and pentane-2,4-dione: [urea] = 0.50M; [HCl] = 5M; [dione] = *ca.* 10^{-3}M

mechanism excluded, two possibilities remain: (a) rapid, equilibrium formation of (II) at low concentration followed by slow cyclisation, or (b) slow formation of (II) followed by rapid cyclisation. The latter is favoured as reaction of urea and pentane-2,4-dione to give (II) is a bimolecular process and unlikely to be faster than cyclisation, which is an intramolecular process. Bruice and Benkovic [6] have shown that when a reaction changes from intermolecular to intramolecular it is greatly enhanced owing to a decrease in the magnitude of the entropy change. It is difficult to compare rate constants directly as the units are different, but the effect is a very large one and we can be reasonably certain that formation of (II) is the slow step in this reaction.

In other cases where cyclisation can occur it has been found impossible to isolate the initial product, *e.g.* pentane-2,4-dione reacts with semicarbazide to give 3,5-dimethylpyrazole-1-carboxamide [7] and with 2,4-dinitrophenylhydrazine to give 1-(2,4-dinitrophenyl)-3,5-dimethylpyrazole.[8] However, when cyclisation is not possible the 1 : 1 adduct can be readily isolated although further reaction may occur, *e.g.* aniline reacts with pentane-2,4-dione to give (IV), which reacts with more aniline to give (V).[9] These examples all suggest that cyclisation is a rapid process.



The rate of reaction was examined as a function of urea concentration (Figure 2). Similar results were obtained with methylurea, where the product is 1,4,6-trimethylpyrimidin-2(1*H*)-one (VI).[10] There is a linear relationship between k_{obs} and the stoicheiometric urea concentration. For further analysis of the results it is necessary to consider the acid–base equilibrium of urea and methylurea. Urea is a weak base which protonates on oxygen.[11] At the concentrations used in this study variation of the stoicheiometric concentration of urea will affect, not only the free urea concentration ([U]), but also the acidity. From a knowledge of the pK_a of urea it was possible to calculate these quantities. The value

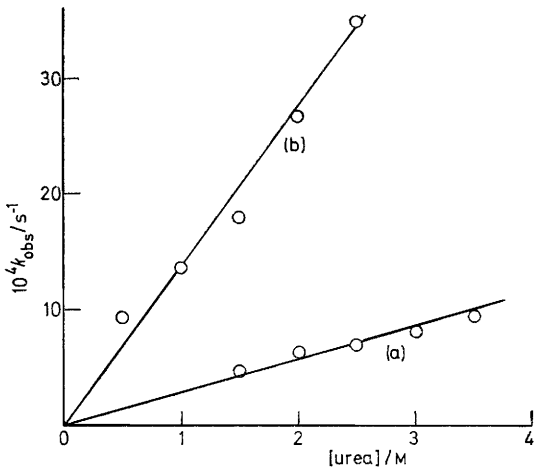


FIGURE 2 Variation of k_{obs} with stoicheiometric (a) urea or (b) methylurea concentration in reaction with pentane-2,4-dione at 40°: [HCl] = 5M; [dione] = *ca.* 10^{-3}M

at 40° has not been measured but at ambient temperatures several workers [12] have reported a value of 0.1.

[6] T. C. Bruice and S. J. Benkovic, *J. Amer. Chem. Soc.*, 1963, **85**, 1.
[7] T. Posner, *Ber.*, 1901, **34**, 3980.
[8] O. L. Brady, *J. Chem. Soc.*, 1931, 759.
[9] W. Koenigs and A. Mengel, *Ber.*, 1904, **37**, 1322; G. Scheibe, *ibid.*, 1923, **56**, 137.
[10] R. Hale, *J. Amer. Chem. Soc.*, 1914, **36**, 104.
[11] R. Stewart and L. J. Muenster, *Canad. J. Chem.*, 1961, **39**, 401.
[12] (*a*) N. F. Hall, *J. Amer. Chem. Soc.*, 1930, **52**, 5115; (*b*) J. Bell, W. A. Gillespie, and D. B. Taylor, *Trans. Faraday Soc.*, 1943, **39**, 137; E. P. Parry, D. H. Hern, and J. G. Burr, *Biochim. Biophys. Acta*, 1969, **182**, 570.

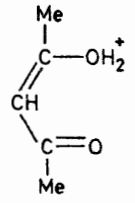
Farlow and Moodie [13] deduced a value of −0.15 at 100°. It is not unreasonable, then, to take the value of 0.1 for analysis of the present results. The pK_a of methylurea is 0.9.[12a]

The acid concentration is outside the ideal range and this complicates analysis of the protonation equilibrium. Moodie *et al.*[14] assumed that protonation of urea follows the acidity function h_0 and successfully analysed their kinetic data. However, protonation of phenylurea in sulphuric acid is known [15] to follow h_A and we have used this acidity scale [16] in the present circumstances. The calculations show that in all cases urea and methylurea are essentially completely protonated. The low concentration of unprotonated urea is, therefore, $K_a[UH^+]/h_A$, where $[UH^+]$ is the same as the stoicheiometric concentration of urea, $[U]_{st}$.

