stirred for 1 h at room temperature. Acetyl chloride (3.0 ml, 42 mmol) was added slowly to the reaction mixture at 273 K. The reaction was continued at room temperature for 1 h and was quenched by adding acetic acid (5 ml). The mixture was poured into ice water (500 ml) containing hydrochloric acid (12.5 ml) to precipitate the crude product which was collected by filtration and washed with water. Recrystallization from alcohol gave 9.8 g of the final product with 78% yield. Single crystals of the compound were obtained by slow evaporation from acetonitrile.

Crystal data

$C_{11}H_8Br_2N_2O_2$
M_r = 360.01
Monoclinic
$P2_1/c$
a = 5.6134 (1) Å
b = 9.9847 (3) Å
c = 21.5896 (2) Å
β = 93.639 (1)°
V = 1207.62 (4) Å^3
Z = 4
D_x = 1.980 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 3648 reflections
θ = 1.89–25.01°
μ = 6.70 mm^{-1}
T = 173 (2) K
Needle
0.45 × 0.09 × 0.05 mm
Colorless

Data collection

Siemens SMART Platform CCD diffractometer
ω scans
Absorption correction: empirical (*SHELXTL-Plus*; Sheldrick, 1996)
T_{min} = 0.433, T_{max} = 0.715
5918 measured reflections

2107 independent reflections
1700 reflections with $I > 2\sigma(I)$
R_{int} = 0.040
θ_{max} = 25.01°
$h = -6 \rightarrow 6$
$k = -10 \rightarrow 11$
$l = -24 \rightarrow 25$

Refinement

Refinement on F^2
$R(F)$ = 0.040
$wR(F^2)$ = 0.10
S = 1.007
2107 reflections
155 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0573P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.76 e Å^{-3}
$\Delta\rho_{min}$ = −1.038 e Å^{-3} (0.86 Å from Br2)
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

Br2—C2	1.899 (4)	N11—C11	1.146 (6)
Br5—C5	1.913 (5)	C7—C8	1.461 (6)
O7—C7	1.239 (5)	C8—C9	1.372 (7)
O9—C9	1.328 (6)	C8—C11	1.438 (6)
N1—C7	1.361 (6)	C9—C10	1.478 (7)
N1—C1	1.406 (6)		
C7—N1—C1	129.3 (4)	N1—C7—C8	116.0 (4)
C6—C1—N1	123.4 (4)	C9—C8—C11	118.2 (4)
C2—C1—N1	117.9 (4)	C9—C8—C7	121.3 (4)
C3—C2—Br2	118.1 (4)	C11—C8—C7	120.5 (4)
C1—C2—Br2	120.6 (4)	O9—C9—C8	121.5 (4)
C6—C5—Br5	119.3 (4)	O9—C9—C10	113.0 (4)
C4—C5—Br5	117.2 (4)	C8—C9—C10	125.5 (4)
O7—C7—N1	123.2 (4)	N11—C11—C8	175.8 (6)
O7—C7—C8	120.8 (4)		

Data collection: *SMART* (Siemens, 1996). Cell refinement: *SAINT* (Siemens, 1996). Data reduction: *SAINT*. Program(s) used to solve structure: *SHELXTL-Plus* (Sheldrick, 1996). Program(s) used to refine structure: *SHELXTL-Plus*. Molecular graphics: *SHELXTL-Plus*. Software used to prepare material for publication: *SHELXTL-Plus*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FR1196). Services for accessing these data are described at the back of the journal.

References

Allen, F. H. & Kennard, O. (1993). *Chem. Des. Autom. News*, **8**, 31–37.
Mahajan, S., Ghosh, S., Sudbeck, E. A., Zheng, Y., Downs, S., Hupke, M. & Uckun, F. M. (1999). *J. Biol. Chem.* **274**, 9587–9599.
Sheldrick, G. M. (1996). *SHELXTL-Plus Reference Manual*. Version 5.0. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Siemens (1996). *SMART* and *SAINT. Area-Detector Control and Integration Software*. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

Acta Cryst. (1999). C**55**, 1365–1368

Neotame, an alkylated dipeptide and high intensity sweetener

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(*Received 12 November 1998; accepted 14 April 1999*)

