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Hydrogen Bonding and Conformational Analysis of (*R*)-Norcarnitine Monohydrate

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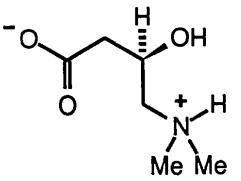
Abstract. (*R*)-4-(*N*,*N*-Dimethylammonio)-3-hydroxybutanoate [(*R*)-norcarnitine] monohydrate, $C_6H_{13}NO_3.H_2O$, $M_r = 165{\cdot}2$, triclinic, $P\bar{1}$, $a = 5{\cdot}9081\ (5)$, $b = 6{\cdot}0438\ (4)$, $c = 6{\cdot}9084\ (7)$ Å, $\alpha = 65{\cdot}584\ (6)$, $\beta = 81{\cdot}957\ (8)$, $\gamma = 77{\cdot}771\ (6)°$, $V = 219{\cdot}1\ (1)$ Å^3, $Z = 1$, $D_x = 1{\cdot}252$ g cm^{-3}, λ(Cu $K\alpha$) = 1·54184 Å, $\mu = 8{\cdot}46$ cm^{-1}, $F(000) = 90$, $T = 296$ K, $R = 0{\cdot}035$ for 1763 observations (of 1772 unique data). Intermolecular hydrogen bonding dominates the structure. The molecule of water contacts three different zwitterions, with O···O distances 2·7767 (13), 2·720 (2) and 2·722 (2) Å. A hydrogen bond between carboxylate and dimethylammonio links the zwitterions in head-to-tail motif, N···O 2·672 (2) Å. Comparison with two other 4-ammonio-3-hydroxybutanoates reveals that the title compound adopts a different conformation along the backbone, N^+—C—C(OH)—C—CO_2^-, with N^+—C—C(OH)—C *anti* and C—C(OH)—C—CO_2^- *gauche*$^-$.

Introduction. (*R*)-Norcarnitine (1) is the key synthon in the syntheses of conformationally rigid inhibitors of carnitine acyltransferases (Gandour, Colucci, Stelly, Brady & Brady, 1986, 1988). Because of our interest in conformations of 4-ammonio-3-hydroxybutanoates (Gandour, Colucci & Fronczek, 1985), we have sought a single crystal for X-ray analysis. For large-scale preparations of norcarnitine we produce the crystalline sodium salt (Colucci, Turnbull & Gandour, 1987), because the hydrochloride and the zwitterion are hygroscopic. We have failed repeatedly to obtain a crystal of the sodium salt that is suitable for X-ray analysis. We have found a suitable crystal of the monohydrate of the title compound in the bottom of a 'benignly neglected' bottle containing zwitterionic (*R*)-norcarnitine in a wet solution of 2-propanol/ethyl ether.



(1)

