Attention should be drawn to one remarkable difference between molecules (I) and (II). The number of intermolecular bonds is considerably larger for molecule (I) than for molecule (II). It should be noted particularly that the oxygen atoms O(12) and O(13) which form the non-centred hydrogen bond do not participate in intermolecular bonds. Distances to more remote H atoms are also included in the lower part of Fig. 1(*b*) in order to demonstrate that there is no significant bonding to O(12) or O(13).

Several hydrogen bonds have previously been reported as being centred. In most of these cases, however, the H atom is assumed to be in a special position (inversion centre $\bar{1}$ or twofold axis). Doubts have been raised as to the centricity in these cases (Kroon, Kanters & Peerdeman, 1971). Potassium hydrogen chloromaleate (Ellison & Levy, 1965) was the first example to exhibit a centred hydrogen bond which was not constrained by a symmetry operation. The present crystal provides a second example. It is emphasized that, within the standard deviations, nearly all distances and angles within molecule (I) obey the symmetry of a mirror plane perpendicular to the plane of the molecule.

The relatively large tilting angles φ (Table 5) in the present structure can be explained by the cations Li(2) which link the hydrogen phthalate ions parpendicular to their average plane (see Fig. 2).

In hydrogen bonds with O···O distances longer than 2·5 Å, the distances O—H increase with decreasing O···O in a well correlated manner. Table 5 clearly demonstrates that, in very short hydrogen bonds, such a correlation no longer exists. All examples cited show comparable O···O distances, whereas the O—H distances scatter considerably. Furthermore, no correlation can be observed between O—H distance and other geometric features such as the φ or O—H···O angles.

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The Structures of the Mono- and Disodium Salts of Hadacidin, an Antibiotic Hydroxamic Acid

BY D. L. ENG-WILMOT, M. B. HOSSAIN AND DICK VAN DER HELM*

Department of Chemistry, University of Oklahoma, Norman, Oklahoma 73019, *USA*

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Abstract

The crystal structures of the mono- and disodium salts of *N*-formyl-*N*-hydroxyglycine (hadacidin), an L-aspartate antagonist for the enzyme adenylosuccinate synthetase, were determined at 138 (2) K. For $C_3H_4NNaO_4.2H_2O$, $M_r = 177{\cdot}12$, monoclinic, $P2_1/c$, $Z = 4$, $a = 8{\cdot}915\ (9)$, $b = 10{\cdot}474\ (11)$, $c = 8{\cdot}485\ (7)$ Å, $\beta = 115{\cdot}29\ (7)°$, $V = 716{\cdot}4$ Å^3, $D_c = 1{\cdot}642$ Mg m^{-3}; final R value was 0·055 for all 1470 data. For $C_3H_3NNa_2O_4.2H_2O$, $M_r = 198{\cdot}97$, monoclinic, $P2_1/c$, $Z = 4$, $a = 7{\cdot}562\ (4)$, $b = 7{\cdot}574\ (3)$, $c =$

* To whom correspondence should be addressed.

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12·876 (15) Å, β = 98·38 (4)°, V = 729·6 Å^3, D_c = 1·811 Mg m^{-3}; final R value was 0·065 for all 1505 data. Both structures were solved by direct methods. Conformationally, there are similarities between the two molecules; the differences are caused by ionization and crystal packing. The hydroxamate groups assume the *cis* planar conformation and are involved in Na coordination. The hydroxamic acid group in the monosodium salt is not conjugated, whereas in the disodium salt, there is significant electron delocalization. The structures are compared with L-aspartic acid.

Introduction

The correlation of structure and activity of microbial antibiotics is of increasing importance and interest, not only in terms of understanding the structural and biochemical basis for activity, but also as an aid in mapping the mode and site of action, determining design features for more useful analogs, and understanding microbial interactions. The antibiotic *N*-formyl-*N*-hydroxyglycine (trivial name, hadacidin) is the simplest known naturally occurring hydroxamic acid. Isolated originally from *Penicillium frequentans*, the chemical structure was determined by Kaczka, Gitterman, Dulaney & Folkers (1962), and its biosynthetic pathway in *P. aurantioviolaceum* has been elucidated (Stevens & Emery, 1966).

By virtue of its secondary hydroxamate group, hadacidin has the ability to coordinate Fe^{3+}; however, its ability to mediate microbial Fe transport (act as a ferric ionophore) has yet to be demonstrated. Regardless, hadacidin exhibits a wide range of biological activities. Its antitumor and anticancer activities were early recognized by its ability to interdict the growth of various carcinomas and sarcomas (Kaczka *et al.*, 1962; White, 1962; Gitterman, Dulaney, Kaczka, Hendlin & Woodruff, 1962). In addition, it has been employed with some success in the treatment of leukemia (Ellison, 1962), although it exhibits teratogenic activity (Shah, 1977). Hadacidin is also a plant-growth inhibitor, inducing asymmetric leaf development (Zaroogian & Curtis, 1964), retardation of chloroplast development (Mego, 1964), and induction of bacterial sporulation (Mitani, Heinze & Freeze, 1977).

