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THE MOLECULAR STRUCTURE OF CAROLIC ACID

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Abstract—The earlier structure proposal for carolic acid as (*E*, *R*)-5-methyl-3-(2'-tetrahydrofurylidene)tetrahydrofuran-2,4-dione has been confirmed using diffractometercollected X-ray data. The extended bond delocalization makes the *cis*/*trans* isomerization of carolic acid understandable.

Carolic acid, a metabolite of *Penicillium charlesii*[1] and *P. fellutanum*,[2] exists in water as a monocyclic α-acyltetronic acid (1). Upon isolation a cyclic ether is formed, for which structures 2–5 can be formulated. It has recently been shown[3] that carolic acid exists in deuteriochloroform solution as a 4:5 mixture of the (*E*)- and (*Z*)-isomers of (*R*)-5-methyl-3-(2'-tetrahydrofurylidene)-tetrahydrofuran-2,4-dione (3 and 4, resp.). This conclusion was based on ^{13}C NMR spectral measurements of both unenriched and enriched carolic acid derived by incorporation of [1-], [2-], and [1,2-^{13}C]-acetate, respectively. It has further been shown[4] that when carolic acid is crystallized from ethanol and dissolved in the dark in pure acetonitrile-d_3 there is only one isomer present. Comparison of the ^{13}C-chemical shifts of this with those of methyl (*E*)- and (*Z*)-3-methoxyacrylate[5] suggest that it is the (*E*)-form (3). In the presence of traces of acid, or under influence of light, equilibration with the (*Z*)-isomer occurs, although the position of the equilibrium appears to be solvent dependent.

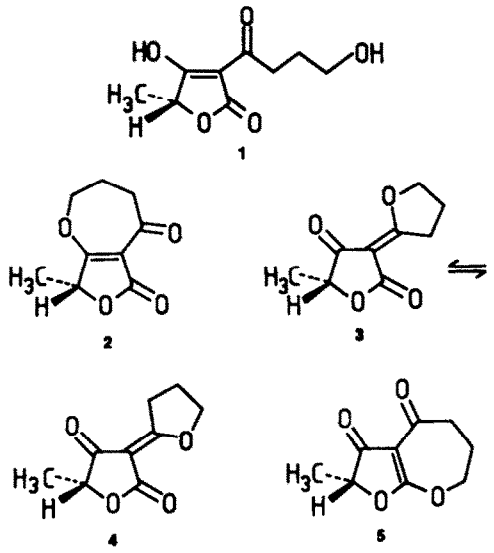


Table 1. Final atomic coordinates with estimated standard deviations in parentheses

Atom	x	y	z
O1	0.3910 (13)	0.8870 (5)	0.0279 (3)
O2	0.6820 (13)	0.0455 (6)	0.9979 (3)
O4	0.9981 (12)	0.0167 (6)	0.1802 (3)
C2	0.5004 (16)	0.0097 (8)	0.0383 (5)
C3	0.3693 (15)	0.0822 (7)	0.1003 (4)
C4	0.1592 (16)	0.9957 (7)	0.1295 (4)
C5	0.1729 (17)	0.8681 (8)	0.0839 (4)
C6	0.2195 (29)	0.7462 (8)	0.1330 (6)
O1'	0.3102 (11)	0.2663 (5)	0.1809 (3)
C2'	0.4419 (14)	0.2054 (7)	0.1251 (4)
C3'	0.6585 (15)	0.2906 (8)	0.0940 (4)
C4'	0.6670 (21)	0.4078 (9)	0.1496 (6)
C5'	0.4115 (17)	0.4041 (7)	0.1900 (5)

To obtain a final proof of structure of carolic acid and obtain information on the bond delocalization making the *cis/trans* isomerization possible, an X-ray study was carried out.