Abstract

The title compound, *N*-[*N*-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester (neotame) hydrate, $C_{20}H_{30}N_2O_5 \cdot H_2O$, is an alkylated dipeptide. The zwitterionic structure, *i.e.* 3-(3,4-dimethylbutylammonio)-3-[*N*-(1-methoxycarbonyl-2-phenylethyl)aminocarbonyl]propanoate hydrate, in the solid state fits the 'L-shaped' topochemical structure proposed for the requirement of sweetness ability for aspartyl-based dipeptide compounds. The structure suggests that the extraordinary potency of neotame is due to the hydrophobic positioning of the alkyl and phenyl groups within the molecule. In this crystalline form, obtained from ethyl acetate/hexane, a single water molecule is also

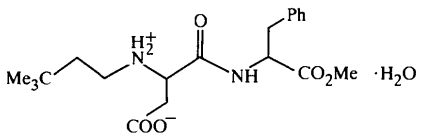
present in the unit cell, linked by hydrogen bonds to an aspartate O atom and the methyl ester carbonyl group.

Comment

Neotame is an alkylated dipeptide discovered by Nofre & Tinti (1996). It has recently been submitted to the US FDA for approval as a table-top sweetener. Neotame is about 8000 times sweeter than sugar and is prepared by the reductive alkylation of aspartame with 3,3-dimethylbutyraldehyde. It is slightly soluble in water (~1.25 g per 100 g), but highly soluble in alcohols and polar organic solvents.

Neotame crystallizes from most common aqueous/organic solvents (water miscible organic solvents, *e.g.* alcohols/water, DMF/water, acetone/water, acetonitrile/water *etc.*) or from polar/non-polar solvent mixtures (*e.g.* ethyl acetate/hexane, acetone/hexane *etc.*).

Neotame crystallized from ethyl acetate/hexane gave crystals that were suitable for X-ray studies, (I). The absolute configuration was derived from that of the aspartame starting material. The structure of neotame in the solid state (Fig. 1) can be compared with that of the



(I)

parent compound, aspartame (Hatada *et al.*, 1985). The presence of the *tert*-butyl group on the amino terminus of the dipeptide alters the backbone, as the phenyl and *tert*-butyl groups form a hydrophobic region in the molecule. There are close contacts between the *tert*-butyl and phenyl groups [the distances from the plane of the phenyl group to the three methyl-group C atoms are: C18 3.28 (10), C19 3.18 (12) and C20 5.20 (12) Å]. This results in the phenyl group lying in a position that is parallel, not perpendicular, to the backbone of the molecule [in neotame, the dihedral angle X (C6—C7—C8—C9) for the phenyl group of phenylalanine is 175.9 (3)°, while the same angle in aspartame is −61.3°].

The solid-state structure of (I) consists of hydrophobic and hydrophilic regions. The hydrophobic region is composed of phenyl–butyl contacts. The hydrophilic regions are built by an extended array of neotame molecules, linked through the carboxyl group and the amine, with a water molecule situated at the side of the cluster, not in the midst of the cluster, as in aspartame.

This structure suggests that neotame is much sweeter than aspartame because of the development of a well oriented hydrophobic structure (Holtje & Kier, 1974). In neotame, the plane of the phenyl group is 4.500 (6) Å from the amino N atom and 5.61 (2) Å from the aspartate C atom. These values are much closer to the optimal

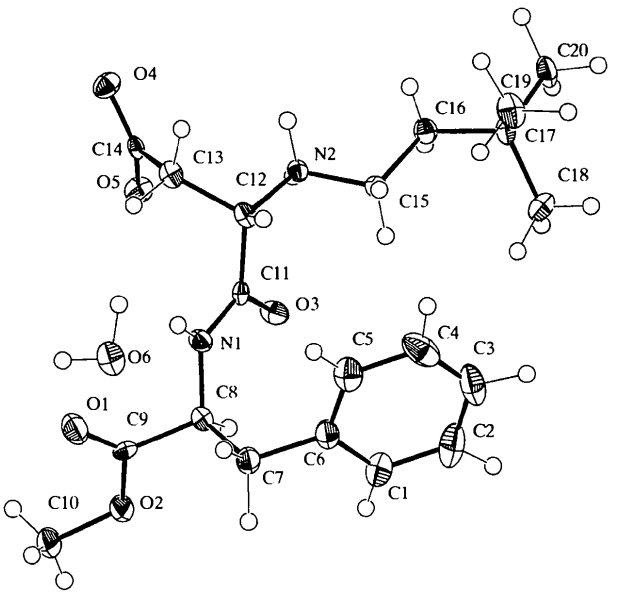


Fig. 1. The molecular structure of the title compound showing 50% probability ellipsoids.

values of 3.5 and 5.5 Å, respectively, suggested for sweet substances.