The mechanism of action of hadacidin has been extensively examined. It is thought that this hydroxamic acid acts as an antimetabolite in purine biosynthesis, specifically inhibiting, competitively and reversibly, the enzyme adenylosuccinate synthetase (Shigeura & Gordon, 1962*a*,*b*) responsible for the conversion of inosinic acid to adenylosuccinic acid. This reaction, the penultimate step in *de novo* synthesis of AMP, is central in purine nucleotide biosynthesis and cycling in microorganisms, higher plants and animal tissues. Elevated levels of this enzyme have also been reported in neoplastic tissues (Jackson, Morris & Weber, 1975).

The site of interaction of hadacidin with adenylosuccinate synthetase is the L-aspartate binding site (Shigeura & Gordon, 1962*a*,*b*; Markham & Reed, 1977). The K_i for hadacidin is 0·3 × 10^{-6} M which is several orders of magnitude lower than the K_m for L-aspartate (1·5 × 10^{-4} M) (Markham & Reed, 1977). It has been suggested that hadacidin and L-aspartate share some common structural–chemical features. It is, therefore, the purpose of this communication to report the molecular and crystal structures of the mono- and disodium salts of hadacidin and compare them with the structure of L-aspartate (Derissen, Endeman & Peerdeman, 1968; Rao, 1973).

Experimental

Crystallization and data collection

Samples of the monosodium salt of hadacidin (NaHAD) were obtained from Dr T. F. Emery, Utah State University, Logan, and were recrystallized in this laboratory. Crystals were grown as thin plates by slow evaporation from ethanol–water. The disodium salt (Na_2HAD) was prepared using the procedure of Kaczka *et al.* (1962); large boat-shaped crystals were obtained from an aqueous solution equilibrated with ethanol.

Both salts crystallized as the dihydrate in the monoclinic space group $P2_1/c$, which was uniquely determined from Laue symmetry. The dimensions of the crystals for data collection were 0·38 × 0·15 × 0·12 (NaHAD) and 0·62 × 0·19 × 0·14 mm (Na_2HAD). Unit-cell dimensions were determined from a least-squares fit of the 2θ values of 25 (NaHAD) and 48 (Na_2HAD) reflections.

The intensity data were measured using Ni-filtered Cu $K\bar{\alpha}$ radiation (λ = 1·54178 Å) with an Enraf–Nonius CAD-4 automatic diffractometer controlled by a PDP8/e computer and equipped with a Nonius cold-stream low-temperature device [working temperature 138 (2) K]. The specific data-collection par-

Table 1. *Data-collection parameters*

	NaHAD	Na_2HAD
Scan technique	θ–2θ	θ–2θ
θ Limit (°)	$2\theta \le 150$	$2\theta \le 150$
Scan time (s)	90	60
Scan angle (°)	(0·7 + 0·14 tan θ)	(0·8 + 0·15 tan θ)
Aperture (mm)	(3·0 + 0·86 tan θ)	(3·0 + 0·86 tan θ)
height (mm)	6	6
distance (mm)	173	173
Intensity monitors (s)	3000	3000
Orientation monitors	200 reflections	200 reflections
Number of unique data	1470	1505
Number of observed data [$I > 2{\cdot}0\,\sigma(I)$]	1262	1449

ameters are tabulated in Table 1. Data were corrected for Lorentz and polarization factors. No absorption correction was made [$\mu = 1{\cdot}92$ (NaHAD), $2{\cdot}51$ mm^{-1} (Na_2HAD)].

Structure determinations

The structures of the title compounds were solved by direct methods using the program *MULTAN* (Main, Lessinger, Woolfson, Germain & Declercq, 1976). For NaHAD, the positions of all 11 non-H atoms were located in an E map generated from the phases of 100 reflections with the highest E values ($E \geq 1{\cdot}80$), and refined isotropically, then anisotropically to an R factor of 0·073 for all 1470 data. The H atoms were located from a difference Fourier synthesis and refined isotropically. Refinement was discontinued when the parameter shifts were less than 0·3 of their standard deviations. Final R values were 0·044 for 1251 observed reflections and 0·055 for all 1470 data.

For Na_2HAD, the positions of all 12 non-H atoms per asymmetric unit were located in an E map generated from the phases of 120 reflections ($E \geq 1{\cdot}66$). One of the Na atoms is in the general position, while the others occupy the special positions at (0,0,0) and (0,0,$\frac{1}{2}$). All of the atom positions were refined to an R value of 0·08 for all 1505 data. The H atoms of the molecule were located from a difference Fourier synthesis and refined isotropically. The H atoms belonging to the two water molecules could not be located unambiguously and therefore were excluded. Refinement was discontinued when the individual parameter shifts were 0·2 of their standard deviations, and converged on final R values of 0·061 (1418 observed data) and 0·065 (1505 data). All refinements were carried out by block-diagonal least-squares methods (Ahmed, 1966), where the value of $\sum w_F(|kF_o| - |F_c|)^2$ was minimized. Each structure amplitude was assigned a weight, $w_F(=1/\sigma_F^2)$, where σ_F was generated from counting statistics (Ealick, van der Helm & Weinheimer, 1975). The scattering factors for the C, N, O and Na^+ atoms were taken from *International Tables for X-ray Crystallography* (1974); those for the H atoms were taken from Stewart, Davidson & Simpson (1965).

