On the Isomerism of Hydroxyurea

VII. The Reaction of Hydroxylamine with Cyanic Acid in Anhydrous Ether

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By the reaction of hydroxylammonium ion and cyanate ion a mixture of two isomeric hydroxyureas is formed, differing *inter alia* by melting point. In previous work the *lower melting* product was found to predominate, when the reaction was performed in aqueous solution at 0° C.

Experiments reported in the present paper indicate that the corresponding reaction between the uncharged molecules in anhydrous ether solution leads to predominantly the *higher melting* product. A possible correlation of the isomerism with the postulated tautomerism of cyanic acid is briefly discussed.

In part II of the present series [1] it was concluded that the ionic process $HONH_3^+ + {}^-OCN \rightarrow CH_4O_2N_2$ (hydroxyurea) in aqueous solution at 0° C leads to roughly equal amounts of the two known isomerides, which for the sake of brevity will be denoted OU_{72} and OU_{140}, respectively. The index is the characteristic decomposition temperature. The proposed ratio was inferred from the preparative yields, making some allowance for the greater lability of OU_{72}.

More accurate polarographic measurements [2] have indicated that under the said conditions rather more of OU_{72} is formed than of its isomer, the ratio OU_{72}/OU_{140} being probably between 1 and 2.

Although the formation of two isomeric products in a chemical process need not by necessity originate in structural ambiguity of the reactants but may be merely a matter of statistic probabilities, it is, however, striking that both cyanic acid and hydroxylamine display certain dualistic properties.

The structure of cyanic acid has been intensely studied by many investigators and has been a subject of much controversy. The most reliable interpretation is probably that given by Birckenbach and Kolb[3] *cf.*[6] from classical

chemical arguments and by Goubeau [4] from Raman-spectroscopic data. According to these authors cyanic acid exists in the tautomeric equilibrium

$$H\text{—}\underline{N}\text{=}C\text{=}\overline{\underline{O}} \quad \rightleftharpoons \quad |\,N \equiv C\text{—}\overline{\underline{O}}\text{—}H,$$
$$ a b$$
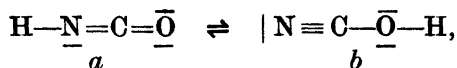
a, which is believed to be the more stable form, predominates in the free cyanic acid and in solutions in "non-polar" solvents, whereas b appears to represent the structure of cyanic acid dissolved in "polar" solvents, all provided that equilibrium is attained. The crystalline salts of cyanic acid presumably contain the mesomeric anion

$$\left(\overline{\underline{N}}\text{=}C\text{=}\overline{\underline{O}} \quad \leftrightarrow \quad |\,N \equiv C\text{—}\overline{\underline{O}}\,| \right)^{-}$$
$$ a b$$
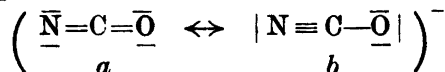
the actual electron-distribution being close to a in the salts of complex-forming metals with a bond type approximating the covalent one and close to b in the essentially ionic salts, such as the alkali cyanates. Most salts have been isolated in one form only, corresponding to either structure a or b, but in a few instances, e. g. mercury, individually existing isomeric salts could be isolated by the authors quoted [3].

Let it be assumed that the isomerism of hydroxyurea is somehow the result of the tautomerism of cyanic acid. It is evident, then, that OU_{72}, which is formed in major amounts by the ionic process in aqueous solution, must be associated with cyanic acid of structure b, since this electron-distribution is predominant in aqueous solution. As a consequence the reaction of free hydroxylamine-base and cyanic acid in, e. g., ether (structure a) should produce exclusively or predominantly the higher melting hydroxyurea OU_{140}.

As a matter of fact this has been experimentally confirmed and some support has therefore been carried to the hypothesis.

The experimentation presented certain difficulties, owing to both reactants being exceedingly unstable. Free hydroxylamine base decomposes rapidly into ammonia, nitrogen and water, and cyanic acid is apt to polymerize and to decompose. After a number of introductory experiments the following procedure was found to work satisfactorily.

