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# Barium (2,6-Dimethylphenyl)carbamoylmethyliminodiacetate Trihydrate, Ba-HIDA

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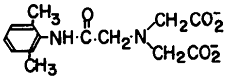
## Abstract

$Ba^{2+}.[C_6H_3(CH_3)_2.NH.CO.CH_2.N(CH_2CO_2)_2]^{-2}.3H_2O$, $Ba^{2+}.[C_{14}H_{16}N_2O_5]^{2-}.3H_2O$, $M_r = 483\cdot68$, is monoclinic, $P2_1/c$, with $a = 17\cdot082\,(8)$, $b = 7\cdot826\,(4)$, $c = 13\cdot900\,(3)$ Å, $\beta = 99\cdot26\,(3)°$, $V = 1834\,(1)$ Å$^3$, $Z = 4$, $D_c = 1\cdot75$, $D_o = 1\cdot73\,(1)$ Mg m$^{-3}$. The structure was determined by Patterson and electron density difference methods and refined by full-matrix least squares to $R = 0\cdot048$ for 3007 reflections; $R_w = 0\cdot057$. The structure comprises alternating layers of anions and water/Ba cations in the (404) planes. Hydrogen bonding is important in bonding the structure. Bond distances and angles are normal.

## Introduction

The compound (2,6-dimethylphenyl)carbamoylmethyliminodiacetic acid, HIDA, a lidocaine analogue, when complexed with $^{99}$Tc was originally developed for myocardial imaging but was of little value. It has, however, aroused interest as a radiopharmaceutical for the evaluation of hepatobiliary function (Harvey, Loberg & Cooper, 1975). The exact nature of the technetium complex is unknown and precise structural details for HIDA were also unkown. As part of a study to characterize, both chemically and structurally, technetium radiopharmaceuticals, we have undertaken the structural characterization of the Ba salt of HIDA in order to study changes in the ion on complexation.



The compound was obtained by dissolving acid HIDA (0·29 g) in a minimum amount of hot water (20 ml), reacting with the stoichiometric amount of barium hydroxide (0·17 g), filtering and then allowing the solution to cool when the title compound separated as colourless crystals.

A plate 0·166 × 0·133 × 0·400 mm, homogeneous under a polarizing microscope, was used for X-ray studies, and the crystal was mounted along the long direction. Symmetry was obtained from precession photographs. The unit cell was determined by a least-squares fit of 15 well centred reflections ($20° < 2\theta < 31°$) at 295 K on a Syntex $P3$ diffractometer. The density of a crystal was determined by flotation in a carbon tetrachloride–bromoform mixture yielding $Z = 4$. The intensities of 4211 independent reflections up to $2\theta = 55°$ were measured with Mo $K\alpha$ radiation ($\lambda = 0\cdot71069$ Å) using a crystal monochromator. The intensities were measured in the $2\theta$(counter)–$\theta$(crystal) scan mode. After removal of reflections with $I < 0$ (290), 3007 reflections were considered observed [$I > 3\sigma(I)$] and were used for the structure determination; 914 were considered unobserved [$3\sigma(I) > I > 0$] and were given no weight in the structure determination unless $|F_c| > |F_o|$ (382). The method of data treatment has been described previously (Hughes, Krishnamachari, Lock, Powell & Turner, 1977; Lippert, Lock, Rosenberg & Zvagulis, 1977). Corrections were not made for absorption ($\mu = 2\cdot26$ mm$^{-1}$) and this will make a maximum error in $F$ of 9%. Corrections were made for Lorentz–polarization effects but an extinction correction was unnecessary. The stability of the experimental system was monitored by measuring two standard reflections after every 48 reflections (302, $51\bar{1}$) and they showed e.s.d.'s of 1·07 and 1·10% with no time variation.

