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(14) The technical assistance of James Blackbourn and James Du Chateau is acknowledged.

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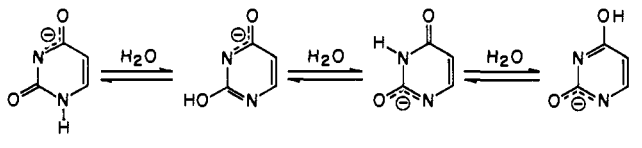
Bifunctional Proton Transfer of the Conjugate Base of Uracil Compared with That of Imidazole in Aqueous Solution[1]

Sir:

Using dynamic NMR techniques,[2] we have observed that the conjugate base of uracil (UH^-, eq 1) undergoes remarkably fast bifunctional proton transfer with water participation, and have studied the reaction mechanism shown in eq 1. In



(1)

^{17}O-enriched water, at pH 8.3–9.3, proton exchange between water molecules at 25° follows the rate law (eq 2).[3]

$$\frac{1}{\tau_W} = \frac{R_W}{2[H_2O]} = 2.1 \times 10^9[OH^-] + \frac{(1.1 \pm 0.2) \times 10^8}{2[H_2O]}[UH^-] \quad (2)$$

The first term in eq 2 is due to hydroxide-catalyzed reaction;[3] the second, with $k = (1.1 \pm 0.2) \times 10^8\ s^{-1}$, involves catalysis by UH^-. k is 300 times greater than the known rate constant k_f for base dissociation (eq 3),[4] and is enormously greater than any plausible rate constant for acid dissociation of UH^-.[5]

$$UH^- + H_2O \underset{k_r}{\overset{k_f}{\rightleftharpoons}} UH_2 + OH^- \quad (3)$$

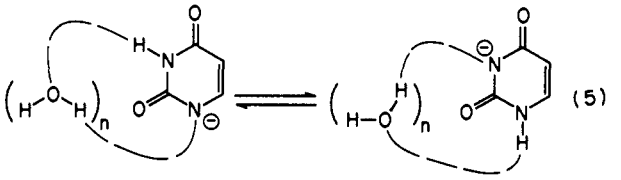
Further consistent evidence was obtained from a kinetic study of NH proton exchange between uracil (UH_2) and water in the pH range 6–8. Assuming that $k \approx 10^8\ s^{-1}$, we may expect that in each reversible cycle $UH_2 \rightleftarrows UH^-$, *both* NH protons of UH_2 exchange with water protons. The experimental rate law for $1/\tau_{NH}$ is given in eq 4.

$$\frac{1}{\tau_{NH}} = \frac{R}{2[UH_2]} = k_r[OH^-] + k_7[UH^-] \quad (4)$$

If both NH protons of UH_2 exchange in each cycle, R must be interpreted as the molar rate of exchange of UH_2; k_r is defined in eq 3, and k_7 is the rate constant for proton transfer between UH_2 and UH^- with water participation.[2] Values obtained at 25° are: $k_r = (1.2 \pm 0.2) \times 10^{10}\ s^{-1}\ M^{-1}$; $k_7 = (2.1 \pm 0.4) \times 10^7\ s^{-1}\ M^{-1}$. k_r is in good agreement with the value, $0.98 \times 10^{10}\ s^{-1}\ M^{-1}$, obtained by relaxation spectrometry at 20°.[4] If only one NH proton of UH_2 were exchanging in each cycle (i.e., if $k < 10^6\ s^{-1}$), the right-hand side of eq 4 would be equal to $2/\tau_{NH}$, and the value inferred for k_r would be inconsistent with that obtained by relaxation spectrometry.

