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# Calcium-Selective Ligands. 1. Structure of 3,12-Bis(carboxymethyl)-6,9-dioxa-3,12-diazatetradecanedioic Acid ($H_4$egta)

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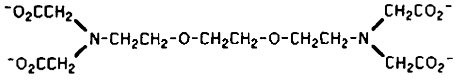
**Abstract.** $C_{14}H_{24}N_2O_{10}$, $M_r$ = 380·35, triclinic, $P\bar{1}$, $a$ = 6·702 (2), $b$ = 6·792 (2), $c$ = 10·048 (3) Å, $\alpha$ = 82·23 (2), $\beta$ = 78·82 (2), $\gamma$ = 71·33 (2)°, $V$ = 424·1 (1) Å$^3$, $Z$ = 1, $D_x$ = 1·49 g cm$^{-3}$, $\lambda$(Mo $K\alpha$) = 0·71073 Å, $\mu$ = 1·19 cm$^{-1}$, $F$(000) = 202, room temperature. $R$ = 0·055 for 1269 observed reflections. $H_4$egta exists in the solid state as an infinite network of hydrogen-bonded zwitterions. Each $R_2R'NH^+$ group is involved in two intramolecular and one intermolecular hydrogen bond to carboxylate O atoms. Additional intermolecular linkages occur *via* short hydrogen bonds [O···O = 2·444 (3), 2·450 (3) Å] between anionic carboxylate groups across the crystallographic inversion center; these hydrogen bonds may be symmetric. The infrared spectrum contains features characteristic of strong O—H—O hydrogen bonding [$\nu_{as}$(O—H—O) ≈ 750 cm$^{-1}$, $\Delta\nu$ ≈ 1000 cm$^{-1}$].

**Introduction.** The potentially octadentate ligand egta$^{4-}$ (see below) exhibits a binding constant for calcium which is five orders of magnitude larger than that for magnesium (Sillén & Martell, 1971). For comparison, the calcium-binding preference exhibited by the familiar ligand edta$^{4-}$ is less than two orders of magnitude. This high degree of calcium selectivity is similar to that exhibited by calcium-binding proteins (Potter & Gergely, 1975). To initiate a study of the bases for this selectivity, the structure of the tetraprotonated neutral $H_4$egta ligand has been determined.



$(^{-}O_2CCH_2)_2N\text{-}CH_2CH_2\text{-}O\text{-}CH_2CH_2\text{-}O\text{-}CH_2CH_2\text{-}N(CH_2CO_2^{-})_2$

egta$^{4-}$

**Experimental.** $H_4$egta purchased from J. T. Baker Chemical Company. Crystal [0·35 (100 → $\bar{1}$00) × 0·12 (001 → 00$\bar{1}$) × 0·07 mm (010 → 0$\bar{1}$0)] obtained by slow cooling of hot aqueous solution (0·26 $M$ in $H_4$egta). Nicolet $R3m$ diffractometer, cell constants from least-squares fitting of setting angles for 24 reflections ($2\theta_{av.}$ = 13·30°). Data collected for $3·5 \le 2\theta \le 50·0°$, $-7 \le h \le 7$, $-7 \le k \le 7$, $0 \le l \le 10$, $\theta/2\theta$ scans. Three control reflections (020, $\bar{4}$00, 01$\bar{4}$), monitored every 97 reflections, showed no significant variation. Lorentz and polarization corrections applied, but no absorption correction; of 1495 unique reflections, 1269 observed [$I \ge 2\sigma(I)$] and used in further calculations. Structure solved by direct methods using *RANT* (Sheldrick, 1983); all non-H atoms refined anisotropically; C-bound H atoms included in calculated positions, carboxylate H atoms fixed on inversion center, positional parameters refined for N—H H atom. Block, weighted $\{w = [\sigma^2(F) + gF^2]^{-1}, g = 3·5 \times 10^{-3}\}$ least-squares refinement on $F$ yielded $R$ = 0·055, $wR$ = 0·076, and $S$ = 1·15 at convergence (mean shift/e.s.d. < 0·01, max. shift/e.s.d. < 0·04, over last four cycles) with largest peak in final Fourier synthesis of +0·33 e Å$^{-3}$ and a minimum of −0·37 e Å$^{-3}$. Neutral-atom scattering factors used (*International Tables for X-ray Crystallography,* 1974); software for diffractometer provided with Nicolet $R3m$; *SHELXTL*

