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# Crystal and Molecular Structure of *N*-Hydroxyoxamide, an Analogue of Hydroxyurea

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*N*-Hydroxyoxamide, $H_2NCOCONHOH$, has been prepared and isolated in the pure state in three different crystalline modifications with the melting points 137, 142 and 147 °C, respectively. A fourth modification with the melting point 131 °C was observed on the hot stage microscope. The crystal structure of one of the modifications (m.p. 142 °C) has been determined using three-dimensional diffractometer collected X-ray data. The crystals are monoclinic, space group $C2/c$, with eight formula units ($C_2H_4N_2O_3$) in the unit cell with the dimensions $a=15.619(7)$, $b=3.551(2)$, $c=14.238(8)$ Å, $\beta=98.25(5)°$. The structure was solved by direct phasing techniques and refined by full-matrix least-squares calculations, $R=0.045$. The molecules are roughly planar, with *ap* conformation of the two carbonyl groups and *sp* conformation of HO–N–C=O.

The structure determination of *N*-hydroxyoxamide, $H_2NCOCONHOH$, was undertaken as part of an X-ray study of analogues of hydroxyurea (HU), which are inhibitors of the DNA synthesis in several cell systems.[1] *N*-Hydroxyoxamide has been shown to inhibit the DNA synthesis in Ehrlich ascites tumour cells,[2] and in regenerating rat liver cells.[3] *N*-Hydroxyoxamide has recently been found to inhibit the same enzyme (ribonucleoside diphosphate reductase from *E. coli*) as does HU, but it was found to be less potent.[4] The compound also reacts more slowly than HU with the free radical salt $(KO_3S)_2NO\cdot$ (Fremy's salt), which has been used as a model compound for the active site of the enzyme, of which the subunit called protein B2 contains a free radical component.[5] Results of an investigation of the reactions of several HU-analogues with the model compound and with the enzyme indicate that the one electron oxidizability of the compounds is the main property necessary for inhibitory action on the enzyme. Details on this work will be given in another report.

The substances used in the biological experiments[2-3] were obtained from Hynes Chemical Research Co., and the melting point reported to be 151 °C.[3] The compound used in our work was synthesized by the same method,[6] but the preliminary crystallographic work showed that four crystalline modifications exist, all with lower melting points (131–147 °C). In addition, crystalline materials with m.p. 151 and 159 °C (decomp.), respectively, were obtained by slow crystallization from aqueous ethanol or acidic aqueous solution during about three weeks, but TLC and the IR spectra showed, that the compounds were partly decomposed. The decomposition products were not isolated or identified.

## EXPERIMENTAL

*Synthesis.* *N*-Hydroxyoxamide was prepared from the ethyl ester of oxamic acid and hydroxylamine.[6] By this method the so-called α-form (m.p. 159 °C, aqueous ethanol) should be obtained, but crystals with m.p. 137 °C were obtained, which is in agreement with the so-called β-form.[7] Anal. $C_2H_4N_2O_3$: C, H, N. IR (KBr): 3440 (s), 3350–2750 (broad band, s), 1740 (m), 1720 (m), 1670 (doublet, s), 1580 (m), 1530 (m), 1440 (m), 1400 (m) $cm^{-1}$. Attempts to obtain single crystals suitable for X-ray work resulted in the isolation of three different crystalline modifications: orthorhombic crystals, m.p. 147 °C ($a=7.21$, $b=3.55$ and $c=15.07$ Å), monoclinic crystals, m.p. 142 °C, and orthorhombic crystals, m.p. 137 °C ($a=7.05$, $b=3.51$ and $c=15.40$ Å). A

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*Table 1.* Crystal data for *N*-hydroxyoxamide.

| | |
|---|---|
| Mol. formula | $C_2H_4N_2O_3$ |
| Mol. weight | 104.10 |
| Melting point, °C | 142 |
| Space group | *C2/c* |
| *a*, Å | 15.619(7) |
| *b*, Å | 3.551(2) |
| *c*, Å | 14.238(8) |
| $\beta$° | 98.25(5) |
| *V*, Å$^3$ | 751.81 |
| *Z* | 8 |
| $D_x$, g cm$^{-3}$ | 1.769 |
| $D_m$, g cm$^{-3}$ | 1.76 |
| $\mu$MoK$\alpha$, cm$^{-1}$ | 1.86 |

fourth modification (m.p. 131 °C) was observed on the hot stage microscope by slow heating of the lowest melting crystals.