Description and discussion

The final atomic coordinates for the monosodium (NaHAD) and disodium (Na_2HAD) salts of hadacidin are tabulated in Tables 2 and 3 respectively.* The general atom-numbering scheme is shown in Fig. 1. The molecule in both salts assumes the same general conformation, although there are individual differences. A stereoview of a single molecule as it appears in NaHAD is shown in Fig. 2. The molecule may be considered to consist of two nearly perpendicular four-atom planes, the carboxylate plane (I) consisting of atoms O(1), O(2), C(1) and C(2), and the hydrox-

Table 2. *Atomic coordinates and U_{eq} for monosodium hadacidin dihydrate* ($\times 10^4$, $\times 10^3$ *for* H *atoms*)

U_{eq} is computed from the expression $U_{eq} = 1/6\pi^2 \sum_i \sum_j \beta_{ij} \mathbf{a}_i . \mathbf{a}_j$. Standard deviations of the last significant figure are given in parentheses.

	x	y	z	U_{eq} (Å^2)
Na	1028·9 (11)	−483·7 (10)	2110·4 (12)	188 (4)
O(1)	7605 (2)	−3459 (2)	2274 (2)	190 (7)
O(2)	4988 (2)	−3922 (2)	1728 (2)	190 (7)
O(3)	3952 (2)	−1250 (2)	2596 (2)	172 (7)
O(4)	1424 (2)	−635 (2)	−521 (2)	204 (7)
$W(1)$	−357 (2)	−2422 (2)	845 (2)	212 (7)
$W(2)$	1586 (2)	−789 (2)	4971 (2)	279 (9)
N(1)	4041 (2)	−1400 (2)	1004 (3)	158 (8)
C(1)	6101 (3)	−3180 (2)	1762 (3)	141 (9)
C(2)	5632 (3)	−1813 (2)	1125 (3)	179 (9)
C(3)	2724 (3)	−1088 (3)	−459 (3)	188 (10)
H(1)	651 (4)	−122 (3)	192 (4)	34 (9)
H(2)	559 (4)	−174 (3)	−2 (5)	31 (9)
H(3)	293 (3)	−122 (3)	−154 (3)	15 (6)
H(4)	429 (6)	−41 (5)	287 (6)	71 (14)
H(1)$W(1)$	−104 (5)	−274 (4)	125 (5)	46 (10)
H(2)$W(1)$	−95 (4)	−223 (3)	−15 (5)	37 (9)
H(1)$W(2)$	262 (4)	−98 (3)	556 (4)	37 (9)
H(2)$W(2)$	94 (5)	−124 (4)	521 (5)	58(12)

Table 3. *Atomic coordinates and U_{eq} for disodium hadacidin dihydrate* ($\times 10^4$, $\times 10^3$ *for* H *atoms*)

U_{eq} is computed from the expression $U_{eq} = 1/6\pi^2 \sum_i \sum_j \beta_{ij} \mathbf{a}_i . \mathbf{a}_j$. Standard deviations of the last significant figure are given in parentheses.

	x	y	z	U_{eq} (Å^2)
Na(1)	377·3 (15)	7225·2 (14)	2410·1 (9)	123 (5)
Na(2)	0·0	10000·0	0·0	130 (7)
Na(3)	0·0	10000·0	5000·0	151 (7)
O(1)	1873 (3)	7701 (3)	948 (2)	155 (9)
O(2)	4409 (3)	8029 (3)	252 (2)	148 (9)
O(3)	7340 (3)	7632 (2)	2414 (2)	109 (8)
O(4)	8868 (3)	4784 (3)	1584 (2)	113 (9)
$W(1)$	2102 (3)	12415 (3)	5474 (2)	151 (10)
$W(2)$	1946 (3)	5454 (3)	3717 (2)	128 (10)
N(1)	6386 (3)	6259 (3)	1920 (2)	92 (9)
C(1)	3544 (4)	7488 (3)	938 (2)	109 (11)
C(2)	4473 (3)	6373 (4)	1847 (2)	112 (11)
C(3)	7187 (4)	4946 (3)	1526 (2)	120 (12)
H(1)	442 (7)	686 (8)	255 (4)	54 (15)
H(2)	404 (7)	514 (6)	176 (4)	46 (14)
H(3)	629 (5)	414 (5)	116 (3)	9 (8)

* Lists of structure factors and anisotropic thermal parameters for the two compounds have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35936 (15 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

amate plane (II) comprising atoms O(3), O(4), N(1) and C(3). The interplanar angles are 76 and 87° respectively for NaHAD and Na_2HAD. There is no evidence of an intramolecular O(3)–O(2) hydrogen bond, as proposed by Fritz & von Stetten (1972).