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programs (Sheldrick, 1983) used for structure solution, refinement, and plotting.*

Initially, acetate protons were fixed on inversion centers. When this constraint was removed, the protons moved slightly off the inversion centers (an average of 3·4$\sigma$). A detailed examination of a difference Fourier map with the acetate protons removed did not reveal two distinct peaks on either side of the inversion center, and the peaks were elongated perpendicular to the O···O axis instead of along the axis. As a result, the acetate H atoms were fixed at an inversion center in the final structural model.

Infrared spectra of H$_4$egta and D$_4$egta were taken (Perkin–Elmer 983) in both Fluorolube (4000–1550 cm$^{-1}$) and Nujol (1550–300 cm$^{-1}$) mulls with KBr windows. Dissolving H$_4$egta in hot 99% D$_2$O yielded crystalline D$_4$egta upon cooling.

**Discussion.** The molecular structure and numbering scheme for H$_4$egta are depicted in Fig. 1 and the inter- and intramolecular hydrogen-bonding interactions are shown in Fig. 2. Final atomic coordinates and equivalent isotropic thermal parameters for all refined atoms are given in Table 1, while derived bond lengths and angles are displayed in Table 2.

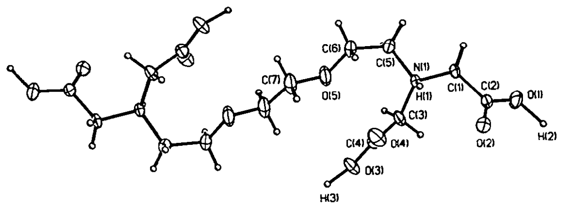

Fig. 1. A thermal-ellipsoid plot (45%) depicting the numbering scheme for H$_4$egta. H(2) and H(3) are shared with other H$_4$egta molecules in the lattice.

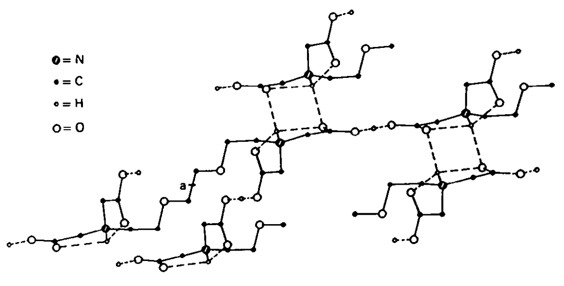

Fig. 2. A diagram illustrating the inter- and intramolecular hydrogen-bonding interactions. The inversion center for the only complete H$_4$egta molecule in the diagram is indicated by 'a'.

H$_4$egta exists in the zwitterionic form. The unique N—H proton was located and its position was refined [N(1)—H(1) = 0·89 (3) Å]. The C—N bond lengths [C—N$_{av.}$ = 1·50 (1) Å] are longer than is typical for a C—N single bond (1·47 Å), which is consistent with the presence of a formal positive charge on the N atom (Birnbaum, 1967). The two carboxylate groups exhibit very similar geometries; the two chemically distinct C—O distances average 1·282 (5) Å [C(2)—O(1) and C(4)—O(3)] and 1·221 (1) Å [C(2)—O(2) and C(4)—O(4)]. As discussed above, the hydrogen bonding between carboxylate groups appears to be symmetric, although a disordered, asymmetrically bridged structure is difficult to distinguish crystallographically (Hamilton & Ibers, 1968). The difference between the

Table 1. *Fractional atomic coordinates* (× 10$^4$) *and isotropic thermal parameters* (Å$^2$ × 10$^3$)

E.s.d.'s in the least-significant digits are given in parentheses.

