Three-dimensional Structure of Usnic Acid

ROLF NORRESTAM,[a] MARIANNE von GLEHN[a] and CARL AXEL WACHTMEISTER[b]

[a] Department of Structural Chemistry, Arrhenius Laboratory, University of Stockholm, S-104 05 Stockholm, Sweden and [b] Wallenberg Laboratory, University of Stockholm, S-104 05 Stockholm, Sweden

The three-dimensional structure of the very common lichen substance usnic acid, $C_{18}H_{16}O_7$, has been determined. By the use of single crystal X-ray diffraction data collected at -110 °C it was possible to determine the positional parameters of both the 50 nonhydrogen atoms and the 32 hydrogens of the asymmetric unit. The two molecules in the asymmetric unit have almost identical conformations. The six oxygens of each molecule are all involved in intramolecular hydrogen bonds of different strengths giving $O \cdots O$ distances ranging from 2.40 to 2.69 Å. Some information on possible racemization mechanisms can be gained from the present study.

Usnic acid, $C_{18}H_{16}O_7$, is one of the most common lichen substances. Up to 20 % of the dry weight of some lichens consist of this yellow acidic enol. Usnic acid, which is toxic to higher animals and exerts hypermetabolic activity, has to some extent been used as an uncoupler of oxidative phosphorylation in studies of the mechanism of this process. The now accepted structural formula, shown in Fig. 1, has been confirmed through total synthesis.[1] The structural formula implies several possibilities for formation of intramolecular hydrogen bonds. The existence of such hydrogen bonds is indicated by the fact that usnic acid, in spite of its high content of proper hydrogen bond donors and acceptors has pronounced lipophilic properties. Spectroscopic studies on usnic acid, using infrared and proton magnetic resonance techniques, have indicated the existence of three hydrogen bonds of markedly different strengths.[2,3] It has been shown [4,5] from determinations of unit cell parameters, space group symmetry and density, that usnic acid crystallizes with two formula units per asymmetric unit. Thus, the existence of strong intermolecular interactions like, e.g.,

hydrogen bonds leading to a dimerization and a further complication of the hydrogen bond scheme cannot be ruled out. On the other hand the spectroscopical investigations [2] suggested that all of the three hydrogen bonds indicated are intramolecular.

The X-ray structural investigation of usnic acid, reported in the present paper, has been carried out to obtain the three-dimensional structure, and thereby also clarify the hydrogen bond scheme and the nature of the intermolecular interactions. The crystalline specimen used
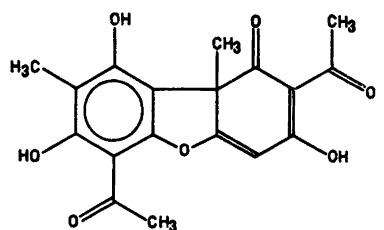
(a)
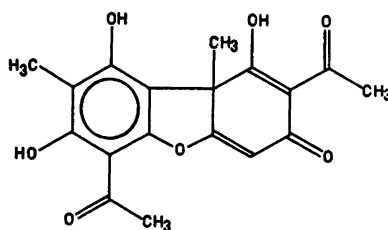
(b)

Fig. 1. Proposed bond schemes for the two most plausible tautomers of usnic acid.

Table 1. Unit cell dimensions (Å) for usnic acid. (Space group: $P2_12_12_1$. Composition of asymmetric unit: $C_{36}H_{32}O_{14}$).

	Jones and Palmer[4]	This study 22 °C	− 110 °C
a	8.09	8.069	8.042
b	19.10	19.058	18.890
c	20.39	20.326	20.264

was obtained by evaporation of a chloroform solution of (−)-usnic acid.

The space group $P2_12_12_1$ was confirmed by X-ray investigations with precession and De Jong-Bouman techniques using MoKα radiation. In order to be able to locate not only the 50 independent nonhydrogens atoms, but also the 32 hydrogens, it was decided to collect single crystal X-ray diffraction data at low temperature. Thus, the diffraction data were collected at about − 110 °C on a single crystal diffractometer using monochromatized CuKα radiation. In all, 2405 reflections significantly above the background were observed. The cell dimensions determined are given in Table 1.

The structure was solved by the application of direct methods using the variance-weighted phase-sum formulae for phase determination and refinement.[5] Of the 31 highest peaks in the obtained electron density map, 28 were chemically meaningful and were used in the subsequent difference electron density maps and least-squares refinements to locate the remaining 22 nonhydrogen and 32 hydrogen atoms. After least-squares refinement of the structural model, allowing all the nonhydrogens to vibrate anisotropically and using fixed isotropic temperature factors for all hydrogens, the R value became 0.04. No attempts to determine the absolute
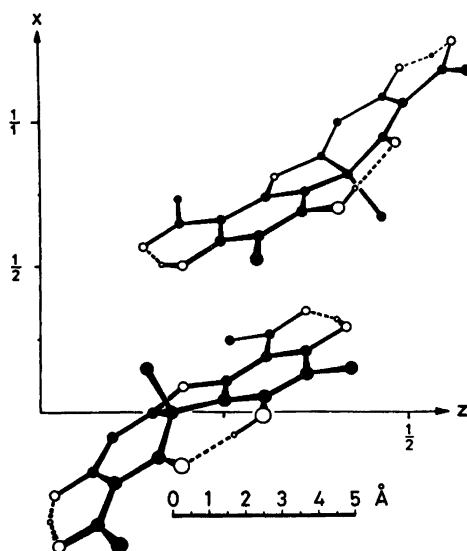

Fig. 2. The molecular geometries of the two molecules of the asymmetric unit. The figures refer to fractional coordinates.
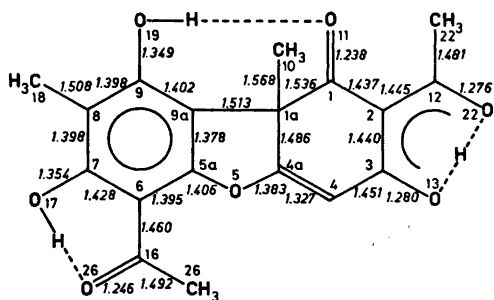

Fig. 3. The obtained intramolecular bond distances averaged over the two molecules of the asymmetric unit.