The melting points were determined with a hot stage microscope (Mikroskop Heiztisch Ernst Leitz G.m.b.H., Wetzlar). The IR spectra were recorded on a Perkin-Elmer grating infrared spectrophotometer model 247. The elemental analyses were performed by Mr. P. Hansen, Chemical Laboratory II, University of Copenhagen.

*X-Ray crystallography.* The monoclinic crystals (m.p. 142 °C) were used for X-ray structure determination. Single crystals were obtained by recrystallization from aqueous ethanol (75 %). The size of the crystal chosen for data collection was $0.1 \times 0.2 \times 0.8$ mm$^3$. The crystal was mounted in a glass capillary and oriented with the *b*-axis parallel to the $\phi$-axis of the goniostat. Some crystal data for

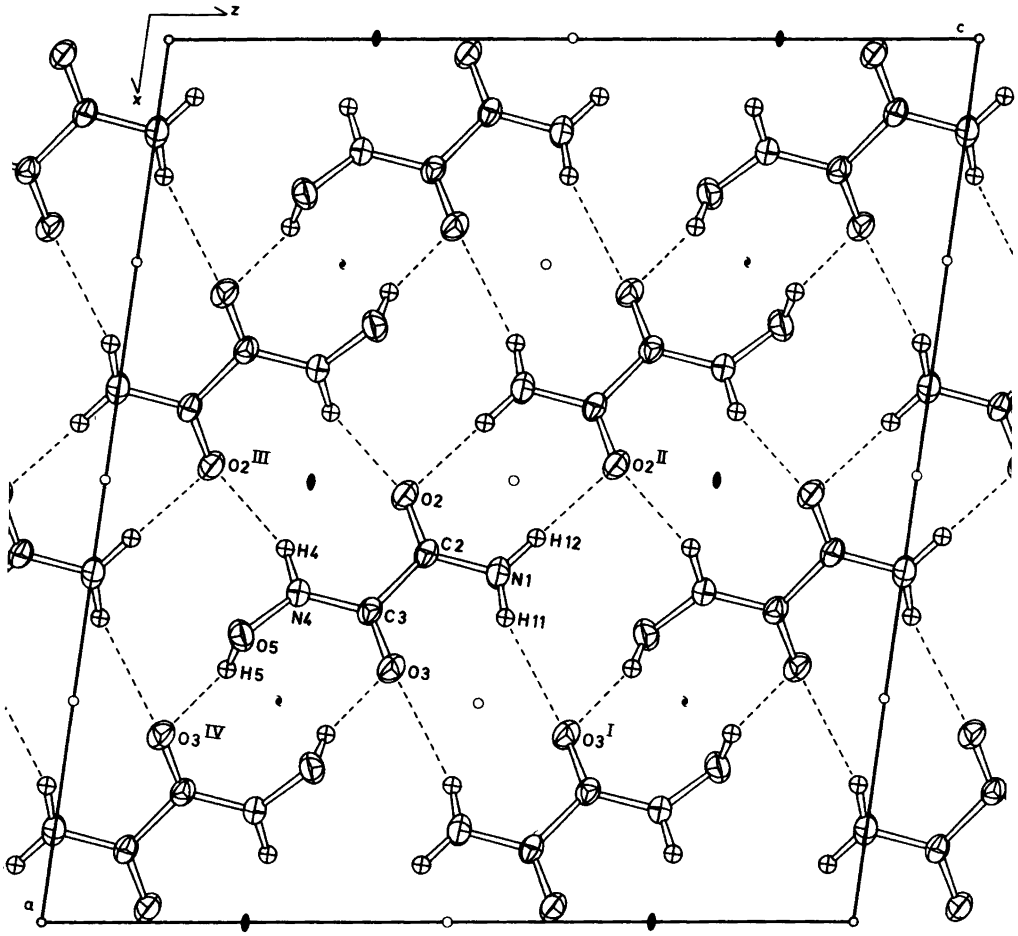


*Fig. 1.* The structure of *N*-hydroxyoxamide viewed along the *b*-axis. Dashed lines indicate hydrogen bonds.

*Table 2.* Fractional coordinates and thermal parameters for the atoms. The thermal parameters ($\times 10^2$) for the non-hydrogen atoms are of the form: $\exp[-2\pi^2(U_{11}h^2a^{*2}+\cdots+2U_{12}hka^*b^*\cdots)]$.

| Atom | *x/a* | *y/b* | *z/c* | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{12}$ | $U_{13}$ | $U_{23}$ |
|---|---|---|---|---|---|---|---|---|---|
| N1 | 0.6046(2) | −.2570(9) | 1.0012(2) | 3.2(1) | 4.5(2) | 1.7(1) | −.8(1) | 0.1(1) | 0.0(1) |
| C2 | 0.5829(2) | −.3163(8) | 0.9095(2) | 2.6(1) | 2.2(2) | 1.7(1) | 0.3(1) | −.1(1) | 0.3(1) |