The Ba atom was found from a Patterson synthesis and subsequent refinement and electron-density difference maps revealed all the remaining atoms. Further full-matrix least-squares refinement, minimizing $\sum w(|F_o| - |F_c|)^2$, and using an anisotropic tempera-

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Table 1. *Atomic positional parameters* ($\times 10^4$) *and isotropic temperature factors* $U_{eq}$ *or* $U$ (Å$^2 \times 10^3$)

| | $x$ | $y$ | $z$ | $U_{eq}$ or $U$ |
|---|---|---|---|---|
| Ba | 511·7 (2) | 925·4 (4) | 2018·5 (2) | 23·8 (2)* |
| C(1) | 3632 (4) | 3172 (9) | 2010 (5) | 43 (2) |
| C(2) | 3539 (5) | 4663 (11) | 1459 (6) | 50 (2) |
| C(3) | 3936 (6) | 4734 (13) | 654 (7) | 63 (2) |
| C(4) | 4388 (6) | 3359 (14) | 443 (7) | 70 (3) |
| C(5) | 4488 (6) | 1945 (13) | 991 (7) | 67 (2) |
| C(6) | 4091 (5) | 1808 (11) | 1803 (6) | 49 (2) |
| C(7) | 3046 (7) | 6065 (14) | 1721 (8) | 74 (3) |
| C(8) | 4203 (7) | 277 (17) | 2402 (9) | 77 (3) |
| C(9) | 2547 (4) | 2245 (8) | 2832 (4) | 33 (1) |
| C(10) | 2227 (4) | 2253 (9) | 3778 (5) | 35 (1) |
| C(11) | 1250 (4) | 1050 (8) | 4655 (4) | 31 (1) |
| C(12) | 598 (3) | 2394 (8) | 4484 (4) | 26 (1) |
| C(13) | 2088 (4) | −800 (8) | 3894 (5) | 33 (1) |
| C(14) | 1535 (3) | −2297 (8) | 3601 (4) | 28 (1) |
| O(1) | 2190 (3) | 3451 (6) | 7098 (4) | 44 (1) |
| O(2) | 264 (3) | 2727 (7) | 5191 (4) | 48 (1) |
| O(3) | 386 (3) | 2978 (6) | 3643 (3) | 36 (1) |
| O(4) | 1830 (3) | −3752 (7) | 3802 (4) | 53 (1) |
| O(5) | 857 (3) | −2018 (6) | 3180 (3) | 36 (1) |
| N(1) | 3241 (3) | 3058 (8) | 2844 (4) | 41 (1) |
| N(2) | 1677 (3) | 832 (6) | 3828 (3) | 26 (1) |
| O(6) | 3415 (5) | 5674 (10) | 4461 (6) | 79 (2) |
| O(7) | 856 (3) | 4718 (8) | 2013 (4) | 51 (1) |
| O(8) | 1216 (4) | 6417 (9) | 5797 (5) | 69 (2) |

* $U_{eq} = \frac{1}{3}(U_{11} + U_{22} + U_{33} + 2U_{13}\cos\beta)$.

ture factor for Ba and fixed temperature factors for H atoms was terminated at $R$ = 0·043 (0·048), $R_w$ = 0·055 (0·057) for the observed (all) reflections with a final maximum shift/error of 0·07. The weighting scheme applied was $w = [\sigma_F^2 + (0{\cdot}03F_o)^2]^{-1}$;* the error in an observation of unit weight was 1·225. Scattering factors were taken from Cromer & Waber (1974) and corrections for anomalous dispersion were applied to Ba (Cromer, 1974). The final positional parameters are given in Table 1.† All calculations were carried out on a CYBER 170/730 computer.‡

