

# The Preferred Ring-Tautomeric Form of a Bicyclic $\gamma$ -Ketocarboxylic Acid: An Equilibrium Driven by Relief of Angular Hybridization Strain

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**Abstract:** ( $\pm$ )-2-*exo*-Carboxy-2-*endo*-methyl-7-oxobicyclo[2.2.1]heptane exists preferentially in its closed, ring-tautomer form, the tricyclic lactol (C<sub>9</sub>H<sub>12</sub>O<sub>3</sub>), which aggregates catemerically by forming hydroxyl-to-carbonyl hydrogen bonds [O $\cdots$ O = 2.7667(16)Å, O-H $\cdots$ O = 170°] among molecules screw related in *b*. This ring-chain equilibrium is driven by relief of angular strain at the 7-ketone, whose origin is the ketone's sp<sup>2</sup> hybridization vs. the angle enforced by the bicyclic system. In the analogous compound with transposed functional groups, the equilibrium favors the keto acid, which is easily isolated.

**Keywords:** Hydrogen bonding, angle strain, keto carboxylic acids, ring-chain tautomerism, X-ray crystallography.

## INTRODUCTION

Our continued interest in the X-ray structures of crystalline ketocarboxylic acids involves the factors controlling their hydrogen bonding. The simultaneous presence of one donor with two potential receptors leads to a total of five basic patterns that have thus far been found to characterize their H-bonding. Most commonly, as in simple acids, carboxyl groups are paired by mutual hydrogen bonding without ketone participation, to form the common acid-to-acid dimer motif. Less frequently, a chain (catemer) is produced by repetition of an intermolecular carboxyl-to-ketone hydrogen bond. Relatively rare arrangements involve internal hydrogen bonds [1], acid-to-ketone dimers [2] and carboxyl catemers [3].

Many of the  $\gamma$ - and  $\delta$ -ketocarboxylic acids we study are capable of ring-chain tautomerism [4, 5] and several are known to exist predominantly or exclusively in the closed, lactol form, sometimes referred to as the "pseudoacid" [6-10]. A search of the X-ray literature (Cambridge Structural Database, Version 5.27, update of May, 2006) [11] reveals some 63 examples of keto-acid lactol structures, of widely varying degrees of complexity. About 90% of these are derived from what are formally  $\gamma$ -keto acids, which yield five-membered lactols, the size known to be most favorable for such rings [4, 12].

In order to examine issues controlling the position of equilibrium in such cases of ring-chain tautomerism, we have determined the X-ray structure of compound **1**, a keto acid known to exist entirely in the closed lactol form.

## MATERIAL AND METHODS

### Crystallization

Compound **1** was prepared as described by Thompson *et al.* [7]. Crystals suitable for X-ray analysis were produced

from hexane/diisopropyl ether, m.p. 384 K. The solid-state (KBr) infrared spectrum displays intense peaks for associated OH at 3225 and for H-bonded C=O at 1724 cm<sup>-1</sup>. Although an IR spectrum of an ether solution revealed no detectable concentration of the keto-acid form, the keto methyl ester could be produced by direct reaction of such a solution with diazomethane.

### X-Ray Data Collection and Processing

X-ray diffraction data were collected on a Bruker Apex2 diffractometer [13], using monochromatic CuK $\alpha$  radiation of 1.54178 Å at 100K using a stream of nitrogen gas. The crystal, a clear, colorless parallelepiped (0.24 x 0.17 x 0.15 mm), was mounted in a nylon Cryoloop using Paratone-N to hold it in place. Crystallographic Data: Formula = C<sub>9</sub>H<sub>12</sub>O<sub>3</sub>, Molecular weight = 168.19, monoclinic, P 2<sub>1</sub>/n (no. 14), a = 6.4030(5) Å, b = 10.6590(3) Å, c = 12.1023(3), alpha = 90 °, beta = 102.083(1) °, gamma = 90 °, V = 807.68(4) Å<sup>3</sup>, Z = 4, D calcd = 1.383 g cm<sup>-3</sup>, mu = 0.856 mm<sup>-1</sup>, 4350 reflections measured, 1465 reflections independent, R<sub>int</sub> = 0.0516, R(F) = 0.0506, wR<sub>2</sub> = 0.1360, goodness of fit = 1.059, and T = 100.0(1) K.

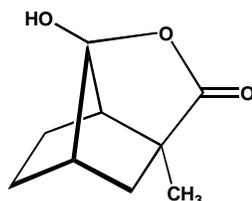
The data were processed using the SHELXTL program package [14]. All of the experimental data are in the X-ray crystallographic files in CIF format and have been deposited with the Cambridge Structural Database as file CCDC 685388. The material can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. (fax: +44 1223 336033 or email: deposit@ccdc.cam.ac.uk).