Experimental. Golden plate crystals of (*R*)-norcarnitine, m.p. 365–366 K, synthesized from enantiomerically pure (*R*)-carnitine by the method of Colucci *et al.* (1987), were obtained after eight months from a 50/50 (*v*/*v*) solution of 2-propanol/ethyl ether with one equivalent water. Crystal size 0·25 × 0·37 × 0·45 mm, capillary mounted for protection against humidity, space group from Laue symmetry $\bar{1}$ and known chirality of the compound, cell dimensions from setting angles of 25 reflections having $14 < \theta < 32°$. Data collection on an Enraf–Nonius CAD-4 diffractometer, Cu $K\alpha$ radiation, graphite monochromator, ω–2θ scans designed for $I = 100\sigma(I)$, subject to max. scan time = 120 s, scan rates varied 0·28–3·30° min^{-1}. The full sphere of data having $2 < \theta < 75°$, $-7 \le h \le 7$, $-7 \le k \le 7$, $-8 \le l \le 8$ measured. Approximately 300 data were measured a second time. Data corrected for background, Lorentz and polarization effects. Standard reflections 400, 030, 002 exhibited only random fluctuations. Absorption corrections were based on ψ scans, with minimum relative transmission coefficient 94·95%. 2149 total data were collected, and redundant data merged, $R_{int} = 0{\cdot}012$, to yield 1772 unique data, 1763 observed with $I > 3\sigma(I)$. Structure solved by direct methods using *MULTAN*11/82 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1982), refined by full-matrix least squares based upon F with weights $w = F_o^2[\sigma^2(I) + (0{\cdot}02F_o^2)^2]^{-1}$ using *SDP* (Frenz, 1980), scattering factors of Cromer & Waber (1974), anomalous coefficients of Cromer (1974). Non-H atoms refined anisotropically, H atoms located by ΔF synthesis and refined isotropically. Final $R = 0{\cdot}03525$ (0·035 for all data), $wR = 0{\cdot}05566$, $S = 2{\cdot}859$ for 158 variables. Maximum shift $0{\cdot}22\sigma$ in the final cycle, max. residual density 0·37, min. −0·34 e Å^{-3}, extinction coefficient $g = 2{\cdot}0\ (2) \times 10^{-4}$, where the correction factor $(1 + gI_c)^{-1}$ was applied to F_c. Refinement of a model corresponding to the *S* isomer under identical conditions yielded $R = 0{\cdot}03536$, $wR = 0{\cdot}05613$ and $S = 2{\cdot}900$. The better fit for the *R* isomer is in agreement

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Table 1. *Fractional atomic coordinates and equivalent isotropic temperature factors*

$$B_{eq} = (8\pi^2/3)\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	B_{eq}(Å^2)
O1	0	0	0	4·36 (2)
O2	−0·0162 (2)	0·3841 (2)	−0·2368 (2)	4·95 (2)
O3	0·5047 (2)	−0·2487 (2)	−0·3956 (2)	4·74 (2)
N	0·6471 (2)	−0·5127 (2)	0·0297 (2)	3·10 (2)
C1	0·0652 (2)	0·1572 (2)	−0·1688 (2)	3·26 (2)
C2	0·2544 (3)	0·0813 (3)	−0·3142 (2)	3·89 (3)
C3	0·3674 (2)	−0·1905 (2)	−0·2313 (2)	3·34 (2)
C4	0·5277 (2)	−0·2491 (2)	−0·0580 (2)	3·31 (2)
C5	0·7907 (3)	−0·5549 (3)	0·2068 (2)	4·53 (3)
C6	0·4847 (2)	−0·6918 (2)	0·1009 (3)	4·11 (3)
O1*W*	0·1698 (3)	0·7033 (3)	−0·6022 (2)	6·65 (3)

Table 2. *Bond distances* (Å), *angles and selected torsion angles* (°)

O1—C1	1·235 (1)	N—C6	1·484 (2)
O2—C1	1·258 (1)	C1—C2	1·523 (2)
O3—C3	1·422 (2)	C2—C3	1·529 (2)
N—C4	1·499 (1)	C3—C4	1·510 (2)
N—C5	1·491 (2)		

C4—N—C5	109·5 (1)	C1—C2—C3	116·5 (1)
C4—N—C6	113·31 (9)	O3—C3—C2	111·12 (9)
C5—N—C6	110·8 (1)	O3—C3—C4	106·8 (1)
O1—C1—O2	124·9 (1)	C2—C3—C4	110·6 (1)
O1—C1—C2	120·14 (9)	N—C4—C3	113·6 (1)
O2—C1—C2	115·0 (1)		

H3O—O3—C3—C2	−71 (2)	O2—C1—C2—C3	176·6 (1)
H3O—O3—C3—C4	168 (2)	C1—C2—C3—O3	168·0 (1)
C5—N—C4—C3	−177·0 (1)	C1—C2—C3—C4	−73·6 (2)
C6—N—C4—C3	−52·8 (2)	O3—C3—C4—N	−58·4 (2)
O1—C1—C2—C3	−4·6 (2)	C2—C3—C4—N	−179·4 (3)

with the known absolute configuration of the starting materials.

Discussion. Table 1 lists the fractional coordinates.* Table 2 presents bond distances, bond angles and selected torsion angles. Fig. 1 shows the asymmetric unit (principal ellipses) with hydrogen-bond contacts (boundary ellipses only), while Fig. 2 shows a stereoview of the unit cell.

