

## On the Isomerism of Hydroxyurea

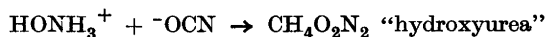
### I. Kinetics of the Reaction between Hydroxylammonium Ion and Cyanate Ion

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Two isomeric substances are known to be formed by the reaction indicated in the title, but contradictory views are held on their structures. As a first approach toward preparation of the pure isomers, for the purpose of further investigations, the kinetics of the reaction has been provisionally examined in aqueous solution at 0° C. It could be described as a bimolecular, second order, irreversible reaction. The velocity constant is approximately 8, using the minute as time unit and molarity as unit of concentration. The reaction is much faster than the analogous process leading to urea.

When aqueous solutions of a hydroxylammonium salt and a cyanate are mixed, it is believed that chiefly the following ionic reaction occurs

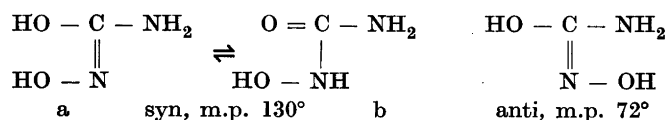


It is analogous to Wöhler's classical synthesis of urea from ammonium ion and cyanate ion<sup>1</sup>, but differs *inter alia* in that crystalline hydroxylammonium cyanate never has been isolated and in that two isomers are known of the "hydroxyurea". Although a number of formulations have been proposed, the structure of the isomers cannot be regarded as finally settled. The problem is particularly interesting because *a priori* both structural and geometrical isomerism as well as tautomerism, or several of these phenomena combined, must be considered possible in an attempt to explain the existence of two discriminate substances. Hydroxylamine and its derivatives, such as oximes, hydroxamic acids, aminooxides etc. have occupied the structural chemists for quite extensive periods and given rise to some of the most violent and fruitful

discussions in the history of chemistry. The same applies to cyanic acid and its derivatives. Some of the interesting problems presented by the reactants may possibly reappear in hydroxyurea.

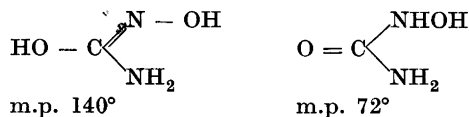
By letting hydroxylammonium nitrate and potassium cyanate react in aqueous solution Dresler and Stein <sup>2</sup> in 1869 first prepared a compound of the empirical formula CH<sub>4</sub>O<sub>2</sub>N<sub>2</sub>, which they, on grounds of analogy to the urea synthesis, named "Hydroxylharnstoff". It showed a melting point of approximately 130° C.

In 1901 the other isomer, m.p. *ca.* 72° C was discovered by Francesconi and Parrozzani <sup>3</sup> by careful fractionation of the reaction mixture from the above process, performed at 0° C between the solid components. The authors suggested that the two compounds were geometrical isomers, similarly to what is known for oximes

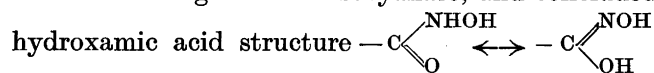


the higher melting isomer being the syn-form, probably in tautomeric equilibrium with the structure b.

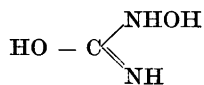
In 1907 Conduché <sup>4</sup> observed that the lower melting isomer alone had retained the ability of hydroxylamine derivatives to undergo condensation with oxo-compounds. On these grounds he advocated the following structural isomerism



Hurd and Spence in 1927 <sup>5</sup> found that hydroxyurea did not undergo a Lossen rearrangement to isocyanate, and concluded that it cannot contain a



According to Hurd and Spence hydroxyurea should be



There is no allusion to the isomerism in their paper.

Other papers dealing with hydroxyurea have little or no relevance to the structural problem. Cordier <sup>6</sup> has investigated the evolution of nitrogen on treatment with hypobromite, but did not obtain conclusive results. Meyer <sup>7</sup>

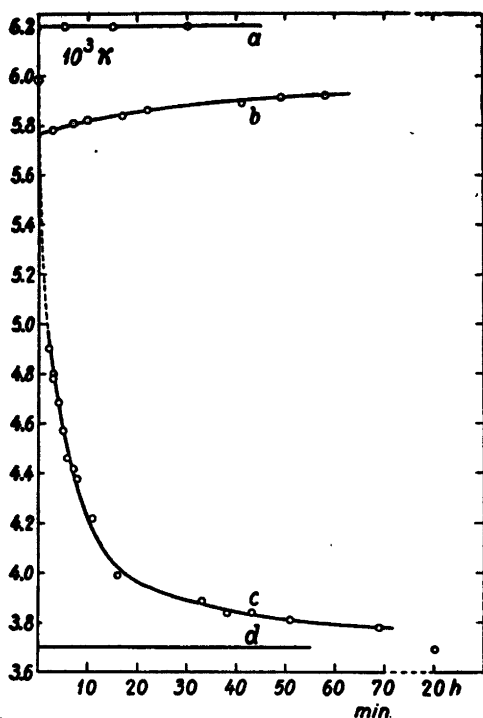
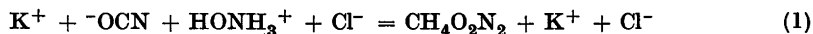