| O2 | 0.5169(1) | −.4820(6) | 0.8725(1) | 2.7(1) | 3.5(1) | 2.0(1) | −.6(1) | −.3(1) | 0.2(1) |
| C3 | 0.6478(2) | −.1563(9) | 0.8497(2) | 2.4(1) | 2.2(2) | 1.8(1) | 0.7(1) | −.1(1) | 0.2(1) |
| O3 | 0.7123(1) | 0.0172(6) | 0.8865(1) | 2.7(1) | 3.8(1) | 2.2(1) | −.8(1) | −.2(1) | −.3(1) |
| N4 | 0.6269(2) | −.2276(7) | 0.7580(2) | 2.4(1) | 3.1(1) | 1.7(1) | −.1(1) | 0.2(1) | 0.0(1) |
| O5 | 0.6749(2) | −.0698(7) | 0.6946(2) | 3.2(1) | 3.8(1) | 2.1(1) | 0.7(1) | 0.8(1) | 0.6(1) |
| | | | | *B* | | | | | |
| H11 | 0.655(2) | −.149(9) | 1.018(2) | 2.0 | | | | | |
| H12 | 0.566(2) | −.317(9) | 1.042(2) | 2.0 | | | | | |
| H4 | 0.577(2) | −.342(9) | 0.735(2) | 2.0 | | | | | |
| H5 | 0.713(2) | −.213(9) | 0.683(2) | 2.0 | | | | | |

*N*-hydroxyoxamide are given in Table 1. The density was measured by flotation in a mixture of carbon tetrachloride and methyl iodide. The unit cell parameters were obtained from the $\theta$ values of 51 automatically centered reflexions measured on a NONIUS CAD-3 diffractometer ($\lambda = 0.71069$ Å). Intensity data were measured using graphite monochromated Mo$K\alpha$ radiation and the $\omega$ scan technique. Of the 695 independent reflexions measured in the $\theta$ range 2.5−25.0°, 448 had net intensities greater than $2.5\sigma(I)$, where $\sigma(I)$ is the standard deviation from counting statistics, and were used in the structure refinements. No absorption corrections were made.