## Discussion

A diagram of the anion is presented in Fig. 1 and selected interatomic distances and angles are given in Table 2. Bond lengths and angles within the anion are normal and agree well with the conventional description of the molecule except for the NH.CO region, where the N(1)—C(9) distance of 1·343 (9) Å is significantly shorter than a C—N single bond [*cf.* C(10)—N(2), N(2)—C(11), N(2)—C(13) (av. 1·464 Å)], implying double-bond character. This arises from interaction with the carbonyl group, and is well-known for the amide group in compounds such as acetamide (C—O, 1·25; C—N, 1·32 Å) and monofluoroacetamide (C—O, 1·24; C—N, 1·31 Å) (Hughes & Small, 1962; Hamilton, 1965). As can be seen in Table 3 and Fig. 1 the conformation of the molecule is such that intramolecular steric reactions are minimized. Thus the phenyl ring is nearly at right angles to

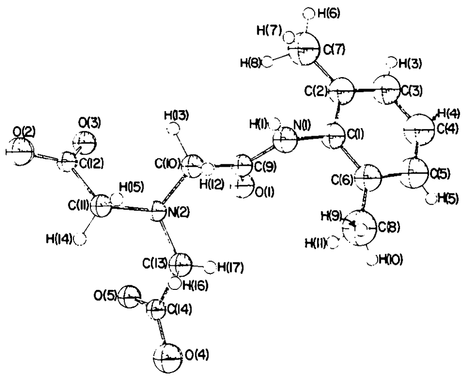

Fig. 1. The HIDA anion, $[C_6H_3(CH_3)_2.NH.CO.CH_2N(CH_2CO_2)_2]^{2-}$, showing the atom numbering.

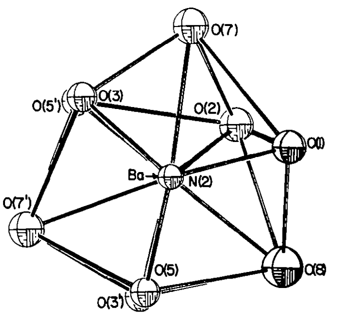

Fig. 2. The environment of the Ba cation, viewed down the rough $C_3$ axis.

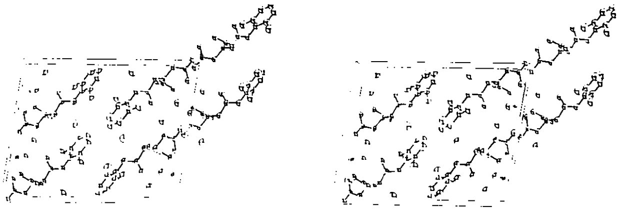

Fig. 3. The packing within the unit cell. **a** and **c*** are parallel to the bottom and side of the page respectively, and the view is down **b**.

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* The value 0·03 was chosen to make $\langle w(|F_o| - |F_c|)^2\rangle$ locally independent of $|F_o|$ and $\sin\theta/\lambda$.

† Lists of structure factors, anisotropic thermal parameters, H-atom positions and bond angles involving H have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36362 (24 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

‡ Most programs for initial data treatment were from the XRAY package (Stewart, 1976). The structure was solved using *SHELX* (Sheldrick, 1976). Final refinements and difference syntheses used the internally written Fourier and full-matrix least-squares programs *SYMFOU* and *CUDLS* written by J. S. Rutherford and J. S. Stephens respectively. The planes and dihedral angles were calculated using *NRC*-22 (Pippy & Ahmed, 1978). The diagrams were prepared using *ORTEP* II (Johnson, 1976).