The NH-to-H_2O chemical shift required in the above experiments was found by direct observation in 80% H_2O–20% D_2O at pH 4 to be 6.1 ppm. The NH protons of uracil are downfield from water and form a single featureless resonance, similar to that reported for UH_2 in dimethyl sulfoxide.[6]

We believe that the high rate constant k represents largely the specific rate of bifunctional proton transfer with water participation in UH^-. This process could be an uninterrupted proton transfer between N_1 and N_3 as in eq 5, or a stepwise

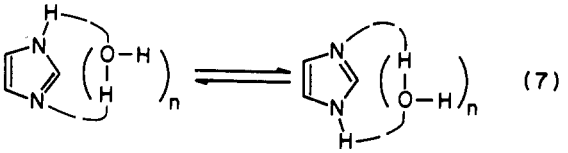


(5)

water-assisted tautomerization involving the carbonyl oxygen atoms, as in eq 1. To distinguish between these possibilities, we measured proton exchange rates in aqueous solutions of imidazole (Im) in ^{17}O-enriched water at pH 7.0–8.2. The results obtained at 25° are represented by the rate law (eq 6).

$$\frac{1}{\tau_W} = \frac{R_W}{2[H_2O]} = 1.9 \times 10^9[OH^-] + 2.7 \times 10^9[H_3O^+] + \frac{k}{2[H_2O]}[Im] + \frac{1.3 \times 10^8}{2[H_2O]}[Im][ImH^+] \quad (6)$$

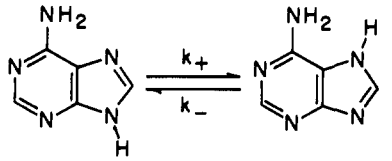
In the present context, only the term proportional to [Im] is of interest. The value obtained for k is $(1.5 \pm 0.5) \times 10^6$. Although k is small compared to the other rate constants, the term accounts for as much as 28% of $1/\tau_W$ in these experiments and is, statistically, highly significant.[8] k is much greater than the known rate constant for base dissociation,[9] and therefore probably represents bifunctional proton transfer with water participation according to eq 7. Note, however, that the rate



(7)

constant for eq 7 is smaller by two orders of magnitude than that obtained for the analogous kinetic process of UH^-.

While this work was in progress, Dreyfus et al.[10] reported a kinetic study of the tautomerization of adenine in aqueous solution. For the uncatalyzed process (eq 8), they report k_+



(8)

$= 50\ s^{-1}$, $k_- = 160\ s^{-1}$. These rate constants, which may include reaction without water participation, are very much smaller again than that obtained for imidazole.

Returning to the reaction mechanism for UH^-, it seems clear that the presence of the C=O groups brings about a marked enhancement of the rate of bifunctional proton transfer with water participation, which supports the reaction mechanism shown in eq 1.

References and Notes

(1) Work supported by the National Science Foundation.
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(8) The rate constant for OH^--catalyzed reaction is listed as $2.1 \times 10^9\ s^{-1}\ M^{-1}$ in eq 2, differing by 10% from that in eq 6. The discrepancy provides an index of the good consistency with which rate constants can be measured, in spite of the complicated kinetics.
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Synthesis of L-Lysine. Simultaneous Resolution/Racemization of α-Amino-ε-caprolactam[1]

Sir:

In recent years there has been some activity[2] concerned with the resolution of α-amino-ε-caprolactam (ACL), an important precursor in the chemical synthesis of L-lysine. Of particular interest are the resolution methods relying on kinetically controlled crystallization[3] of one enantiomer on seed crystals of the same enantiomer. Generally this type of resolution can be carried out only if the racemic modification exists as a true racemic mixture, rather than a racemic compound or racemic solid solution, in the solid phase.[3] In the case of ACL, several salts, such as the hydrochloride,[2b] hydrobromide,[2g] β-naphthalenesulfonate,[2e] and α-amino-β-naphthalenesulfonate,[2e] meet this requirement and have been resolved in this manner. Earlier work in this laboratory[2c] had shown that the coordination complex of ACL with nickel(II) chloride of empirical formula **1** can also be resolved by kinetically controlled crystallization from ethanol solution induced by seed crystals of formula **2** or **3**. It had also been shown[4] that optically active ACL can be racemized by heating in alcohol solution with catalytic amounts of nickel(II) chloride. These facts encouraged us to attempt the resolution of DL-ACL by preferential crystallization of **2** under conditions of simultaneous racemization of D-ACL in solution. Such a process would theoretically transform all of the DL-ACL to **2**[5] and could be of practical interest if carried out at a reasonably high rate.[9]