## RESULTS AND DISCUSSION

( $\pm$ )-2-*exo*-Carboxy-2-*endo*-methyl-7-oxobicyclo[2.2.1]-heptane exists preferentially, even in solution, as the ring-closed tricyclic lactol **1** (see Fig. (1)), the form in which it crystallizes as well. 7-Oxobicyclo[2.2.1]heptanes have internal carbonyl angles at C7 of 97-98° [15], and are thus strained by some 22-23° relative to the natural carbonyl angle. This destabilizes sp<sup>2</sup> relative to sp<sup>3</sup> hybridization and renders a C7 carbonyl particularly susceptible to addition,

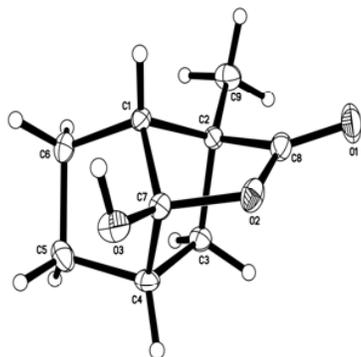
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strongly favoring **1** in this equilibrium, even though the result does not improve the C1-C7-C4 angle in an absolute sense [C1-C7-C4 = 96.01(11) $^\circ$ ]. By contrast, 2-oxonorbornanes, with about 10 $^\circ$  less strain in their internal carbonyl angles [16-19], are far less susceptible to carbonyl addition. Thus, the case of **1** may be dramatically contrasted with that of 7-*syn*-carboxynorbornan-2-one, in which these two functions are merely transposed, and in which the keto-acid form predominates and is easily isolatable [20, 21].



**Fig. (1).** The molecular structure of compound **1**.

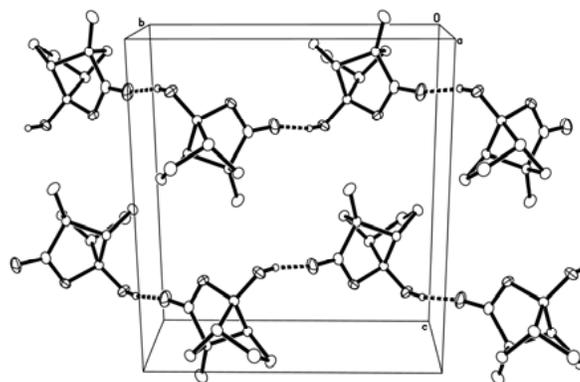
Fig. (2) shows the asymmetric unit, whose only significant rotation involves the hydroxyl group; this is turned so that the H3-O3-C7-O2 torsion = 87 $^\circ$ . In simple bicyclo[2.2.1]heptane systems, the C2-C1-C7 angle is typically 100-103 $^\circ$  [13-17, 22]. In **1**, because of the compression imposed by lactol formation, this angle is 92.89(11) $^\circ$ , and this in turn produces a twist in the C2-C3 bond that mitigates eclipsing strain between the C2-methyl and the endo-H at C3 (H3A-C3-C2-C9 = -34 $^\circ$ ). The analogous torsion on the other side of the system, H6A-C6-C5-H5B, is -12 $^\circ$ .



**Fig. (2).** The asymmetric unit of **1** with its numbering, which follows that of the parent keto acid. Displacement ellipsoids are set at the 40% probability level.

Fig. (3) illustrates the packing arrangement and the H-bonding scheme for **1**. As in other simple lactols, the H bonding is catemeric, proceeding from the hydroxyl of one molecule (O3) to the carbonyl (O1) of a neighbor [O3 $\cdots$ O1 = 2.7667(16) Å, O3-H3 $\cdots$ O1 = 170 $^\circ$ ], in this case one screw-related in *b* (see Table 1).

This pattern arises out of the diminished repertoire of H-bonding modes that result from the presence in the lactol form of only one H-bond donor and one acceptor. Each of the cell's four asymmetric units participates in a separate H-bonding chain, creating two parallel sets of counter-directional pairs, each pair being centrosymmetrically related about  $\frac{1}{2}$ ,  $\frac{1}{2}$ ,  $\frac{1}{2}$ .



**Fig. (3).** A partial packing diagram with extracellular molecules, illustrating the H-bonding arrangement for **1**. All carbon-bound hydrogens are removed for clarity. Displacement ellipsoids are set at the 40% probability level.

We characterize the geometry of H bonding to carbonyls using a combination of the H $\cdots$ O=C angle and the H $\cdots$ O=C-X torsion angle. These describe the approach of the H atom to the O in terms of its deviation from, respectively, C=O axially (ideal = 120 $^\circ$ ) and planarity with the carbonyl (ideal = 0 $^\circ$ ). In **1**, these approach angles for the hydrogen bond are 165 & 35 $^\circ$ , respectively, indicating significant departures, imposed by restraints other than H-bonding, from the ideal packing arrangement.

Within the 2.6-Å range surveyed for non-bonded intermolecular C-H $\cdots$ O packing interactions [23], one close contact was found (2.54 Å) from H3B to O3 in an adjacent molecule (see Table 1). Using compiled data for a large number of C-H $\cdots$ O contacts, Steiner and Desiraju [24] find statistical directionality even as far out as 3.0 Å, and conclude that these are legitimately viewed as "weak hydrogen bonds", with a greater contribution to packing forces than simple van der Waals attractions.

**Table 1.** Hydrogen Bonding and Close Contact (Å,  $^\circ$ )

D(onor)-H $\cdots$ A(ceptor)	D-H	H $\cdots$ A	D-A	D-H $\cdots$ A
O3 - H3 $\cdots$ O1 <sup>a</sup>	0.84	1.93	2.7667(16)	170
C3 - H3B $\cdots$ O3 <sup>b</sup>	0.99	2.54	3.4404(19)	151

symmetry codes: <sup>a</sup>-x+5/2, y+1/2, -z+1/2; <sup>b</sup>-x+3/2, y-1/2, -z+1/2.

## CONCLUSIONS

The X-ray crystal structure of compound **1** has been determined and has been shown to contain the ketol function that is favored, relative to the open-chain alternative, by angle strain in the keto acid.

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