The bond distances and the corresponding bond and torsion angles in the two structures are presented in Figs. 1 and 3 respectively. There are three noticeable differences between the two molecules. These are the hydroxamate group, the ionized carboxylate group, and the torsion angles around the N(1)–C(2) and C(1)–C(2) bonds.

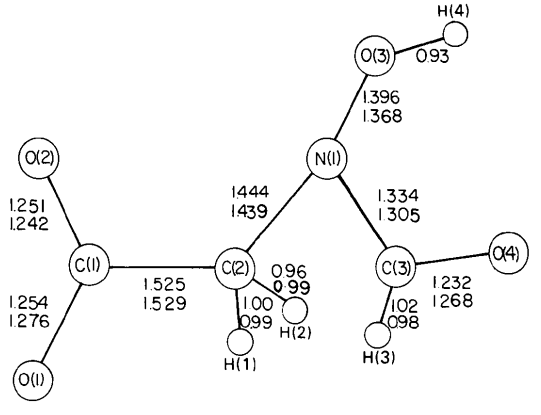

Fig. 1. General atom-numbering scheme and bond lengths (Å) in mono- and disodium hadacidin (upper and lower values respectively). The e.s.d.'s in $NaHAD.2H_2O$ are 0·003 Å (C–H, 0·03–0·05 Å); in $Na_2HAD.2H_2O$, 0·003–0·004 Å (C–H, 0·03–0·06 Å).

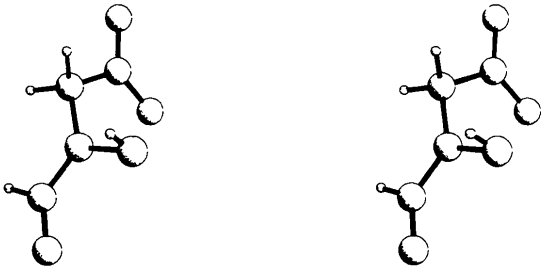

Fig. 2. Stereoscopic view of a single molecule of hadacidin.

(1) *Hydroxamate groups*

The hydroxamate groups of both molecules are in the planar *cis* conformation, as might be expected if the group is involved in metal-ion coordination or hydrogen bonding (Smith & Raymond, 1980). The r.m.s. deviation for the O(3), O(4), N(1) and C(3) atoms from the least-squares plane through these atoms is 0·007 (NaHAD) and 0·006 Å (Na_2HAD), while the deviation of H(3) from this plane is 0·013 and 0·056 Å respectively. The torsion angle about the N(1)–C(3) bond is approximately 2°. The monosodium salt exists as the free acid, that is, the nitroso oxygen [O(3)] is protonated [H(4); pKa_2 = 8·83, Fritz & von Stetten, 1972]. The hydrogen atom, H(4), lies 0·90 Å from the hydroxamate plane, and is nearly perpendicular to it, being involved in an intermolecular hydrogen bond with O(2) $(1-x,\ y-\frac{1}{2},\ \frac{1}{2}-z)$. The C(3)–N(1), C(3)–O(4) and N(1)–O(3) distances compare favorably with those in the primary acetohydroxamic acid (Bracher & Small, 1970; *cf.* Table 4). In Na_2HAD, the hydroxamate bond lengths are systematically different from those in NaHAD, and probably reflect the effect of true electron delocalization over the four atoms (see Figs. 1 and 3). Both C(3)–N(1) and N(1)–O(3) bonds are 0·028 Å shorter, while the C(3)–O(4) bond is 0·035 Å longer than in NaHAD. Possible corrections for thermal motion would be quite small, of the order of

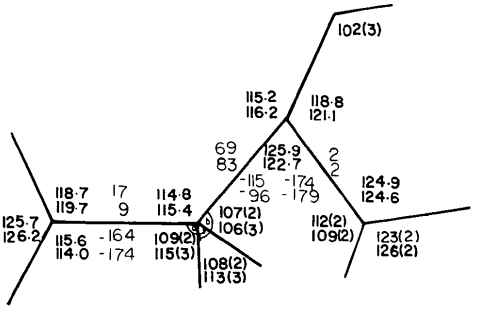

Fig. 3. Bond and torsion angles (°) in the two sodium salts of hadacidin. The upper and lower values are for $NaHAD.2H_2O$ and $Na_2HAD.2H_2O$ respectively. The e.s.d.'s for the bond angles are 0·2°; for the torsion angles, 0·2–0·4°.