Fig. 1. Specific conductivity at 0° C of aqueous solutions. a) 0.1 M potassium cyanate; b) 0.1 M hydroxylammonium chloride; c) Equal volumes of 0.1 M potassium cyanate and 0.1 M hydroxylammonium chloride; d) 0.05 M potassium chloride.

attempted a condensation of hydroxyurea (mixture of isomers) with  $\beta$ -keto-esters, but failed to isolate the anticipated isoxazolone derivatives. Instead a small yield was obtained of a substance, which analyzed as an equimolar addition product.

A detailed discussion of the proposed structures will be postponed until the experimental material presented in this and the subsequent papers in this series can be included.

For the purpose of further investigation into the structural problem it was desirable to prepare the isomers of hydroxyurea in a pure state. The methods previously described in the literature give extremely small yields. As a first approach towards an improved method of preparation the kinetics of the reaction (1), leading to the formation of hydroxyurea, has been provisionally examined.



Since the reactants are ionic, whereas hydroxyurea may be assumed to be undissociated or practically so, the method that presents itself is conductometry. Preliminary experiments showed that at 0° C the isomers were suf-

ficiently stable and the reaction in aqueous solution slow enough to be followed conductometrically.

In Fig. 1. the specific conductivity  $\kappa$  at 0° C of aqueous solutions is plotted against a time basis. In order to secure that no secondary reactions occurred at the platinized electrodes the stock solutions of the two components were first measured. Whereas potassium cyanate (*a*) showed a constant conductivity, a small increase with time was observed for hydroxylammonium chloride (*b*). This is not due to catalytic oxydation, since the process takes place in hydrogen atmosphere as well. The phenomenon has been observed previously by Ross<sup>8</sup>, who regarded it as being due to catalytic decomposition on the electrode surface. Curve *c* represents the course of the conductivity of a mixture of the components in stoichiometric proportions prepared by mixing equal volumes of 0.1 *M* solutions. Samples were withdrawn from the reaction vessel at intervals and measured. In this way the influence of the above secondary reaction was reduced to a minimum, which for the present purpose may be neglected. During the first ten minutes the reaction is too rapid for this technique; the corresponding data were therefore measured separately using the conductivity cell as reaction vessel; apart from that, the conditions were identical. As shown by curve *c* the conductivity falls off rapidly to the value of 0.05 *M* potassium chloride (*d*). This result is compatible with the assumptions that the reaction at 0° C follows the scheme (1), that the process is irreversible and that both isomers are only weakly dissociated. It may also be inferred from curve *c* that no detectable degradation of hydroxyurea involving formation of ions occurs at 0° C within 20 hours. The experiment obviously cannot give any information about the proportions of the two isomers formed.

On the basis of the conductometric data the formation of hydroxyurea can be described as a bimolecular, second order reaction. Since the reactants are present in the same molar concentration, initially  $c_0$ , we should have

$$kt = \frac{1}{c} - \frac{1}{c_0} \quad (2)$$

$k$  being the rate constant and  $c$  denoting the concentration of any reactant at any time  $t$  during the reaction. The specific conductivity  $\kappa$  of the reaction mixture at any time is

$$\kappa = \kappa_{\text{KCl}} + \kappa_{\text{HONH}_2^+} + \kappa_{\text{-OCN}} \quad (3)$$

According to (1)  $\kappa_{\text{KCl}}$  is constant during the reaction. Let  $\Lambda$  denote the molar conductivity, then for dilute solutions we have  $\kappa = \Lambda c/1000$ . Introducing this in (3) we obtain

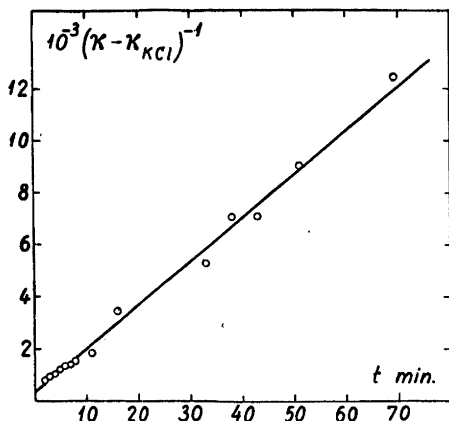


Fig. 2.