| | $x$ | $y$ | $z$ | $U_{eq}$*/$U_{iso}$ |
|---|---|---|---|---|
| C(1) | 2215 (3) | 10095 (3) | 8800 (2) | 28 (1) |
| C(2) | 2121 (3) | 12130 (3) | 9314 (2) | 25 (1) |
| C(3) | 5010 (3) | 10210 (3) | 6807 (2) | 29 (1) |
| C(4) | 7383 (3) | 9899 (3) | 6532 (2) | 30 (1) |
| C(5) | 4497 (4) | 6827 (3) | 7885 (2) | 34 (1) |
| C(6) | 6732 (4) | 5434 (3) | 7478 (2) | 40 (1) |
| C(7) | 9692 (4) | 4835 (4) | 5751 (3) | 43 (1) |
| N(1) | 4392 (3) | 9019 (2) | 8098 (2) | 23 (1) |
| O(1) | 213 (3) | 13339 (2) | 9562 (2) | 38 (1) |
| O(2) | 3747 (2) | 12448 (2) | 9481 (2) | 32 (1) |
| O(3) | 8059 (3) | 10403 (3) | 5287 (2) | 40 (1) |
| O(4) | 8419 (3) | 9311 (3) | 7461 (2) | 42 (1) |
| O(5) | 7479 (3) | 5897 (3) | 6092 (2) | 40 (1) |
| H(1) | 5290 (36) | 8970 (33) | 8649 (22) | 21 (5) |
| H(2) | 0 | 15000 | 10000 | 103 (17) |
| H(3) | 10000 | 10000 | 5000 | 55 (11) |

* Equivalent isotropic $U$ is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

Table 2. *Bond lengths* (Å) *and angles* (°)

E.s.d.'s in the least-significant digits are given in parentheses.

| | | | |
|---|---|---|---|
| C(1)—C(2) | 1·519 (3) | C(1)—N(1) | 1·491 (2) |
| C(2)—O(1) | 1·278 (2) | C(2)—O(2) | 1·223 (3) |
| C(3)—C(4) | 1·511 (3) | C(3)—N(1) | 1·493 (2) |
| C(4)—O(3) | 1·285 (2) | C(4)—O(4) | 1·220 (3) |
| C(5)—C(6) | 1·506 (3) | C(5)—N(1) | 1·510 (3) |
| C(6)—O(5) | 1·415 (3) | C(7)—O(5) | 1·423 (3) |
| C(7)—C(7$^i$) | 1·492 (5) | O(1)—H(2) | 1·222 (2) |
| O(3)—H(3) | 1·225 (2) | N(1)—H(1) | 0·89 (3) |
| H(1)···O(2) | 2·45 (2) | H(1)···O(4) | 2·27 (2) |
| H(1)···O(2$^i$) | 2·11 (2) | | |
| | | | |
| C(2)—C(1)—N(1) | 111·6 (2) | C(1)—C(2)—O(1) | 112·2 (2) |
| C(1)—C(2)—O(2) | 120·7 (2) | O(1)—C(2)—O(2) | 127·0 (2) |
| C(4)—C(3)—N(1) | 111·2 (2) | C(3)—C(4)—O(3) | 112·8 (2) |
| C(3)—C(4)—O(4) | 120·0 (2) | O(3)—C(4)—O(4) | 127·2 (2) |
| C(6)—C(5)—N(1) | 113·5 (2) | C(5)—C(6)—O(5) | 110·3 (2) |
| O(5)—C(7)—C(7$^i$) | 107·9 (2) | C(1)—N(1)—C(3) | 112·1 (1) |
| C(1)—N(1)—C(5) | 108·7 (2) | C(3)—N(1)—C(5) | 112·8 (2) |
| C(6)—O(5)—C(7) | 110·8 (2) | C(1)—N(1)—H(1) | 107 (1) |
| C(3)—N(1)—H(1) | 107 (1) | C(5)—N(1)—H(1) | 109 (1) |
| H(2)—O(1)—C(2) | 116·2 (2) | H(3)—O(3)—C(4) | 114·5 (2) |
| N(1)—H(1)···O(2) | 100 (1) | N(1)—H(1)···O(4) | 111 (2) |
| N(1)—H(1)···O(2$^i$) | 142 (2) | | |