Table 2. *Selected interatomic distances* (Å) *and angles* (°)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ba–O(3) | 2·810 (4) | Ba–O(3) | 2·841 (4) | Ba–O(2) | 2·720 (5) | Ba–O(1) | 2·892 (5) |
| Ba–N(2) | 2·947 (4) | Ba–O(5) | 2·856 (4) | Ba–O(5) | 2·815 (4) | Ba–O(7) | 3·026 (6) |
| Ba–O(7) | 3·034 (6) | Ba–O(8) | 2·897 (8) | C(1)–C(2) | 1·39 (1) | C(2)–C(3) | 1·41 (1) |
| C(3)–C(4) | 1·38 (2) | C(4)–C(5) | 1·34 (2) | C(5)–C(6) | 1·42 (1) | C(6)–C(1) | 1·38 (1) |
| C(2)–C(7) | 1·47 (1) | C(6)–C(8) | 1·46 (2) | C(1)–N(1) | 1·44 (1) | N(1)–C(9) | 1·343 (9) |
| C(9)–O(1) | 1·233 (8) | C(9)–C(10) | 1·51 (1) | C(10)–N(2) | 1·465 (9) | N(2)–C(11) | 1·474 (8) |
| C(11)–C(12) | 1·523 (9) | C(12)–O(2) | 1·246 (8) | C(12)–O(3) | 1·259 (7) | N(2)–C(13) | 1·454 (8) |
| C(13)–C(14) | 1·519 (9) | C(14)–O(4) | 1·259 (8) | C(14)–O(5) | 1·232 (7) | | |

Hydrogen-bond distances (Å)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| O(2)$^a$–O(8) | 2·76 (1) | O(3)–O(7) | 2·88 (1) | O(3)–O(8) | 3·00 (1) | O(4)$^b$–O(7) | 3·02 (1) |
| O(4)$^b$–O(6) | 2·76 (1) | O(5)$^b$–O(7) | 3·03 (1) | N(1)–O(6) | 3·03 (1) | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| O(3)–Ba–O(3)$^c$ | 128·2 (1) | O(3)–Ba–O(2)$^d$ | 120·9 (1) | O(3)–Ba–O(1)$^d$ | 94·4 (1) | O(3)–Ba–N(2) | 56·8 (1) |
| O(3)–Ba–O(5) | 92·1 (1) | O(3)–Ba–O(5)$^e$ | 65·4 (1) | O(3)–Ba–O(7) | 58·9 (1) | O(3)–Ba–O(7)$^c$ | 69·7 (1) |
| O(3)–Ba–O(8)$^f$ | 158·3 (2) | O(3)$^c$–Ba–O(2)$^d$ | 90·8 (1) | O(3)$^c$–Ba–O(1)$^d$ | 129·0 (1) | O(3)$^c$–Ba–N(2) | 120·8 (1) |
| O(3)$^c$–Ba–O(5) | 65·0 (1) | O(3)$^c$–Ba–O(5)$^e$ | 92·1 (1) | O(3)$^c$–Ba–O(7) | 152·9 (1) | O(3)$^c$–Ba–O(7)$^c$ | 58·6 (1) |
| O(3)$^c$–Ba–O(8)$^f$ | 63·1 (2) | O(2)$^d$–Ba–O(1)$^d$ | 88·5 (1) | O(2)$^d$–Ba–N(2) | 142·3 (1) | O(2)$^d$–Ba–O(5) | 147·0 (1) |
| O(2)$^d$–Ba–O(5)$^e$ | 71·7 (1) | O(2)$^d$–Ba–O(7) | 67·7 (2) | O(2)$^d$–Ba–O(7)$^c$ | 121·6 (2) | O(2)$^d$–Ba–O(8)$^f$ | 73·1 (2) |
| O(1)$^d$–Ba–N(2) | 56·3 (1) | O(1)$^d$–Ba–O(5) | 90·1 (1) | O(1)$^d$–Ba–O(5)$^e$ | 135·2 (1) | O(1)$^d$–Ba–O(7) | 69·1 (2) |
| O(1)$^d$–Ba–O(7)$^c$ | 149·9 (1) | O(1)$^d$–Ba–O(8)$^f$ | 68·1 (2) | N(2)–Ba–O(5) | 55·9 (1) | N(2)–Ba–O(5)$^c$ | 122·1 (1) |
| N(2)–Ba–O(7) | 85·5 (1) | N(2)–Ba–O(7)$^c$ | 94·0 (1) | N(2)–Ba–O(8)$^f$ | 101·7 (2) | O(5)–Ba–O(5)$^e$ | 128·0 (1) |
| O(5)–Ba–O(7) | 141·1 (1) | O(5)–Ba–O(7)$^c$ | 66·0 (1) | O(5)–Ba–O(8)$^f$ | 75·8 (2) | O(5)$^e$–Ba–O(7) | 66·3 (1) |
| O(5)–Ba–O(7)$^c$ | 62·3 (1) | O(5)$^c$–Ba–O(8)$^f$ | 136·1 (2) | O(7)–Ba–O(7)$^c$ | 118·1 (2) | O(7)–Ba–O(8)$^f$ | 121·3 (2) |
| O(7)$^c$–Ba–O(8)$^f$ | 119·3 (2) | C(6)–C(1)–C(2) | 123·2 (7) | C(1)–C(2)–C(3) | 116·7 (8) | C(2)–C(3)–C(4) | 119·9 (9) |
| C(3)–C(4)–C(5) | 123 (1) | C(4)–C(5)–C(6) | 119 (1) | C(5)–C(6)–C(1) | 118·1 (8) | C(1)–C(2)–C(7) | 120·7 (8) |
| C(7)–C(2)–C(3) | 122·7 (9) | C(1)–C(6)–C(8) | 122·7 (9) | C(8)–C(6)–C(5) | 119·2 (9) | C(2)–C(1)–N(1) | 118·3 (7) |
| C(6)–C(1)–N(1) | 118·4 (7) | C(1)–N(1)–C(9) | 123·0 (6) | N(1)–C(9)–O(1) | 122·4 (6) | O(1)–C(9)–C(10) | 122·1 (6) |
| N(1)–C(9)–C(10) | 115·5 (5) | C(9)–C(10)–N(2) | 111·3 (5) | C(10)–N(2)–C(11) | 110·6 (5) | C(10)–N(2)–C(13) | 111·3 (5) |
| C(11)–N(2)–C(13) | 110·4 (5) | N(2)–C(11)–C(12) | 113·5 (5) | C(11)–C(12)–O(2) | 115·8 (5) | C(11)–C(12)–O(3) | 119·4 (5) |
| O(2)–C(12)–O(3) | 124·5 (6) | N(2)–C(13)–C(14) | 112·8 (5) | C(13)–C(14)–O(4) | 115·4 (5) | C(13)–C(14)–O(5) | 119·3 (5) |
| O(4)–C(14)–O(5) | 125·4 (6) | | | | | | |