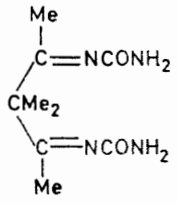
The change in k_{obs} as the urea concentration, and hence the acidity changes is consistent with reaction between one protonated and one unprotonated species. The most likely pair is free urea and protonated diketone, although this is kinetically indistinguishable from protonated urea and free diketone. However, it is difficult to imagine *O*-protonated urea attacking a polarised carbonyl group and the former process is favoured.

There is one further complication: pentane-2,4-dione can exist either in the diketo or the keto–enol form. Neat pentane-2,4-dione is predominantly in the keto–enol form [17] but in acid solution the proportion depends upon the pH. The work of Schwarzenback and Wittner [18] indicates that, under the present experimental conditions, little of the keto–enol form is present but, as the keto–enol tautomerism is much faster than reaction with urea, this may still be the form undergoing reaction. Both forms of pentane-2,4-dione may be protonated and the keto–enol form is the more basic one.[18]

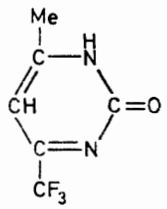
There are grounds for believing that it is the protonated keto–enol (VII) form which reacts with urea. 3-Methylpentane-2,4-dione reacts with methylurea to give the expected cyclic product and the spectral changes are similar to those shown in Figure 1. However, 3,3-dimethylpentane-2,4-dione, where formation of a keto–enol form is not possible, undergoes an entirely different reaction to give (VIII). A similar change of product has been reported for the reaction with *o*-phenylenediamine.[19] Of course, the presence of the two methyl groups does prevent proton transfer to give a cyclic product of type (I), so the evidence is not unambiguous. The introduction of a 3-methyl group in pentane-2,4-dione reduces the rate of reaction with urea by a factor of three. This could be a steric effect but it may reflect the smaller proportion of the keto–enol form.[20] Other compounds which do not have a substantial amount of the enol form present (acetone and hexane-2,5-dione) do not react with urea at all under the experimental conditions used in this



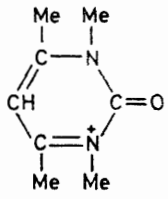
(VII)



(VIII)



(IX)



(X)

study. If the reactive species were the diketo-molecule then reaction with urea is analogous to the reaction of hydroxylamine and acetone, which is addition across the double bond to form a carbinolamine. Here the rate-determining step at neutral pH is acid-catalysed dehydration of the carbinolimine.[21] With 4-chlorobenzaldehyde at pH 8 it is possible to observe the disappearance of the aldehyde as dehydration is slow.[22] However, the entirely different experimental conditions (low pH and high urea concentration) used in the reaction of urea and pentane-2,4-dione suggests that there is a different rate-determining process. We believe that this is nucleophilic substitution of urea on protonated pentane-2,4-dione in the keto–enol form, with water as the leaving group. The complete mechanism is shown in the Scheme.

Some confirmation of this comes from a study of the reactions of urea with fluorinated diketones. If reaction involves addition across the carbonyl double bond then 1,1,1,5,5,5-hexafluoropentane-2,4-dione should react faster than pentane-2,4-dione as the fluorine atoms will increase polarisation of the carbonyl group. In fact no reaction at all occurs. Fluorination increases the proportion of the keto–enol form,[20] but the effect on protonation of the hydroxy-group to give water as the leaving group will be much greater. Thus, the lack of reactivity can be understood in terms of the proposed mechanism. There is reaction with 1,1,1-trifluoropentane-2,4-dione to give (IX) but the reaction rate is reduced by a factor of seven. This is consistent with the proposed mechanism.

[13] D. W. Farlow and R. B. Moodie, *J. Chem. Soc.* (*B*), 1971, 407.
[14] V. C. Armstrong, D. W. Farlow, and R. B. Moodie, *J. Chem. Soc.* (*B*), 1968, 1099.
[15] J. W. Barnett and C. J. O'Connor, *J.C.S. Perkin II*, 1973, 1331.
[16] K. Yates and J. C. Riordan, *Canad. J. Chem.*, 1965, **43**, 2328.
[17] J. B. Conant and A. F. Thomson, *J. Amer. Chem. Soc.*, 1932, **54**, 4039.
[18] G. Schwarzenback and E. Felder, *Helv. Chim. Acta*, 1944, **27**, 1044.
[19] S. E. Drewes and P. C. Coleman, *Tetrahedron Letters*, 1975, 91.
[20] G. Allen and R. A. Dwek, *J. Chem. Soc.* (*B*), 1966, 161.
[21] W. P. Jencks, *J. Amer. Chem. Soc.*, 1959, **81**, 475.
[22] J. E. Reimann and W. P. Jencks, *J. Amer. Chem. Soc.*, 1966, **88**, 3973.