Table 2. Hydrogen bond distances (Å) and angles (°) in the two independent molecules.

Hydrogen bond	O···O	O−H	H···O	∠O−H···O
O(19)−H···O(11)	2.66	0.99	1.69	166
	2.69	0.84	1.86	170
O(17)−H···O(26)	2.54	0.88	1.69	163
	2.53	1.00	1.58	156
O(13)···H···O(22)	2.40	1.27	1.16	164
	2.41	1.07	1.38	158

configuration from the diffraction data have been made.

The observed molecular geometries and intramolecular distances are shown in Figs. 2 and 3 together with the atomic labels used in this study. As seen, the two molecules have almost identical conformations, they both adopt a kind of butterfly conformation. No short intermolecular distances indicating intermolecular hydrogen bonds were found. The three hydroxyl hydrogens in each molecule are all involved in strong intramolecular hydrogen bonds, giving $O \cdots O$ distances ranging from 2.4 to 2.7 Å. The hydrogen bond distances and angles, listed in Table 2, indicate that the bond strength increases in the order $O(19) - H \cdots O(11)$, $O(17) - H \cdots O(26)$ and $O(13) \cdots H \cdots O(22)$ in consistence with the interpretation of the NMR and IR spectra reported by Forsén et al.[2] The very short $O \cdots O$ distance of 2.40 Å in the chelated $O(13) \cdots H \cdots O(22)$ hydrogen bond is significantly shorter than those found in, e.g., the dibenzoylmethanes [7] where a similar intramolecular hydrogen bond situation leads to $O \cdots O$ distances of about 2.47 Å. Distances of about 2.40 Å appears actually to represent the lower limit of $O \cdots O$ distances in hydrogen bonds found sofar.[8] The oxygen-hydrogen distances in the $O(13) \cdots H \cdots O(22)$ hydrogen bond (cf. Table 2) suggests that the hydrogen is attached to different oxygen atoms in the two independent molecules in the crystal structure. This would be in agreement with the infrared spectroscopical studies on acetylacetones [9], which indicate that strong but unsymmetrical intramolecular hydrogen bonds would be a general feature of β-diketones. The existence of two different enolic tautomers, due to the differences of the $O(13) \cdots H \cdots O(22)$ hydrogen bonds, would also be an explanation for the two molecules per asymmetric unit in the crystal structure. However, the standard deviations of the oxygen – hydrogen distances, 0.05 Å, and the expected systematic errors when locating hydrogens by X-ray diffraction techniques [10] does not permit any definitive decisions between the alternatives, symmetrical or unsymmetrical hydrogen bonds between O(13) and O(22). Further studies using single crystal neutron diffraction techniques have been initiated.

Fig. 3 shows the intramolecular bond scheme drawn in accordance with the observed bond distances. This bond scheme agrees largely with one of the tautomers of the earlier proposed bond scheme (Fig. 1a) and excludes the other tautomer (Fig. 1b). The only major difference being the complete delocalization of the double bonds over the region $O(13) - C(3) - C(2) - C(12) - O(22)$, which leads to $C - O$ bond lengths of 1.28 Å and $C - C$ bond lengths of 1.44 Å.

Usnic acid of natural origin is represented by both its enantiomers which differ by the configuration around the quaternary carbon atom, C(1a), and is furthermore known to easily undergo thermal racemization in, e.g., boiling xylene solution. The hitherto most widely accepted racemization mechanism is the one suggested by Stork [11] and involves a homolytic loosening of the $C(1a) - C(1)$ bond to form a resonance stabilized diradical. Other suggestions,[12] on the other hand, include a homolytic loosening of the $C(1a) - C(9a)$ bond. A striking support to any of these suggested mechanisms would of course be to observe a correspondingly elongated bond length, due to a weakened $C - C$ bond, in the crystal structure. A certain support for Stork's mechanism might be gained from this study since the bond lengths obtained for the four bonds $C(1a) - C(1)$, $C(1a) - C(4a)$, $C(1a) - C(9a)$, and $C(1a) - C(10)$ around the quaternary carbon atom C(1a) are 1.54, 1.49, 1.51, and 1.57 Å, respectively. Thus, the $C(1a) - C(1)$ distance of 1.54 Å is somewhat larger than the usual $C(sp^3) - C(sp^2)$ bond distance [13] of 1.516 Å. No easy connection between the long (1.57 Å) $C(1a) - C(10)$ distance and a racemization reaction can be formulated. It is noteworthy that the hydrogen bond $O(19) - H \cdots O(11)$, although the weakest of the three intramolecular hydrogen bonds, is of decisive importance for the thermal stability of usnic acid. Thus, the activation energy for racemization of (−)-usnic acid in decalin or toluene is some 4 kcal higher than in typical electron donor solvents as dioxane or tetrahydropyran, which evidently can break the $O(19) - H \cdots O(11)$ bond.[12,14] On the other hand, acetylation of (−)-usnic acid at the hydroxyl group containing O(19) gives a monoacetate [2] for which the corresponding low activation energy is largely independent of solvent type.[14]

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