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(±)-7-Oxo-1,2,3,4,4a,5,6,7-octahydronaphthalene-1-acetic acid: catemeric hydrogen bonding and diastereomeric disorder in a bicyclic unsaturated *ε*-keto acid

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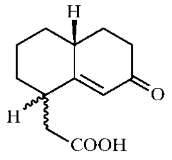
The 68.5:31.5 mixture of diastereoisomers obtained in the synthesis of the title compound, $C_{12}H_{16}O_3$, yielded sharply melting crystals containing the same ratio of epimers, in a disordered crystallographic arrangement. The disorder resides almost entirely in the carboxymethyl side chain, but places the two sets of carboxyl O atoms at nearly identical paired spatial positions. Neither component displays significant carboxyl disorder, and the molecules aggregate as hydrogen-bonded carboxyl-to-ketone catemers [O···O = 2.673 (4) Å and O—H···O = 158°] having glide-related components, with centrosymmetrically related pairs of chains following axes perpendicular to *b*. Close intermolecular C—H···O contacts exist for both the ketone and the carboxyl group. The energetics of the epimers and of their crystallization mode are discussed.

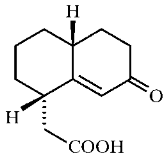
Comment

Our study of the crystal structures of keto carboxylic acids concerns the molecular factors that determine their five known hydrogen-bonding modes. The dominant carboxyl-pairing mode is known to be inhibited whenever centrosymmetry is thwarted (Lalancette & Thompson, 2003) or molecular flexibility is severely curtailed (Barcon *et al.*, 2002). Consequently, we have often focused our attention on single enantiomers and on cyclic systems. The title compound, (I), an example of the latter case, allows full rotation about only two of its 12 C—C single bonds, and the observed hydrogen bonding involves formation of carboxyl-to-ketone chains (catemers). Also revealed is a disorder due to the presence of two isomers occupying the same site in the crystal.

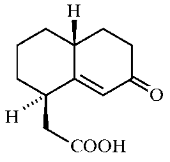
Fig. 1 illustrates an asymmetric unit of (I), with the atom-numbering scheme. The disorder indicated by the ghost bonds and atoms used for C1′ and C9′ is due to the presence of two diastereomers arising from the chiral centers at C1 and C4a. This disorder depends on positioning the carboxymethyl side chain on an equatorial bond, (I*A*), *versus* an axial bond, (I*B*), but also entails an accompanying flexing of the ring system. Compound (I) was prepared from achiral materials and is racemic. Hence, the total number of stereoisomers possible ($2^2 = 4$) represents two diastereomeric racemates, and solution of the data set reveals that both diastereomers are present at the same site in the asymmetric unit. Independent of other information, the disorder was optimally modeled in the least-squares refinement using a 65.6 (11):34.4 (11) ratio for the *cis*/*trans* pair of molecules epimeric at C1, designated (I*A*) and (I*B*), respectively. Subsequent ^{1}H NMR analysis of the bulk material from which the experimental crystal had been obtained by recrystallization found a 68.5:31.5 ratio. The lack of diastereomer selectivity in the crystallization process and the sharp melting point found for these crystals (see *Experimental*) imply that (I*A*) and (I*B*) fit equally well into any position in the crystal lattice with essentially no sacrifice in stability. Thus, it does not appear that either the packing arrangement or the melting point would vary for any mixture of (I*A*) and (I*B*), including the pure materials. We have not attempted it experimentally, but the implication is that separation of these epimers by recrystallization probably cannot succeed, at least for the crystallization mode observed here.



(I)



(I*A*)



(I*B*)

We believe that the observed 68.5:31.5 bulk ratio represents a near-equilibrium mixture of epimers (see *Experimental*). If attached to a simple cyclohexane ring, a carboxymethyl substituent such as ours should occupy an equatorial bond more than 90% of the time at equilibrium, reflecting a free-energy advantage of *ca* 1.7 kcal mol^{-1} (Hirsch, 1967; 1 kcal mol^{-1} = 4.184 kJ mol^{-1}). At the temperature of our preparative reaction (353 K), our 68.5:31.5 equilibrium corresponds to a free-energy difference of only *ca* 0.55 kcal mol^{-1}. This diminished equatorial preference relative to cyclohexane is probably associated with the close juxtaposition in (I*A*) between atom C9 and the vinyl atom H8 five atoms away. The arrangement around the double bond in (I*A*) places the C atom equatorially attached to C1 in the plane of the alkene and at a distance of 2.65 Å from atom H8. In terms of steric hindrance, this spatial relationship is at least the functional equivalent of a 1,3-diaxial C—H interaction in a

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saturated cyclohexane system, where the distance would typically be *ca* 2.8 Å. The corresponding distances in the minor component, (I*B*), between atom C9′ and its own axial H atoms are only 3.35 and 3.40 Å for atoms C3 and C4a, respectively. This occurs because (at least in the crystal) a twist about the C7—C8 bond rotates the alkene and thus C1′ so that its substituents are no longer strictly axial and equatorial with respect to its ring, as may be seen in Fig. 1. The extent of this rotation is also visible and measurable in Fig. 1 as the C1—C8a—C1′ angle [27.6 (3)°].