The water molecule is apparently tightly held, at least in the formation of X-ray quality crystals. When the hydrated substance is dissolved in ethyl acetate for crystallization, the water is still present when the material is crystallized by the addition of hexane. The water molecule is positioned so that it forms weak or very weak hydrogen bonds to the ester carbonyl and one of the aspartate O atoms. There is also a chain

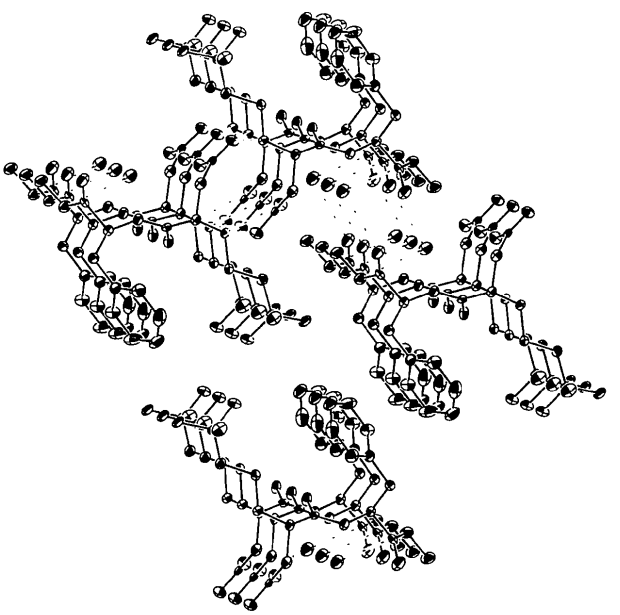


Fig. 2. Diagram illustrating the clustering about the aspartate and amino groups that form the hydrophilic core of the structure.

arrangement involving the aspartate O atom on one molecule, the ammonium site on a second, and the other aspartate O atom on a third molecule (Fig. 2). The amide H atom does not participate in significant hydrogen bonding; there are no contacts between the amide N and any other heteroatom of less than 3.2 Å.

These results can be compared with previously reported calculated and quoted crystallographic results (Mattern *et al.*, 1997; Goodman *et al.*, 1998). We find that the present structure of neotame fits the paradigm of an 'L' formed by the peptide backbone and the phenyl group of phenylalanine. However, the set of dihedral angles (Fig. 3) indicates that the present structure is the same as the calculated '*f*' conformation and the determined (1*A*) structure (Mattern *et al.*, 1997; Goodman *et al.*, 1998).

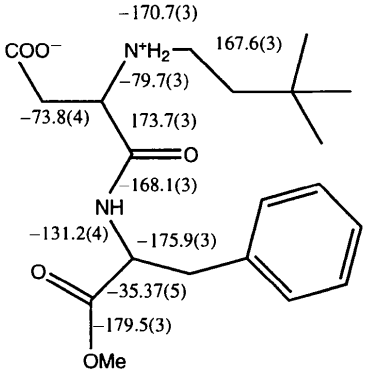


Fig. 3. Diagram illustrating the torsion angles (°) along the backbone of the title compound. All angles are displayed relative to the carbon terminus of the molecule.