Table 4. *Summary of the dimensions defining the hydroxamate groups of some natural and synthetic primary and secondary hydroxamic acids*

Compound	Conformation	C–N (Å)	N–O (Å)	C=O (Å)	O–N–C (°)	N–C–O (°)	Reference
Hadacidin mono Na^+	*cis*	1·334 (4)	1·396 (3)	1·233 (3)	118·9 (2)	124·9 (3)	*a*
Trichostatin *A*	*cis*	1·363 (9)	1·395 (8)	1·253 (9)	119·4 (6)	121·7 (7)	*b*
Acetohydroxamic acid	*cis*	1·321 (6)	1·393 (5)	1·234 (6)	120·9 (4)	123·1 (4)	*c*
Benzohydroxamic acid	*cis*	1·288	1·409	1·286	119·5	121·6	*d*
Salicylohydroxamic acid	*cis*	1·316 (4)	1·390 (4)	1·258 (4)	121·2 (3)	120·4 (3)	*e*
N,N'-Dihydroxy-*N,N'*-diisopropylhexanediamide	*trans*	1·328 (2)	1·396 (2)	1·241 (2)	120·1 (1)	119·5 (1)	*f*

(*a*) This paper; (*b*) Eng-Wilmot & van der Helm (1981); (*c*) Bracher & Small (1970); (*d*) Göttlicher & Ochsenreiter (1974); (*e*) Larsen (1978); (*f*) Smith & Raymond (1980).

0·003–0·004 Å. The value of 1·268 Å for the ionized C(3)–O(4) bond is in excellent agreement with the corresponding distance in ferrichrome *A* and aluminochrome *A* (van der Helm, Baker, Loghry & Ekstrand, 1981). Although the Na–O contacts are ionic, a portion of the lengthening of this bond may result from the participation of O(4) in the coordination of three Na^+ ions in Na_2HAD, as opposed to only one Na^+ ion in NaHAD.

The bond distances and angles defining the hydroxamate groups of the known natural and synthetic hydroxamic acids are summarized in Table 4; such a comparison allows two interesting observations. First, it is apparent that the electronic nature (electron withdrawing or releasing) of the carbonyl carbon [C(3)] substitution exerts a large effect on the delocalization of the hydroxamate group, as reflected in the lengthening of the C–N bonds and a shortening of the C=O bonds, when comparing benzo- and salicyclohydroxamic acids (as electron-withdrawing groups), and hadacidin and acetohydroxamic acid (as electron-releasing groups). Secondly, in most of the *cis* compounds the N–C–O angle is larger than the O–N–C angle.

(2) *Carboxylate groups*

The second difference between the two salts is in the C(1)–O(1) distance of the planar ionized carboxylic acid group, O(1)–C(1)–O(2), $pKa_1 = 3{\cdot}1$ (Fritz & von Stetten, 1972). In NaHAD, the C–O bond lengths and the associated angle agree with those for an average carboxylate group (Borthwick, 1980), and are similar to those in disodium maleate monohydrate (James & Williams, 1974) and L-aspartic acid (Derissen *et al.*, 1968). However, there is an apparent disparity in these results and the empirical relation proposed (Borthwick, 1980). In Na_2HAD, the C(1)–O(1) distance is 0·021 Å longer. The O(1) atoms in both salts are involved in three short contacts each; in NaHAD, two of these are moderate hydrogen bonds with *W*(1) (Table 5). In Na_2HAD, however, O(1) is involved in the ionic coordination of all three Na^+ ions per asymmetric unit. The O(2) atom in each molecule acts as an acceptor in two hydrogen bonds. The strong (2·589 Å) intermolecular hydrogen bond in NaHAD with the protonated nitroso oxygen O(3) does not influence the length of the C(1)–O(2) bond, as was observed in sodium hydrogen fumarate (Gupta & Sahu, 1970).

(3) *Torsion angles*

The main difference in the conformation of the two molecules of hadacidin is in the orientation of the plane of the hydroxamate group (I) with respect to that of the carboxylate group (II). These differences, probably caused by the differences in the hydrogen bonding, Na–O contacts and crystal-packing schemes, manifest themselves in the torsion angles about the N(1)–C(2) and C(1)–C(2) bonds shown in Fig. 3. The angle C(3)–N(1)–C(2)–C(1) is −115° in NaHAD and −96° in Na_2HAD, indicating that in the latter salt the carboxylate group is nearly perpendicular to the hydroxamate moiety. The N atom lies nearly in the plane of the carboxylate group, for both molecules, which is reflected in the torsion angles around the C(1)–C(2) bond (mean value 13°).

It has been demonstrated that hadacidin is a potent metabolic antagonist with antitumor activity; it acts as an L-aspartate antimetabolite for the enzyme adenylosuccinate synthetase. This enzyme is responsible for the transitory attachment of the carbon backbone of L-aspartate to the purine ring through the α-amino N. A comparison of the chemical structures of L-aspartic acid, L-alanosine, a new amino acid being touted in cancer chemotherapy (Jayaram & Cooney, 1979), and hadacidin is given in Fig. 4. Chemically, the three molecules share the same number of functional groups

Table 5. *Hydrogen-bond distances* (Å) *and angles* (°)

H atoms of water molecules in Na_2HAD were not found.