Intermolecular hydrogen bonding controls crystal packing. One hydrogen bond, between dimethylammonio N and carboxylate O2 of a molecule that is translated $x + 1$ and $y - 1$, links the zwitterions in a head-to-tail motif. This strong nearly linear hydrogen bond has an O···N distance of 2·672 (2) Å and an angle of 170 (2)° about H1N. This hydrogen bond forms in the *syn* direction to carboxylate, which is the preferred orientation (Gandour, 1981; Ippolito, Alexander & Christianson, 1990). The three other hydrogen bonds involve the water molecule. Water donates hydrogen bonds to carboxylate O2 of the zwitterion [O···O, 2·720 (2) Å; angle about H1*W*, 145 (3)°] and carboxylate O1 of a zwitterion that is translated $y + 1$ and $z - 1$ [O···O, 2·777 (2) Å; angle about H2*W*, 161 (3)°]. Both hydrogen bonds form in the *anti* direction to the carboxylates. This hydrogen-bonding pattern produces a chain motif where water bridges the carboxylates on adjacent zwitterions. Water accepts a hydrogen bond from hydroxyl O3 of a zwitterion that is translated $y + 1$ [O···O, 2·722 (2) Å; angle about H3O, 165 (2)°]. These three hydrogen bonds to waters undoubtedly influence the conformation of the zwitterion.

Table 3 compares selected structural parameters of three 4-ammonio-3-hydroxybutanoates: ammonio [(*RS*)-GABOB] (Tomita, Harada & Fujiwara, 1973); dimethylammonio [(*R*)-norcarnitine] (this work); trimethylammonio [(*R*)-carnitine] (Gandour *et al.*, 1985). The C4—N distance and C3—C4—N angle increase with the size of the ammonio group.

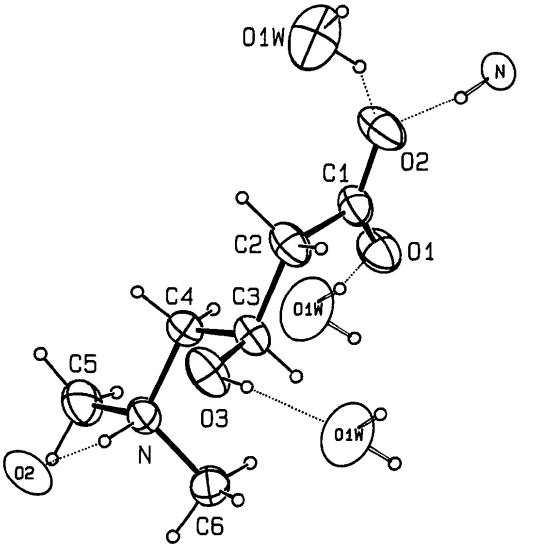

Fig. 1. Numbering scheme and thermal ellipsoids drawn at the 50% probability level. H atoms are drawn with arbitrary radii. Principal ellipses indicate the atoms of the asymmetric unit; only boundary ellipses indicate atoms that hydrogen bond.

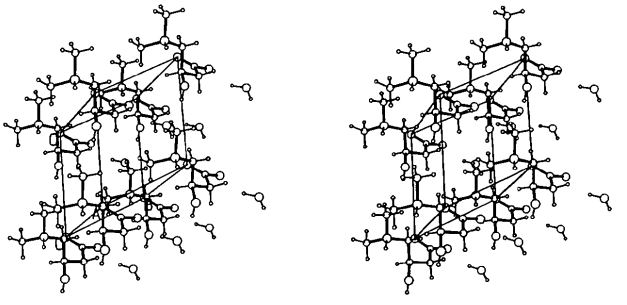

Fig. 2. Stereoview of the unit cell viewed approximately along the *a* axis with *c* vertical. The origin is defined to be the position of O1 (lower left, background).