$(DL\text{-ACL})_3NiCl_2$ $(L\text{-ACL})_3NiCl_2 \cdot EtOH$
1 **2**

$(D\text{-ACL})_3NiCl_2 \cdot EtOH$
3

We wish to report that the nickel(II) chloride catalyzed racemization of optically active ACL in alcohol solution is greatly accelerated by alkoxide ions, provided that the molar ratio of ACL to nickel(II) is maintained above ~3.5:1.[10] Moreover, resolution of DL-ACL from supersaturated ethanol solutions by means of kinetically controlled crystallization induced by seed crystals of **2** can take place under these racemization conditions. The process is carried out most conveniently at the boiling point of the solution (~80°). This mode of operation allows continuous removal of solvent and results in relatively high conversion of DL-ACL to crystalline **2**. In a typical experiment DL-ACL, 5.40 g (42 mmol), was dissolved in 25 ml (10.5 mmol) of 0.42 M ethanolic nickel(II) chloride at reflux and 0.72 ml (1.58 mmol) of 2.19 M ethanolic sodium ethoxide was added to the resulting dark blue solution. A small amount of sodium chloride that formed was removed by filtration. Seed crystals of **2**, $[\alpha]^{25}D$ −23.3° (*c* 4, 1 N hydrochloric acid[11]), average diameter 3.6 μm, 1.50 g (26.8 mmol), were added to the filtrate, and the mixture was boiled gently under nitrogen atmosphere with slow mechanical stirring. An ethanol solution (30 ml) containing 4.60 g (36 mmol) of DL-ACL and 11.6 mmol of nickel(II) chloride was added dropwise to the reaction mixture during 1.5 h while the overall level of the mixture was maintained at 30 ml by simultaneous evaporation of ethanol. The reaction mixture was then filtered, and the crystals were washed with cold ethanol and dried in vacuo at 70°, yield 7.70 g (50% conversion[12]). The product had equivalent weight (Cl^-, Ni^{2+}) and elemental analysis (C, H, N) consistent with the formula $(ACL)_3NiCl_2 \cdot EtOH$; $[\alpha]^{25}D$ −22.3° (*c* 4, 1 N hydrochloric acid[11]), i.e., 96% enantiomeric excess. The crystals had an average diameter of 5.3 μm. The mother liquor, when acidified with hydrochloric acid, had a slightly positive rotation corresponding to approximately 5% enantiomeric excess of D-ACL.

Still higher conversions of DL-ACL to **2** are possible if a continuous mode of operation is adopted. We were able to obtain up to 92% conversion[12] by charging an ethanol solution containing DL-ACL, nickel(II) ion, chloride ion, and ethoxide ion[13] in respective molar ratios 4.50:1.00:1.85:0.15 together with seed crystals of **2**. Ethanol was removed continuously by evaporation while a feed ethanol solution containing the same reagents in ratios 3.12:1.00:1.97:0.03 was added. Approximately 20% of the grown crystals were removed every hour and fresh seed crystals, corresponding to 25 wt % of the crystals removed, were added. The enantiomeric excess of the product was about 97%.

The resolved complex is decomposed instantly by reaction with hydrogen chloride in methanol solution. The hydrochloride of L-ACL crystallizes in ~95% yield, with respect to the enantiomeric excess of L-ACL in the complex, and is 100% enantiomerically pure. The enantiomeric enrichment taking place during the crystallization is due to the fact that DL-ACL hydrochloride is a true racemic mixture in the solid phase[2b] and so remains in solution.

$$(L\text{-ACL})_3NiCl_2 + 3HCl \rightarrow NiCl_2 + 3L\text{-ACL} \cdot HCl$$

The current simultaneous resolution/racemization process has several unique features worth emphasizing.