D–H···*A*	*D*–H	H···*A*	*D*–*A*	*D*–H–*A*
NaHAD				
$W(1)^{i}$–H(1)^{i}···O(1)	0·88 (4)	1·92 (4)	2·799 (3)	176 (4)
$W(1)^{ii}$–H(2)^{ii}···O(1)	0·81 (4)	2·13 (4)	2·938 (3)	174 (4)
$W(2)^{iii}$–H(1)^{iii}···O(2)	0·86 (4)	1·91 (4)	2·766 (3)	169 (4)
$W(2)^{iii}$–H(2)^{iii}···*W*(1)	0·84 (4)	2·03 (4)	2·856 (3)	171 (4)
O(3)^{iv}–H(4)^{iv}···O(2)	0·93 (5)	1·66 (5)	2·589 (3)	174 (4)
Na_2HAD				
$W(1)^{iv}$···O(2)			2·961 (3)	
$W(2)^{v}$···O(2)			2·761 (3)	
$W(1)^{vi}$···O(3)			2·691 (3)	
$W(2)^{vii}$···O(3)			2·685 (3)	

Symmetry code: (i) $x+1, y, z$; (ii) $x+1, -\frac{1}{2}-y, \frac{1}{2}+z$; (iii) $x, -\frac{1}{2}-y, z-\frac{1}{2}$; (iv) $1-x, y-\frac{1}{2}, \frac{1}{2}-z$; (v) $x, 1\frac{1}{2}-y, z-\frac{1}{2}$; (vi) $1-x, 2-y, 1-z$; (vii) $1-x, \frac{1}{2}+y, \frac{1}{2}-z$.

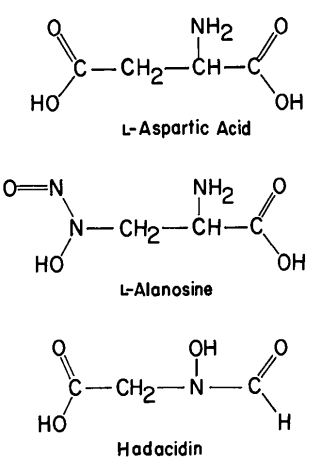

Fig. 4. Chemical structures of L-aspartic acid, L-alanosine and hadacidin.

(three). The β-carboxy group in L-aspartic acid is a nitrosohydroxyamino group in L-alanosine, the α-carbon and amino group are a hydroxylamine in hadacidin (pKa_2 9·82 for the α-amino group of aspartic acid; 8·83 for the hydroxyamino group in hadacidin), and the α-carboxy group is an aldehyde in hadacidin. Like L-alanosine, hadacidin is a potent inhibitor of adenylosuccinate synthetase [K_i for hadacidin 0·3 μM (Markham & Reed, 1977); K_i for L-alanosine <1 μM (Jayaram & Cooney, 1979)]. However, the general characteristics of L-aspartate antimetabolites enumerated by Jayaram & Cooney (1979) do not seem to apply in the case of hadacidin; certainly this disparity deserves explanation in light of its antitumor activity.

In the crystalline state, there are several substantial conformational differences between L-aspartic acid and hadacidin. In hadacidin, the nitroso oxygen O(3) lies in the plane of the atoms C(2), C(3), N(1), O(3) and O(4) (σ_{rms} 0·003 and 0·002 Å for NaHAD and Na_2HAD respectively), while in L-aspartic acid (Derissen *et al.*, 1968) the corresponding atoms do not form a plane (σ_{rms} 0·413 Å). In addition, in L-aspartic acid there is free rotation about the C^{α}–C^{β} bond (torsion angle −178°); in hadacidin this angle is −115 and −96° respectively. A least-squares fit of the molecules also reveals these differences, as presented in Fig. 5, a fit of NaHAD with L-aspartic acid. In solution, however, the conformation of the two molecules may be the same; one of them may assume the conformation of the other, or both may assume a conformation which is dictated by the constraints of the L-aspartate binding site of the enzyme.

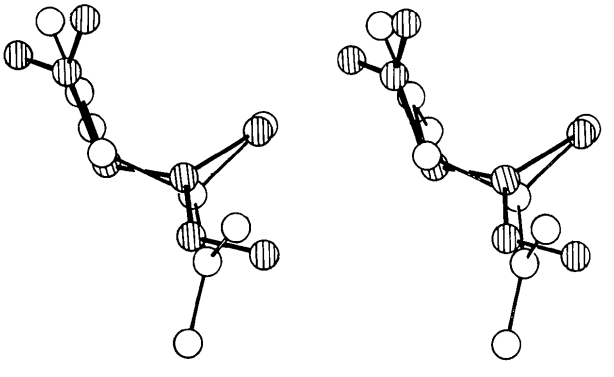

Fig. 5. Least-squares fit of hadacidin (NaHAD) and L-aspartic acid. The coordinates used for NaHAD are related by inversion to the ones given in Table 2.