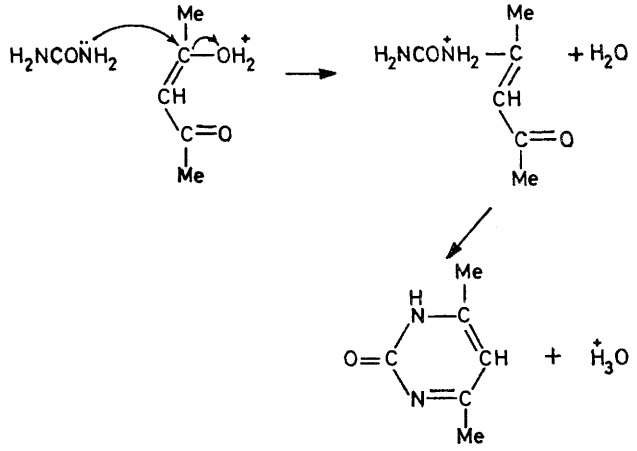
We can now examine the kinetics of the proposed reaction scheme. For the slow step the rate is $k[KH^+][U]$, where KH^+ is protonated diketone. Little is known about the acid–base equilibrium of a diketone and, therefore, let us say that its protonation follows an unspecified acidity scale h. The concentration of the protonated form is then $[K]h/K'_a$ and, as protonation is slight, [K] is the same as the stoicheiometric concentration of diketone, $[K]_{st}$. K'_a Is the acid dissociation constant for (VII). Substitution in the rate equation gives (1). As the reaction is of the first order in diketone the observed

$$\text{rate} = {}^{k}[K]_{st}[U]_{st}K_a h/K'_a h_a \qquad (1)$$

rate is given by (2). Therefore k_{obs} will vary according to the ratio of the two acidity functions as well as $[U]_{st}$. If

$$k_{obs} = {}^{k}[U]_{st}K_a h/K'_a h_a \qquad (2)$$

h is similar to h_A, and in moderately dilute solution acidity functions do not differ very much, then k_{obs} is a linear function of $[U]_{st}$. This is the behaviour shown in



SCHEME

Figure 1 and so the kinetics are consistent with the proposed scheme.

We report a number of miscellaneous observations. *NN'*-Dimethylurea reacts to give (X) at a rate similar to that of urea. There is a reaction with *NN*-dimethylurea but the spectral changes are entirely different and no product could be isolated. Thiourea reacts readily with pentane-2,4-dione to give 4,6-dimethyl-2-mercaptopyrimidine [23] at a rate which is similar to that of urea, but there was no reaction with guanidinium chloride. Guanidinium carbonate in water reacts readily to give 2-amino-2,4-dimethylpyridine [24] and it is probable that we observed no reaction because high acid concentration removes any free guanidine, which is further support for the proposed scheme.

With a large excess of urea in the preparative procedure white crystals identified as (II) were obtained. In acid solution the spectrum of (III) was identical with that of (I) and rapid cyclisation must occur. It appears that (III) forms only when it is precipitated because of its low solubility and does not play any part in the formation of (I) in solution. It was not possible to isolate (II) although many different experimental conditions were tried.

EXPERIMENTAL

Materials.—Urea and hydrochloric acid were AnalaR grade. Other compounds were laboratory grade and distilled or recrystallised before use. 3-Methyl- [25] and 3,3-dimethyl-pentane-2,4-dione [26] were prepared by known methods.

Products.—Pyrimidones and related compounds were made by the method of Kosolapoff and Roy [27] and were identified by mass spectral and/or elemental analysis. The structures of the salts of 4,6-dimethyl-, 1,4,6-trimethyl-, and 1,3,4,6-tetramethyl-pyrimidin-2(1*H*)-one, were confirmed by ^{1}H n.m.r. spectroscopy.

Kinetics.—One drop of an aqueous solution of the diketone was added to a urea–acid buffer contained in a cuvette in a thermostatted cell holder (40°) of a Unicam SP 700 spectrometer. The variation of absorbance (urea, 303 nm; methylurea, 306 nm) with time was monitored and the first-order rate constants were calculated by the Kzedy–Swinbourne [28] method. Spectra were recorded on a Unicam SP 800 spectrophotometer with a thermostatted block and in some cases rate constants were calculated from these spectra. Values of h_A were obtained by interpolation of published data.[16]

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[26] C. Mao, F. C. Frostick, E. H. Man, R. M. Manyik, R. L. Wells, and C. R. Hauser, *J. Org. Chem.*, 1969, **34**, 1425.
[27] G. M. Kosolapoff and C. H. Roy, *J. Org. Chem.*, 1961, **26**, 1895.
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