## STRUCTURE DETERMINATION

The structure of *N*-hydroxyoxamide was solved by direct methods using the MULTAN system.[8] Full-matrix least-squares refinement of positional parameters for all atoms and anisotropic temperature parameters for the non-hydrogen atoms led to a final *R*-value of 0.045. The initial positions of the four hydrogen atoms were obtained from a difference electron density map. The quantity minimized was $\sum w(|F_o|-|F_c|)^2$, where $w = 1/\sigma^2(I)$. The scattering factors used for hydrogen were those of Stewart, Davidson and Simpson,[9] and for oxygen, nitrogen and carbon those of Cromer and Mann.[10]

Final parameters for the atoms are given in Table 2. Notation of the atoms is given in Fig. 1. The observed and calculated structure factor data are available from the author on request. The programs used in the crystallographic analysis were the same as earlier reported.[11]

## RESULTS AND DISCUSSION

The configuration of *N*-hydroxyoxamide was found to be that of a hydroxamic (not hydroximic) acid, and the difference between the so-called $\alpha$ and $\beta$ forms cannot be a question of geometrical isomerism, as earlier postulated.[7]

The conformation of the molecule in the crystalline modification investigated is shown in Fig. 1. The molecule is roughly planar, as are all the HU-analogues with enzyme inhibitor effect so far investigated. The two carbonyl groups are placed *antiperiplanar* with a torsion angle O2−C2−C3−O3 of ±178.1(3)°, and the conformation of HO−N−C=O is *synperiplanar*, the torsion angle O3−C3−N4−O5 being ∓6.8(5)°.

*Table 3.* Bond lengths (Å) and angles (°) for *N*-hydroxyoxamide.

| | | | |
|---|---|---|---|
| N1−C2 | 1.318(4) | N1−H11 | 0.88(3) |
| C2−O2 | 1.238(5) | N1−H12 | 0.92(3) |
| C2−C3 | 1.524(6) | N4−H4 | 0.90(3) |
| C3−O3 | 1.233(5) | O5−H5 | 0.82(3) |
| C3−N4 | 1.324(4) | | |
| N4−O5 | 1.373(5) | | |
| N1−C2−C3 | 113.4(3) | H11−N1−H12 | 125(3) |
| N1−C2−O2 | 125.3(3) | H11−N1−C2 | 116(2) |
| O2−C2−C3 | 121.3(2) | H12−N1−C2 | 119(2) |
| C2−C3−N4 | 113.0(2) | C3−N4−H4 | 122(2) |
| C2−C3−O3 | 121.2(2) | H4−N4−O5 | 118(2) |
| O3−C3−N4 | 125.8(3) | N4−O5−H5 | 111(3) |
| C3−N4−O5 | 119.4(2) | | |

*Table 4.* Hydrogen bond distances (Å) and angles (°).

Symmetry code: I $-x+1\frac{1}{2}, -y-\frac{1}{2}, -z+2$
II $-x+1, -y-1, -z+2$
III $-x+1, y, -z+1\frac{1}{2}$
IV $-x+1\frac{1}{2}, y-\frac{1}{2}, -z+1\frac{1}{2}$

| X–H···Y | X···Y | H···Y | ∠X–H···Y |
|---|---|---|---|
| N1–H11···O3$^{I}$ | 3.206(11) | 2.65(3) | 122(3) |
| N1–H12···O2$^{II}$ | 2.944(09) | 2.03(4) | 173(3) |
| N4–H4···O2$^{III}$ | 2.848(11) | 2.02(3) | 153(3) |
| O5–H5···O3$^{IV}$ | 2.678(06) | 1.90(4) | 160(3) |

Bond lengths and angles are given in Table 3 and agree with the values found in similar compounds, *e.g.* oxamide.[12] The packing of the molecules in the crystals is shown in Fig. 1. The crystal structure is stabilized by a three-dimensional network of hydrogen bonds, each molecule being involved in eight hydrogen bonds to five different neighbouring molecules. The hydrogen bond O5–H5···O3$^{IV}$ connects the layers of molecules in the $y$ direction. Hydrogen bond distances and angles are given in Table 4.

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