(4) *Hydrogen bonding, sodium coordination and crystal packing*

Differences in the molecular dimensions and conformation in the title compounds can be attributed in part to the hydrogen bonding and Na-contact schemes, which are diagrammatically shown in Fig. 6. The details of the hydrogen-bond parameters are listed in Table 5. The very strong intermolecular O(3)–H···O(2) hydrogen bond [2·589 (3) Å] linking the hydroxamate and carboxylate groups in NaHAD does not exist in the Na_2HAD structure. The nitroso oxygen atom, O(3), in NaHAD is a donor in the strong hydrogen bond, while in Na_2HAD it acts as an acceptor in two strong [2·691 (3) and 2·685 (3) Å] hydrogen bonds with $W(1)$. In NaHAD, atom O(4) makes short contacts with two Na^+ ions; in Na_2HAD it is involved in three ionic contacts with Na^+ ions.

In NaHAD, the Na^+ ion resides in a highly distorted octahedral environment, as shown in Fig. 7. The distortion of the octahedron is caused primarily by the hydroxamate O atoms, O(3) and O(4). The Na–O

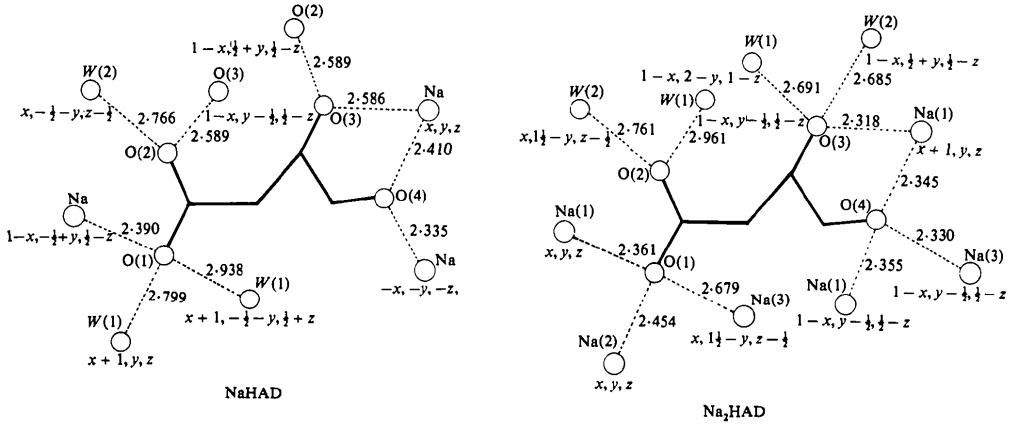

Fig. 6. Hydrogen bonding and Na^+–O contacts in mono- and disodium hadacidin. The e.s.d.'s of these contacts are 0·002 Å.

contact distances are in the range 2·283 (2) to 2·586 (2) Å; the mean Na–O length of 2·398 Å is in agreement with the expected value of 2·40 Å (Shannon & Prewitt, 1969). The axial angles are: O(1)^{b}–Na–W(1) 166·61 (9), O(3)–Na–O(4)^{a} 151·52 (8) and O(4)–Na–W(2) 157·61 (9)°. (The superscripts denote the symmetry transformation applied and are listed in Table 6.) Of the 12 non-axial angles, two deviate significantly from 90° [O(3)–Na–O(4) 65·86 (7), O(4)^{a}–Na–W(2) 114·14 (8)°]; the other ten angles vary from 77·24 (7) to 101·27 (8)°, with a mean value of 89·45°. Each Na^+ ion shares an edge with its centrosymmetrically related neighbor (Na–Na distance 3·41 Å).

In Na_2HAD, the Na^+ ion coordination is complex; each of the three Na^+ ions per asymmetric unit resides in a different coordination environment (Fig. 8). Na(1) is 5-coordinated in a distorted trigonal bipyramid. The axial angle O(4)^{c}–Na(1)–O(4)^{d} is 164·03 (9)° and the equatorial angles, O(1)–Na(1)–W(2), O(1)–Na(1)–O(3)^{c} and O(3)^{c}–Na(1)–W(2), of 114·23 (9), 124·83 (9) and 118·29 (9)° respectively, are clear evidence of this geometry. The major deviation from a regular polyhedron results from coordination by both of the hydroxamate O atoms [O(3)–Na(1)–O(4) 71·86 (7)°]. The five Na–O contact distances are nearly equal, in the range 2·319 (2) to 2·361 (2) Å. The mean Na–O distance of 2·343 Å is significantly shorter than the 2·402 Å observed in disodium maleate monohydrate (James & Williams, 1974), where the Na^+ ions reside in square-pyramidal environments.

For Na(2) and Na(3), the Na–O contact distances vary substantially [2·391 (2)–2·540 (2) Å for Na(2), 2·329 (2)–2·678 (2) Å for Na(3)]. The mean Na–O distances of 2·463 (2) and 2·483 (2) Å are significantly longer than the expected value (Shannon & Prewitt, 1969), but are comparable to the mean distances observed in sodium formate, 2·451 Å (Markila, Rettig & Trotter, 1975), sodium hydrogen fumarate, 2·44 Å (Gupta & Sahu, 1970), and sodium acetate trihydrate, 2·46 Å (Cameron, Mannan & Rahman, 1976). The distortion of the coordination octahedra around Na(2) and Na(3) is far less than that in NaHAD, with non-axial angles in the range 81·37 (7)–98·63 (7)° for Na(2) and 79·85 (7)–100·16 (7)° for Na(3).