* Tables of H-atom parameters, torsion angles, anisotropic thermal parameters and structure-factor amplitudes have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53604 (14 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. *Comparison of selected bond distances* (Å), *angles and torsion angles* (°) *in* 4-*ammonio*-3-*hydroxybutanoates*

	(*RS*)-GABOB[a] (ammonio)	(*R*)-Norcarnitine[b] (dimethylammonio)	(*R*)-Carnitine[c] (trimethylammonio)
C3—C4	1·516 (9)	1·510 (2)	1·528 (2)
C4—N	1·477 (8)	1·499 (1)	1·521 (1)
C1—C2—C3	111·4 (6)	116·5 (1)	113·4 (1)
C2—C3—C4	110·8 (5)	110·6 (1)	105·6 (1)
C2—C3—O3	111·1 (5)	111·12 (9)	108·7 (1)
O3—C3—C4	107·0 (5)	106·8 (1)	113·1 (1)
C3—C4—N	109·5 (5)	113·6 (1)	117·3 (1)
C1—C2—C3—C4	−173 (1)	−73·6 (2)	−171·6 (2)
C1—C2—C3—O3	67 (1)	168·0 (1)	66·7 (2)
C2—C3—C4—N	168 (1)	−179·4 (3)	−179·7 (2)
O3—C3—C4—N	−70 (1)	−58·4 (2)	−61·5 (5)

References: (*a*) Tomita *et al.* (1973). (*b*) This work. (*c*) Gandour *et al.* (1985).

(*R*)-Carnitine has significantly different C2—C3—C4, C2—C3—O3 and O3—C3—C4 angles from GABOB and (*R*)-norcarnitine, which have similar values for these parameters. The dimethylammonio group in (*R*)-norcarnitine rotates into a conformation where the H atom on the N atom eclipses O3. The unsubstituted ammonio group in (*RS*)-GABOB can only have an H atom eclipse O3, but the trimethylammonio in (*R*)-carnitine must have a methyl group eclipse. The steric repulsion between methyl and O3 results in larger C3—C4—N and O3—C3—C4 angles but smaller C2—C3—C4 C2—C3—O3 angles. Backbone conformation, C1—C2—C3—C4 and C2—C3—C4—N, in (*RS*)-GABOB and (*R*)-carnitine is *anti, anti*; but in (*R*)-norcarnitine, it is *gauche*$^-$, *anti*. This conformational change results in a larger C1—C2—C3 angle in (*R*)-norcarnitine compared to the other compounds.

Intramolecular interactions control conformation about the C3—C4 bond while intermolecular forces influence conformation about the C2—C3 bond. The '*gauche* effect' of polar bonds O3—C3—C4—N dominates the C3—C4 conformation (see Gandour *et al.*, 1985, and references therein). The C1—C2—C3—C4 torsion angle favors *anti* and *gauche*$^-$ more than *gauche*$^+$ (Gandour *et al.*, 1985; Colucci, Gandour & Mooberry, 1986). Intramolecular hydrogen bonding between hydroxyl and carboxylate in GABOB requires an *anti* conformation for C1—C2—C3—C4. An *anti* conformation occurs in (*R*)-carnitine without intramolecular hydrogen bonding. For (*R*)-norcarnitine, the interactions with water must influence the change to *gauche*$^-$.

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Structure of Heteronemin

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Abstract. (5α,5′α,12β,16β,17aα)-5′,17a-Dihydro-4,4,8-trimethyl-*D*-homoandrostano[17,17a-*c*]furan-5′,12,16-triol 5′,16-diacetate, $C_{29}H_{44}O_6$, $M_r = 488{\cdot}77$, crystallized as a hemiacetonitrile solvate, $C_{29}H_{44}O_6.1/2C_2H_3N$, $M_r = 509{\cdot}20$, monoclinic, *C*2, $a = 36{\cdot}917$ (11), $b = 6{\cdot}289$ (2), $c = 12{\cdot}421$ (2) Å, $\beta = 104{\cdot}51$ (2)°, $V = 2791{\cdot}7$ (11) Å^3, $Z = 4$, $D_x = 1{\cdot}212$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71073 Å, μ =

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