The reaction was performed at $0°$ C in anhydrous ether solution. Under these conditions hydroxylamine is sufficiently soluble and relatively stable, and cyanic acid is very soluble and does not polymerize too rapidly. The reactants were freshly prepared immediately prior to use.

Cyanic acid was obtained [10] by depolymerization of cyanuric acid $(HNCO)_3$; the latter was prepared according to Walther [5] by heating urea with anhydrous zinc chloride at $220°$ C. The product was recrystallized from water and dried to constant weight at $105°$ C.

The cyanic acid generator is shown in Fig. 1. A few grammes of cyanuric acid was placed in the quartz combustion tube and a slow stream of dry nitrogen was passed through it, while the part containing the cyanuric acid was heated with a flame until sublimation occurred. The trimer partly sublimes and partly undergoes depolymerization, and the heating and nitrogen flow were regulated in such a way that the sublimate was redeposited within the
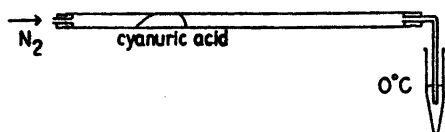
Fig. 1. Cyanic acid generator.

quartz tube and only the gaseous monomer was allowed to leave the outlet. It was absorbed in some milliliters of anhydrous ether in the centrifuge tube, which was immersed in an ice-water bath to retard polymerization of the cyanic acid. By proper operation the contents of the centrifuge tube was a clear solution with the characteristic acetic acid-like smell of cyanic acid.

Hydroxylamine was most conveniently obtained by the method of Hurd [7] with some technical modifications. A solution of sodium butoxide was prepared by refluxing 7.8 g (1/3 mole) of sodium with 100 ml of redistilled butanol-1. The equivalent amount (23 g) of hydroxylammonium chloride (analytical grade, finely ground and thoroughly dried), 3 mg of phenolphthalein and 30 ml of butanol were placed in a 250 ml pyrex-flask fitted with a magnetic stirring device and a delivery funnel containing the butoxide solution. The funnel was heated to about 40° C by exposing it to infra-red radiation in order to prevent crystallization. The butoxide solution was added dropwise with continuous stirring at such a rate that the pink colour never predominated. The "neutralization" required 1.2 hour. Sodium chloride was filtered off and washed with butanol and anhydrous ether and the combined colourless liquids were cooled to —10° C. Hydroxylamine was obtained in good yield as large colourless flakes. It was washed with anhydrous ether and dried *in vacuo* at —10° C to remove solvents; the melting point, taken immediately, was
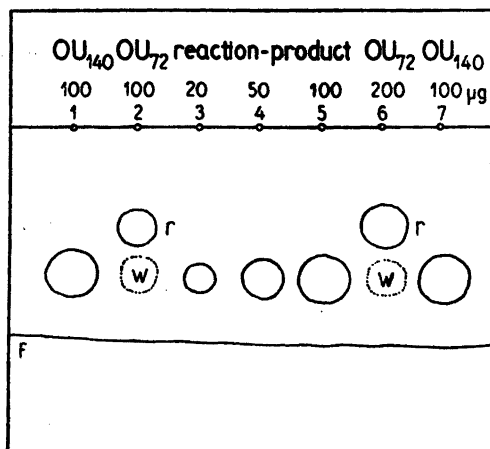

Fig. 2. Descending paper-chromatogram of the reaction product and authentic samples of hydroxyurea isomerides. Whatman paper no. 1; Solvent ethanol-hydrochloric acid; 25.0° C; spray-reagent picryl chloride, subsequent exposure to ammonia vapour. General technique vide Ref.[8]; r means red, other spots orange; w weak.
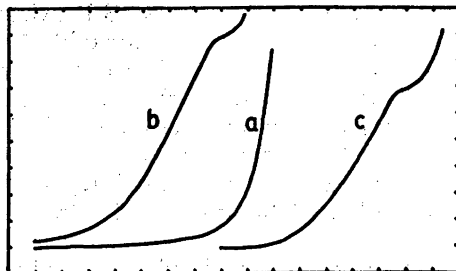
Fig. 3. Polarographic current-voltage curves recorded at 22° C pH 7.2; capillary characteristics of the mercury electrode are height of mercury column h = 24 cm; rate of mercury outflow m = 3.02 mgsec⁻¹; drop time 3.3 sec. One unit on the ordinate equals 0.66 microamps, one unit on the abscissa equals 0.1 volt. All curves begin at −1.0 volt vs. "saturated calomel electrode".

a. 0.1 M potassium phosphate buffer° pH 7.2 (blank)
b. 3.0 mg reaction product in 5 ml of buffer as under a.
c. 0.25 mg authentic lower melting hydroxyurea (OU₇₂) in 5 ml of buffer.