Dimeric carboxyls often appear with C—O bonds and C—C—O angles fully or partially averaged by disorder, since that mode permits either tautomeric or rotational transposition of the two O atoms without disruption of the overall hydrogen-bonding scheme. Carboxyls involved in non-dimeric arrangements, however, are invariably highly ordered. In (I), these C—O lengths are 1.205 (5) and 1.250 (6) Å, representing significantly less differentiation of the O atoms than is seen in other catemeric cases. Our own survey of 56 keto acid structures that are not dimers gives average values of 1.20 (1) and 1.32 (2) Å for such lengths, in accord with typical values of 1.21 and 1.31 Å cited for highly ordered dimeric carboxyls (Borthwick, 1980). Accompanying this apparent partial averaging in length is a set of distorted C—C—O bond angles for the carboxyl (Table 1), which deviate considerably from the ideal. (The surveys of highly ordered dimeric carboxyls cited above give average values in the ranges 123–125 and 112–113°.) However, all the carboxyl atoms in (I) have very high anisotropies, more consistent with diastereomeric disorder rather than with the routine 'carboxyl' disorder arising from tautomeric hydrogen exchange or other oxygen-transposing mechanisms. In addition, we were unable to find significant electron density for any partial H atom associated with O2. We therefore believe that the various distortions in the carboxyl are actually an artifact of the diastereomeric disorder evident in C1 and C9, and of our inability to separate the merged carboxyls for modeling purposes.

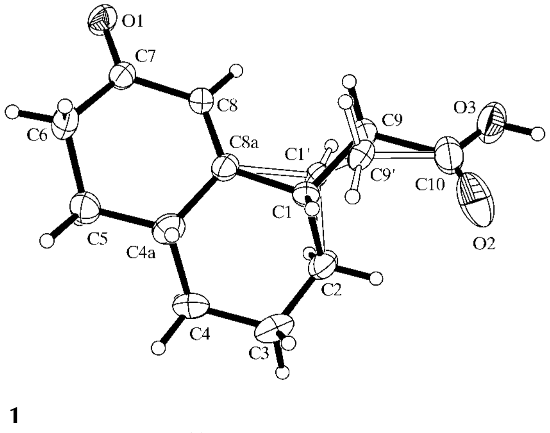

Figure 1
The asymmetric unit of (I) with the atom-numbering scheme. The disorder in atoms C1 and C9 is represented by ghost bonds, with primed numbering for the minor isomer, (I*B*). Displacement ellipsoids are drawn at the 20% probability level and H atoms are shown as small spheres of arbitrary radii.

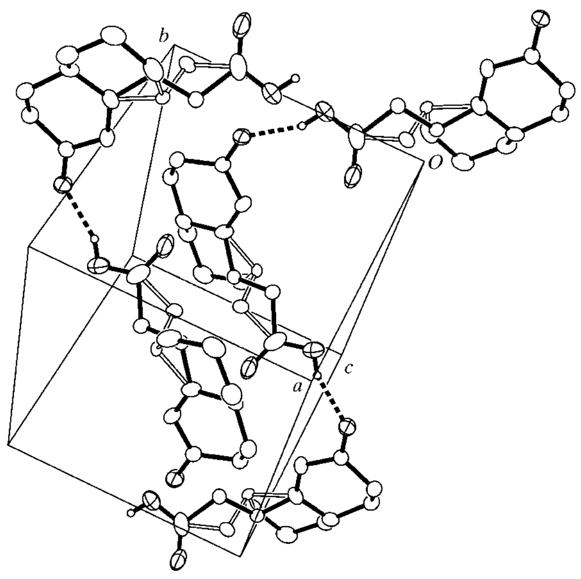

Figure 2
A packing diagram for (I), including extracellular molecules to illustrate the counterdirectionally paired carboxyl-to-ketone glide catemers. All C-bound H atoms have been removed for clarity. Displacement ellipsoids are drawn at the 20% probability level.

Fig. 2 illustrates the packing of the disordered molecules of (I) and their hydrogen-bonding arrangement, which involves catemers having glide-related components. The centrosymmetry of the cell generates counterdirectional pairs of chains, the glide axes of which lie perpendicular to *b*. Overall, the prevalence of subtypes among catemers has been found to be screw > translation > glide.

We characterize the geometry of hydrogen bonding to carbonyls using a combination of the H···O═C angle and the H···O═C—C torsion angle. These describe the approach of the H atom to the O atom in terms of its deviation from, respectively, C═O axiality (ideal = 120°) and planarity with the carbonyl group (ideal = 0°). In (I), these angles are, respectively, 132 and −18.9°.