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* Lists of H-atom coordinates, anisotropic thermal parameters, and observed and calculated structure factors have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42744 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

two chemically distinct sets of C—O distances is 0·059 (6) Å. This value is consistent with the strongly hydrogen-bonded nature of these carboxylate groups; the O···O hydrogen-bond distances of 2·444 (3) Å [O(1)···O(1$^{i}$)] and 2·449 (3) Å [O(3)···O(3$^{i}$)] rank among the shortest that have been observed (Emsley, 1980). In an anionic carboxylate, these two distances would be identical, and in a non-hydrogen-bonded carboxylic acid, this difference is typically 0·1 Å (Manojlović & Speakman, 1967).

The H atom bound to N is involved in three non-linear hydrogen-bonding interactions. Two of these interactions involve the carbonyl O atoms of the acetate groups attached to that N atom [N(1)···O(2) = 2·746 (2) Å and N(1)···O(4) = 2·717 (3) Å], while one involves the carbonyl group in an adjacent molecule [N(1)···O(2$^{i}$) = 2·862 (2) Å]. Similar trifurcated hydrogen bonds have been identified in a recent survey (Jeffrey & Mitra, 1984). The bridging geometry is very similar to that seen in $H_4$edta (Cotrait, 1972).

Correlations have been developed between O···O bond distances in hydrogen-bonded systems and the positions of the infrared stretching and bending modes associated with the hydrogen bond (Novak, 1974). The infrared spectrum of $H_4$egta appears to be consistent with these correlations. As is characteristic of systems containing strong hydrogen bonds, there is no evidence of an O—H stretching band in the region of 3500–2000 cm$^{-1}$. Instead, a broad feature spanning 1500–500 cm$^{-1}$ (maximum at approximately 750 cm$^{-1}$) is apparent in the infrared spectrum of $H_4$egta. This band is similar in breadth and position to the band identified as $\nu_{as}$(O—H—O) in the infrared spectrum of $H_4$edta (Novak, Cotrait, Joussot-Dubien & Lascombe, 1965), which arises from a hydrogen bond approximately equal in length to that in $H_4$egta. As expected, this feature moves to lower frequency (maximum at approximately 550 cm$^{-1}$) upon deuteration. The correlation between the position of the O—H—O stretching mode and the out-of-plane ($\gamma$) bending mode of the hydrogen bond would predict a $\gamma$ mode for $H_4$egta at 1250 cm$^{-1}$. A band at 1220 cm$^{-1}$ (which moves to 878 cm$^{-1}$ in $D_4$egta) is observed, and is assigned to this out-of-plane bending motion.

Such correlations are less successful in predicting the position of the in-plane ($\delta$) bending mode of O···O hydrogen bonds, due to strong coupling with other bands. In fact, the $\delta$ mode was not readily apparent in the infrared spectrum of $H_4$egta. However, upon deuteration two bands appeared (1280, 1320 cm$^{-1}$). Assignment of these bands as $\delta$ bands is consistent with assignments made in other strongly hydrogen-bonded systems (Emsley, 1980). The $\delta$ bands would be expected to occur very close to the C=O stretch in $H_4$egta, based on the observed band positions in $D_4$egta; this may be why these bands were not seen in the infrared spectrum of the protonated species.

Table 3. *Infrared band assignments for* $H_4$*egta and* $D_4$*egta* (cm$^{-1}$)

| | $H_4$egta | $D_4$egta |
|---|---|---|
| $\nu$(C=O) | 1741 | 1690 |
| $\nu$(C–O) | 1400 | 1414 |
| $\nu$[N–H(D)$^+$] | 3052 | 2157 |
| $\delta$[N–H(D)$^+$] | 1356 | — |
| $\nu$[O–H(D)–O] | 1500–500 (max. 750) | 1300–? (max. 550) |
| $\gamma$[O–H(D)–O] | 1228 | 878 |
| $\delta$[O–H(D)–O] | — | 1280, 1320 |

N—H (N—D) stretching and bending modes have also been identified in the infrared spectrum. Possible band assignments are summarized in Table 3.

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