EXPERIMENTAL

X-Ray diffraction. The crystals of carolic acid used in the X-ray investigation were obtained upon voluntarily evaporation of an acetonitrile soln of the compound. The space group $P2_12_12_1$ (No. 19) was unequivocally established from systematic absences. The three dimensional X-ray data were obtained using a three circle Enraf–Nonius diffractometer and Zr filtered MoKα radiation. A reflection was designated not observed if $I \leq 2.5\sigma(I)$. With this criterion 615 out of 1012 (independent measured) reflections were regarded as observed. Lorentz and polarization corrections were applied, but no extinction or absorption corrections were made. The crystal size was $(0.7 \times 0.3 \times 0.3)$ mm^3, ω-scan was used. The maximum value of $\sin\theta/\lambda$ was 0.617 Å^{-1}.

Accurate unit cell dimensions were determined by a least squares refinement of data measured from a Guinier powder photograph taken with CuKα1 radiation and calibrated with silicon as an internal standard.

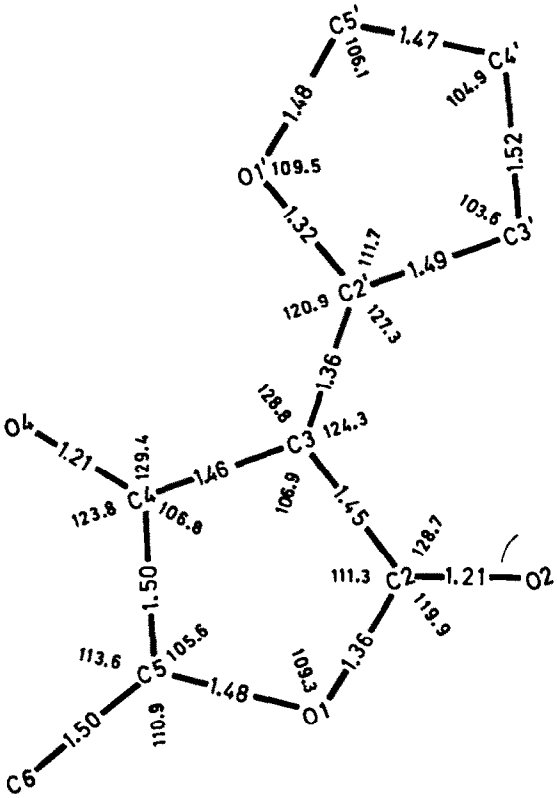


Fig. 1. Bond distances (Å), angles (°) and atom-numbering scheme for carolic acid. Estimated standard deviations for the bond distances and angles are 0.01 Å and 0.7°, respectively.

The structure was solved by direct methods using the SHELX 76 system of crystallographic programs[6] and an IBM 360/165 computer. The least squares refinement was performed on an Univac 1110 computer using the X-ray 76 system.[7] The quantity minimized was $\Sigma w(F_o - F_c)^2$. The weighting scheme was $w = (a + F_o + bF_o^2)^{-1}$ with $a = 10.0$ and $b = 0.10$. Contributions from unobserved reflections were included if $F_c > F_o$. The positional H-parameters were calculated and then refined separately ($\sin\theta/\lambda < 0.40$ Å^{-1}).

Atomic scattering factors were taken from *International Tables for X-ray Crystallography*.[8] The final R index ($R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$) was 6.7%.

RESULTS

Crystal data. Carolic acid has a formular weight of 182.17. The crystals are colourless prisms. Space group $P2_12_12_1$ (No. 19), $a = 5.046(1)$ Å, $b = 10.005(3)$ Å, $c = 17.276(4)$ Å; $Z = 4$, $D_m = 1.39(1)$ g cm^{-3}, $D_x = 1.39$ g cm^{-3}.

DISCUSSION

The present X-ray investigation confirms the correctness in the proposal[3] of 3 as the formula of carolic acid and makes it possible to state that carolic acid is (*E*, *R*)-5-methyl-3-(2'-tetrahydrofurylidene)tetrahydrofuran-2,4-dione.