32° C; Ref.[7] 33° C. The substance was used forthwith for the actual experiment as described below. The remaining crop was stored at 0° C; nevertheless it was completely decomposed the following day.

Anhydrous ether (4 ml) was saturated with hydroxylamine at 0°. A freshly prepared solution of cyanic acid in anhydrous ether (0° C) was added dropwise. A colourless, crystalline precipitate was formed, and the addition of cyanic acid was continued until no further precipitation occurred. The contents of the reaction vessel were centrifuged, and the supernatant ether poured off. The solid was washed with 2 × 1 ml cold anhydrous ether, in which both hydroxyureas are insoluble, and dried in vacuo. The product gave the characteristic blue-violet colour produced by OU_{140} on addition of ferric chloride. Paper-chromatographic analysis according to the previously reported technique [8] proved that the product was identical with OU_{140} isolated from the ionic process. In Fig. 2 is reproduced a descending paper-chromatogram of the product (Nos. 3—5) run together with authentic samples of the two known isomerides. The irrigation solvent was a mixture of 70 ml of ethanol and 30 ml of 4 N hydrochloric acid. In this solvent both hydroxyureas are sufficiently stable and the isomerization is very slow [8]. The weak OU_{140}-spot to be seen in the runs 2 and 6 is due to the fact that the sample of OU_{72} was 1 month old, and hence partly isomerized. The spot in run No. 5 is comparable in size to the authentic spot in runs Nos. 1 and 7. As the amount applied to the paper is the same, it may be concluded that the reaction product consists almost entirely of OU_{140}. There was not on the original paper-sheet any trace of the characteristic red OU_{72}-spot to be seen in the runs 3—5.

The still more sensitive polarographic method [9], however, revealed the presence of approximately 10 % OU_{72}. In Fig. 3a is reproduced a blank current-voltage curve of the supporting buffer, pH 7.2 (vide Ref.[9]), curve b is a polarogram of 3.0 mg reaction product dissolved in 5 ml of the same buffer. It

represents the usual OU_{72}-wave at -1.5 V *vs.* SCE. Curve c is a polarogram recorded under identical conditions of a solution of 0.25 mg of authentic OU_{72} in 5 ml of buffer. From the relative heights (linear relationship has been found between concentration and wave height, Ref.[9] Fig. 4) of b and c it may be estimated, that the 3.0 mg of reaction-product weighed out contain approximately 0.3 mg or 10 % of the lower melting isomer. The identity of the wave b was further established by adding authentic OU_{72} to the cell-solution; this caused an increase in wave-height but neither displacement nor distortion of the wave.

The thermal decomposition interval of the product (Kofler hot-stage microscope) was in accordance with the above results. The content of OU_{72} was evidently too small to produce any visible change at 72° C, but decomposition and melting occurred abnormally low and over a large interval, 120—135° C. The decomposition temperature normally found for the pure OU_{140} is 135—140° C, depending upon the rate of heating.

The formation of hydroxyurea isomerides described in the present paper is directly comparable with previous experiments on the ionic process [1,2], in that both reactions were carried out at 0° C and cyanic acid was added to hydroxylamine and not *vice versa*. The observed ratio OU_{72}/OU_{140} was over 1 with the ionic process and approximately 0.1 with the reaction described in this paper. This result strongly suggests that the isomerism of hydroxyurea has some relation to the postulated tautomerism of cyanic acid, a point of view, which is quite interesting, because it means that the isomerism of hydroxyurea is at least formally analogous to that of urea and isourea, which, as far as the parent compounds are concerned, do not seem capable of individual existence. A detailed discussion of formation mechanisms and structure will be presented in a final publication.

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