Both the ketone group (2.64 Å to H9*A*) and atom O3 (2.64 Å to H4*A*) were found to have close C—H···O contacts to separate neighboring molecules, related by a screw axis and by translation, respectively. These distances lie within the 2.7 Å range we usually employ for non-bonded H···O packing interactions (Steiner, 1997). Using compiled data for a large number of C—H···O contacts, Steiner & Desiraju (1998) found significant statistical directionality even as far out as 3.0 Å, and concluded that these are legitimately viewed as 'weak hydrogen bonds', with a greater contribution to packing forces than simple van der Waals attractions.

The solid-state (KBr) IR spectrum of (I) displays separated C═O absorptions at 1721 and 1638 cm^{-1}, typical for, respectively, a carboxyl lacking, and a conjugated ketone having, hydrogen bonding. The peak at lower frequency is broadened, presumably by the slightly differing degrees of conjugation in (I*A*) and (I*B*) due to the C7—C8 twist in the latter. In $CHCl_3$ solution, where carboxyl dimers predominate, these absorptions appear, normally and with similar breadth, at 1712 and 1667 cm^{-1}, along with an alkene peak at 1622 cm^{-1} and a typical carboxyl-dilution shoulder near 1745 cm^{-1}.

Experimental

Compound (I) was prepared *via* the pyrrolidine enamine of cyclohexanone. Alkylation with ethyl bromoacetate (Segre *et al.*, 1957; Stork *et al.*, 1963) was followed by neutralization with sodium ethoxide. Concentration *in vacuo* and distillation then yielded the alkylated enamine, the Robinson annulation of which with methyl vinyl ketone provided the bicyclic keto ester, which was purified by distillation. Subsequent saponification yielded (I) as a solid containing a 68.5:31.5 mixture of epimers (I*A*) and (I*B*), as assessed by ^{1}H NMR [vinyl peaks at δ 5.77 (*s*) and 5.93 (*d*, J = 2 Hz), respectively]. Equilibration experiments with the ethyl ester of the C_{13} side-chain ($C_{15}H_{22}O_3$) homolog of (I) suggest that this ratio probably represents a near-equilibrium mixture of (I*A*) and (I*B*), likely arising during the annulation sequence itself, rather than merely during saponification. Recrystallization of (I) from ethyl acetate gave crystals suitable for X-ray analysis, which melted sharply at 368–371 K.

Crystal data

$C_{12}H_{16}O_3$
M_r = 208.25
Monoclinic, $P2_1/n$
a = 10.354 (2) Å
b = 8.269 (2) Å
c = 13.512 (3) Å
β = 108.27 (2)°
V = 1098.5 (4) Å^3
Z = 4

D_x = 1.259 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 34 reflections
θ = 2.2–9.4°
μ = 0.09 mm^{-1}
T = 296 (2) K
Hexagonal rod, colorless
0.25 × 0.22 × 0.14 mm

Data collection

Siemens *P*4 diffractometer
$2\theta/\theta$ scans
2624 measured reflections
1942 independent reflections
1083 reflections with $I > 2\sigma(I)$
$R_{\rm int}$ = 0.038
$\theta_{\rm max}$ = 25.0°

$h = -12 \rightarrow 1$
$k = -9 \rightarrow 1$
$l = -15 \rightarrow 16$
3 standard reflections
every 97 reflections
intensity variation: <1.7%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.062$
$wR(F^2) = 0.171$
S = 1.02
1942 reflections
156 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0617P)^2 + 0.3911P]$
where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\rm max} < 0.001$
$\Delta\rho_{\rm max}$ = 0.18 e Å^{-3}
$\Delta\rho_{\rm min}$ = −0.22 e Å^{-3}
Extinction correction: *SHELXL*97 in *SHELXTL* (Sheldrick, 1997)
Extinction coefficient: 0.017 (4)

Table 1
Selected geometric parameters (Å, °).

O2—C10	1.205 (5)	O3—C10	1.250 (6)
O2—C10—C9	132.8 (6)	O3—C10—C9	104.6 (5)

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O3—H3···O1$^{\rm i}$	0.82	1.89	2.573 (4)	158

Symmetry code: (i) $\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{2}+z$.

All H atoms for (I) were found in electron-density difference maps but were placed in calculated positions (C—H distances of 0.97 Å for methylene, 0.98 Å for methine and 0.93 Å for vinyl H, and an O—H distance of 0.82 Å for the hydroxyl H atom) and were allowed to refine as riding models on their respective C and O atoms, with $U_{\rm iso}$(H) = 1.2$U_{\rm eq}$(C) and 1.5$U_{\rm eq}$(O).

Data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXS*97 in *SHELXTL* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 in *SHELXTL*; molecular graphics: *SHELXP*97 in *SHELXTL*; software used to prepare material for publication: *SHELXL*97.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FR1467). Services for accessing these data are described at the back of the journal.

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