The three Na ions are in different environments with respect to their nearest Na^+ ion neighbors. Na(2) and Na(3), by sharing an edge of their polyhedra, form an endless chain along the b axis (Na–Na distance 3·75 Å). Na(3) also shares an edge with Na(1) (Na–Na distance 3·50 Å). Both Na(2) and Na(3) share only one corner, while Na(1) shares five corners with its neighbors. This sharing of edges and corners forms a two-dimensional layer of Na coordination polyhedra.

There is a noticeable similarity in the crystal-packing schemes of the two salts. In both structures, the Na^+ ions lie either in or close to the crystallographic (100) plane and are surrounded by the O atoms from the carboxylate and hydroxamate groups. The water molecules are interspersed in the region of the coordination spheres. The hadacidin molecules, in both structures, connect these layers.

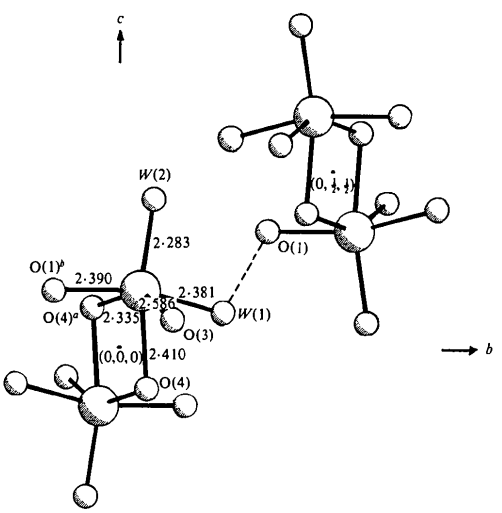

Fig. 7. Sodium coordination in $NaHAD.2H_2O$, per asymmetric unit, as viewed down the a axis.

Table 6. *Symmetry codes for superscripts*

(*a*) $-x,-y,-z$; (*b*) $1-x, y+\frac{1}{2}, \frac{1}{2}-z$; (*c*) $x-1, y, z$; (*d*) $1-x, \frac{1}{2}+y, \frac{1}{2}-z$; (*e*) $-x, 2-y, -z$; (*f*) $x, 2\frac{1}{2}-y, z-\frac{1}{2}$; (*g*) $-x, y-\frac{1}{2}, \frac{1}{2}-z$; (*h*) $x, 1\frac{1}{2}-y, z-\frac{1}{2}$; (*i*) $-x, \frac{1}{2}+y, \frac{1}{2}-z$; (*j*) $x, 1\frac{1}{2}-y, \frac{1}{2}+z$; (*k*) $x-1, 1\frac{1}{2}-y, \frac{1}{2}+z$; (*l*) $-x, 2-y, 1-z$

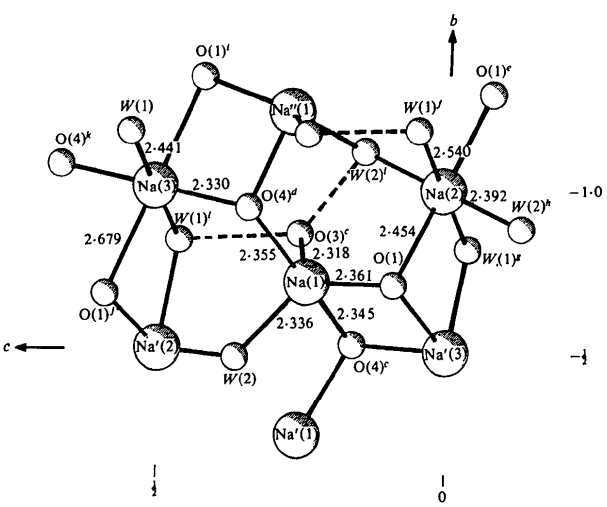

Fig. 8. Sodium coordination in the asymmetric unit of $Na_2HAD.2H_2O$, as viewed down the c axis.

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1,2,4-Triazole Complexes. XV. The Structure of Tetraaquasulphato(1,2,4-triazole)manganese(II)

BY S. GORTER AND D. W. ENGELFRIET

Gorlaeus Laboratories, X-ray and Electron Diffraction Section, University of Leiden, PO Box 9502, 2300 *RA Leiden, The Netherlands*

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Abstract

$[Mn(C_2H_3N_3)(H_2O)_4SO_4]$ is monoclinic, space group $P2_1/c$ with $a = 6{\cdot}5022\ (4)$, $b = 12{\cdot}134\ (4)$, $c = 12{\cdot}849\ (2)$ Å, $\beta = 90{\cdot}57\ (6)°$, $Z = 4$. Final $R = 0{\cdot}029$ for 1529 independent reflexions. The coordination polyhedron around Mn consists of four O atoms of water molecules, one O atom of the sulphate group and N(4) of the triazole ring *cis* with respect to the sulphate ligand. There is extensive hydrogen bonding.

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