Atoms are related to those given in Table 1 by (*a*) $-x, 1-y, 1-z$; (*b*) $x, 1+y, z$; (*c*) $-x, y-\frac{1}{2}, \frac{1}{2}-z$; (*d*) $x, \frac{1}{2}-y, z-\frac{1}{2}$; (*e*) $-x, \frac{1}{2}+y, \frac{1}{2}-z$; (*f*) $x, \frac{1}{2}-y, \frac{1}{2}+z$.

Table 3. *Least-squares planes and torsional angles*

| | Plane | Distance of atoms from the plane (Å) |
|---|---|---|
| (1) | C(*i*), $i = 1$–6 | C(1) 0·002 (7); C(2) −0·004 (9); C(3) −0·002 (10); C(4) 0·012 (10); C(5) −0·011 (10); C(6) 0·002 (9); C(7) −0·009 (12); C(8) −0·031 (12); N(1) −0·011 (6) |
| (2) | N(1)C(9)C(10) | O(1) −0·063 (5) |
| (3) | C(12)O(2)O(3) | C(11) 0·151 (6) |
| (4) | C(14)O(4)O(5) | C(13) 0·036 (7) |

Dihedral angles (plane numbers given) (°)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| (1)–(2) | 82 (1) | (1)–(3) | 31 (1) | (1)–(4) | 80 (1) | (2)–(3) | 110 (1) |
| (2)–(4) | 90 (1) | (3)–(4) | 94 (1) | (1)–(1′) | 47 (1) | | |