The lactone ring is planar within the uncertainty and the O atoms O2 and O4 only show small displacements from the lactone ring plane (0.015 and 0.028 Å, respectively). The cyclic ether is not quite planar as C4' and C5' are situated approx. 0.1 Å on each side of the (least squares) ether ring plane. The molecule as such (non-H atoms) does not deviate much from the planarity of the lactone ring (0.001–0.280 Å) with the exception of C6 (1.19 Å); cp. (Figs. 1 and 2).

Outstanding features of the lactone and the cyclic ether moieties are the great differences of the C–O distances involving O1 and O1', respectively. It seems well documented that the dissymmetry of the C5–O1–C2 fragment in the lactone moiety is characteristic for lactone systems.[9] Resonance of the type (O=C–O–$\leftrightarrow$O–C=$\overset{+}{O}$–) is considered to play a role.[10] For the cyclic ether carrying an exocyclic bond it is reasonable to anticipate a similar type of resonance (–O–C=C<$\leftrightarrow$–$\overset{+}{O}$=C–$\overset{-}{C}$<).[11] X-Ray investigations of kawain a 6-substituted 4-methoxy-5,6-dihydro-2-pyrone,[12] and some chromone systems[13] lend further support to this point of view.

It has been shown that resonance is an important factor in the stability of the equilibrium configurations of acrolein.[14] The bond distances of the acrolein moiety (C2', C3, C4, O4) in carolic acid compare well with the

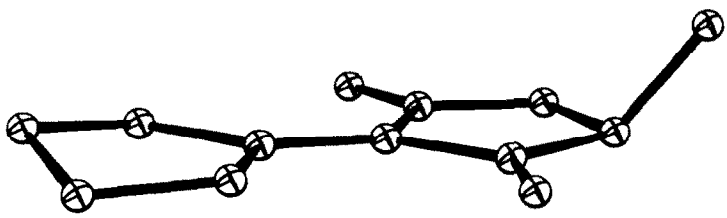
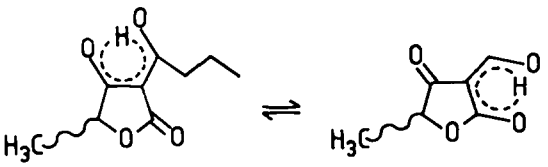


Fig. 2. Perspective drawing of the molecule.

corresponding distances in acrolein itself (C=O: 1.22, =C–C=: 1.45; C=C 1.36 Å).[14] Therefore, it seems reasonable to consider C3–C4 to be somewhat delocalized.

The three delocalized systems discussed so far are interconnected in such a way that delocalization of the unshared electrons of the ring oxygens is probably extended over the system O1', C2', O1, C2, O2, C3, C4, O4.

The planarity of the molecule and the X-ray investigation of kawain[12] support this view, since the bond distances of the vinylic ether system conjugated to the lactone moiety in the latter compound compare well with the corresponding distances in carolic acid itself (C6–O1: 1.46, O1–C2: 1.37, C2–O2: 1.22, C2–C3: 1.45, C3–C4: 1.32, C4–O4: 1.33 Å). Further support is to find in the ^{13}C NMR spectra of the (*E*)- and (*Z*)-isomers of carolic acid (**3** and **4**, respectively), for which the chemical shifts for the relevant C-atoms show a striking similarity to the shifts of the equivalent C-atoms in the two monoenelic forms of 3-butyryl-5-methyltetronic acid (**6α**, **6β**).[15]



6α **6β**

Although carolic acid and 3-acyltetronic acids chemically are very different, the electron distribution in the two types of compounds is remarkably similar. The bond delocalization demonstrated in this paper makes it understandable that carolic acid easy isomerizes in the presence of acid and that the acidic nature of 3-acyltetronic acids makes it impossible to demonstrate the existence of only one isomer.

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