$$\kappa - \kappa_{\text{KCl}} = A_{\text{HONH}_3^+} \cdot \frac{c}{1000} + A_{\text{-OCN}} \cdot \frac{c}{1000}$$

or, writing  $\frac{1000}{A_{\text{HONH}_3^+} + A_{\text{-OCN}}}$  as  $L$  we obtain  $c = L (\kappa - \kappa_{\text{KCl}})$ . Inserting this

expression for  $c$  into (2) this becomes

$$(\kappa - \kappa_{\text{KCl}})^{-1} = k \cdot t \cdot L + \frac{L}{c_0} \quad (4)$$

As shown in Fig. 2 the experimental data satisfy equation (4) within the not very great experimental accuracy; the plot of  $(\kappa - \kappa_{\text{KCl}})^{-1}$  against  $t$  is linear. The slope of the best line, estimated from the graph, is approximately  $k \cdot L = 1.7 \cdot 10^2$ ; the intersection is  $L/c_0 \approx 4 \cdot 10^2$ . Introducing  $c_0 = 0.05$  in the latter we get  $L \approx 20$ . As however the intersection in Fig. 2 cannot be determined with any great accuracy a somewhat better value of  $L$  is probably provided in the following way. The initial conductivity  $\kappa_0$  of the reaction mixture (curve  $c$ , Fig. 1) is assumed to be the arithmetic mean of those of the two components, *i. e.*  $\kappa_0 = 0.006$ . Since  $\kappa_0 = \kappa_{\text{KCl}} + \frac{A_{\text{HONH}_3^+} + A_{\text{-OCN}}}{1000} \cdot 0.05$

$$\text{we get } L = \frac{1000}{A_{\text{HONH}_3^+} + A_{\text{-OCN}}} = 22$$

Substituting this value for  $L$  in  $kL = 1.7 \cdot 10^2$  we obtain a rate constant of approximately 8 at  $0^\circ$ , using the minute as time unit and moles per 1 as unit of concentration. The reaction is thus considerably faster than the analogous process between ammonium ion and cyanate ion leading to the formation of urea. Rate constants for this reaction in aqueous solution were determined by

Walker and Hambly<sup>10</sup> for temperatures between 25° and 80° C. The value at 25° C expressed in the same units as above was 0.00227. By a rough extrapolation to 0° C an order of magnitude of 10<sup>-5</sup> is obtained.

### EXPERIMENTAL

Potassium cyanate was prepared according to Erdmann<sup>11</sup> by oxidation of potassium ferrocyanide with potassium dichromate. It was recrystallized repeatedly from 80 % ethanol, quickly washed with absolute ethanol and ether, dried and stored over sulphuric acid. The product contained only traces of carbonate (weak opalescence with barium chloride solution). On titration with silver nitrate it gave an equivalent weight of 81.20, calculated for KOCN 81.11. Hydroxylammonium chloride of analytical grade was used.

The specific conductivities were measured by means of the conventional bridge method at a frequency of 1 000 cycles. All measurements were made against the standard  $\kappa = 0.002501$  for 0.02 *N* potassium chloride in water at 20° C<sup>9</sup>. The all-glass cell with sealed-in platinized platinum electrodes was thermostated in a Dewar vessel containing a mixture of ice and water. The carbon dioxide was removed from the solution and the temperature equilibration accelerated by passing a stream of carbon dioxide-free air through the cell for about 2 minutes before the first measurement.

The reaction vessel, the stock solutions and the pipettes were precooled to 0° C and the appropriate volumes measured at the same temperature. When the reaction was performed in the measuring cell, the potassium cyanate solution was first introduced and then the hydroxylammonium solution was added quickly, and immediate mixing effectuated by an air current as above. In this way the catalytic decomposition of hydroxylammonium was reduced to a minimum. When a separate reaction vessel was used, 3 ml samples were withdrawn at intervals with a precooled pipette and quickly transferred to the cell.

### REFERENCES

1. Wöhler, F. *Ann. Physik* **12** (1828) 252.
2. Dresler, W., and Stein, R. *Ann.* **150** (1869) 242.
3. Francesconi, L., and Parrozzani, A. *Gazz. chim. ital.* (2) **31**, II (1901) 334.
4. Conduché, A. *Ann. chim. et phys.* (8) **12** (1907) 540.
5. Hurd, C. D., and Spence, L. U. *J. Am. Chem. Soc.* **49** (1927) 266.
6. Cordier, V. von, *Monatsh.* **35** (1914) 12.
7. Meyer, A. *Bull. soc. chim. France* (4) **11** (1912) 583.
8. Ross, W. H. *Proc. Trans. Nova Scotian Inst. Sci.* **11** (1902/06) 109.
9. Landolt-Börnstein: *Physik.-chem. Tabellen* 5. Aufl. (1923) II 1098.
10. Walker, J., and Hambly, F. J. *J. Chem. Soc.* **67** (1895) 757.
11. Erdmann, H. *Ber.* **26** (1893) 2438.

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