Torsional angles (°)

| | | | | | |
|---|---|---|---|---|---|
| C(2)C(1)N(1)C(9) | 99 (1) | C(6)C(1)N(1)C(9) | −82 (1) | C(1)N(1)C(9)C(10) | 180 (1) |
| N(1)C(9)C(10)N(2) | −157 (1) | C(9)C(10)N(2)C(11) | −169 (1) | C(9)C(10)N(2)C(13) | 68 (1) |
| C(10)N(2)C(11)C(12) | 76 (1) | C(10)N(2)C(13)C(14) | −160 (1) | N(2)C(11)C(12)O(2) | −174 (1) |
| N(2)C(11)C(12)O(3) | 12 (1) | N(2)C(13)C(14)O(4) | −168 (1) | N(2)C(13)C(14)O(5) | 13 (1) |

the amide group [82 (1)°], the amide group is roughly at right angles to the N(1)C(9)C(10) plane [110 (1)°] which in turn is at right angles to the carboxylate groups [110 (1), 90 (1)°] which are at right angles to each other [94 (1)°]. Further, the torsional angles show the tendency of the chain to stabilize in the *trans* conformation about each bond.

The Ba cation is surrounded by ten carboxylate oxygen and amine N(1) atoms, and water molecules in a coordination polyhedron which can be described as a facially *fac*-tricapped cube, with the apex atom joining the three capped faces removed, or a trigonal prism, capped on the three square faces and one triangular face. Either description relates to a system with pseudo-threefold symmetry and the coordination polyhedron, viewed down this pseudo-$C_3$ axis, is illustrated in Fig. 2. The packing in the unit cell is shown in Fig. 3.

The anions are arranged in layers roughly along the (202) planes such that the carboxylate groups lie close to the (001) faces and the phenyl rings lie close to the $x = \frac{1}{2}$ plane. Thus at $x = 0$, $z = \frac{1}{2}$ we have a non-polar dimeric chain along the **b** direction. Within the chain the C(12)-carboxylate groups of molecules related by the $0,\frac{1}{2},\frac{1}{2}$ inversion centre are hydrogen bonded through O(2)$^a$–O(8), O(3)–O(8) [2·76 (1), 3·00 (1) Å]. At the phenyl ends, chain–chain interactions in the (202) layers are purely van der Waals, since up the **b** direction the phenyl rings are canted with respect to each other and do not overlap significantly; there is no $\pi$–$\pi$ interaction. The only interanion interactions between (202) layers are van der Waals and ionic, since although the Ba ions and water molecules lie between the layers, acting as spacers, there are no hydrogen-bonding cross-linking interactions between the layers. Thus, though the water molecule O(6)H(61)H(62) provides the main spacing interaction between the phenyl rings, its hydrogen bonding is to N(1) in one molecule and to O(4) in a **b**-translationally equivalent one. Similarly, O(7)H(71)H(72) only provides an interanion link in the **b** direction between O(3) and O(4), O(5) of **b**-translationally equivalent molecules.

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# Comparison of Observed and Calculated Densities. XII.* Deformation Density in Complex Anions. II. Experimental and Theoretical Densities in Sodium Formate

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## Abstract

$X$–$X$ (high order) and $X$–$N$ electron density difference maps are derived from low-temperature (120 K) neutron and X-ray diffraction studies on sodium formate (NaHCOO) crystals. For comparison, theoretical deformation density maps are presented based on 4-31G + BP SCF calculations. The overall agreement between the experimental and theoretical results is reasonable. [Crystal data at 120 K: space group $C2/c$, $a$ = 6·239 (2), $b$ = 6·749 (2), $c$ = 6·097 (2) Å, $\beta$ = 116·61 (2)°, $V$ = 229·5 (1) Å$^3$, $Z$ = 4, $D_c$ = 1·968 Mg m$^{-3}$. $R(F)$ for the conventional neutron refinement is 0·027 for 1081 reflections.]

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* Part XI: Lauer, Meyer, Schulte, Schweig & Hase (1979). *Chem. Phys. Lett.* **67**, 503–507.

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