Experimental

To a slurry of α-aspartame (29.5 g, 0.1 mol) and 3,3-dimethylbutyraldehyde (10 g, 0.1 mol) in methanol (500 ml) was added Pd/C (4%, 50% wet, 1.2 g). The mixture was hydrogenated at room temperature and 30 psi (1 psi ≈ 6.89 × 10^3 Pa) for 12 h. The mixture was filtered through a dicalite bed and washed with methanol (50 ml). The methanol was reduced to half its volume (250 ml) on a rotary evaporator under reduced pressure at room temperature and then water (250 ml) was added. The remaining methanol was distilled to a level of 17–30%. The mixture was left stirring at room temperature for 2–12 h. The precipitated solid was filtered off, washed with water (50 ml) and dried in a vacuum oven at 313 K/house vacuum/16 h to get 26.7 g (71%) of white solid (> 97% pure by HPLC). The crude product was crystallized from ethyl acetate/hexane (1:2) to give a white crystalline solid [yield 21.36 g (56%), m.p. 353–356 K]. $[\alpha]_D$ −54.84° (*c* = 1, methanol); ^{1}H NMR ($CDCl_3$, p.p.m.): δ 0.62 (*s*, 9H, *tert*-butyl), 1.1 (*m*, 2H, CH_2), 1.23–1.95 (*m*, 4H, CH_2), 2.7–3.0 (*dd*, 2H, CH_2), 3.3 (*dd*, 1H, CH), 3.45 (*s*, 1H, OCH_3), 4.4 (*m*, 1H, CH), 7.0–7.15 (*m*, 5H, phenyl), 8.43 (*d*, 1H, NH). Analysis calculated for $C_{20}H_{30}N_2O_5{\cdot}H_2O$: C 60.54, H 8.07, N 7.06, H_2O 4.55%; found: C 60.59, H 7.88, N, 7.02, H_2O 4.71%.

Crystal data

$C_{20}H_{30}N_2O_5{\cdot}H_2O$
M_r = 396.48
Monoclinic
$P2_1$
a = 12.7274 (3) Å
b = 5.5573 (2) Å
c = 15.1610 (3) Å
β = 102.9351 (12)°
V = 1045.13 (6) Å^3
Z = 2
D_x = 1.260 Mg m^{-3}
D_m not measured

Mo *Kα* radiation
λ = 0.71073 Å
Cell parameters from 3713 reflections
θ = 2–25°
μ = 0.093 mm^{-1}
T = 173 (2) K
Block
0.60 × 0.20 × 0.10 mm
Colorless

Data collection

Bruker CCD area-detector diffractometer
φ and ω scans
Absorption correction: empirical ψ scan (Bruker, 1998)
T_{min} = 0.95, T_{max} = 0.99
4069 measured reflections
2699 independent reflections

2559 reflections with $I > 2\sigma(I)$
R_{int} = 0.051
θ_{max} = 25°
h = −14 → 15
k = −6 → 5
l = −17 → 17
Intensity decay: <1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.058
$wR(F^2)$ = 0.182
S = 1.411
2699 reflections
378 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.12P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.004
$\Delta\rho_{max}$ = 0.41 e Å^{-3}
$\Delta\rho_{min}$ = −0.42 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected torsion angles (°)*

C6—C7—C8—N1	−60.4 (5)	C12—C13—C14—O4	−139.3 (3)
C6—C7—C8—C9	175.9 (3)	C12—C13—C14—O5	40.9 (4)
C11—C12—C13—C14	−73.8 (4)	C15—C16—C17—C18	60.5 (4)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O6—H6*OA*···O1^i	0.88 (7)	2.10 (7)	2.965 (4)	167 (5)
O6—H6*OB*···O5	0.99 (9)	2.11 (9)	3.098 (4)	176 (7)
N1—H1N···O6^{ii}	0.80 (6)	2.44 (7)	3.241 (5)	173 (5)
N2—H21N···O4^{iii}	0.79 (8)	2.10 (7)	2.865 (4)	162 (6)
N2—H22N···O5^{iv}	0.95 (4)	1.87 (4)	2.818 (4)	175 (4)
N2—H22N···O4^{iv}	0.95 (4)	2.44 (4)	3.025 (4)	120 (3)

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

All non-H atoms were refined anisotropically to convergence. Atoms H7*B*, H20*B* and H20*C* were treated ideally with fixed independent parameters [U(H) = 1.2U_{eq}(C_{methyl})].

Data collection: *SMART* (Bruker, 1998). Cell refinement: *SMART*. Data reduction: *SHELXTL* (Sheldrick, 1997). Program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997). Molecular graphics: *Xtal*3.4 (Hall *et al.*, 1995). Software used to prepare material for publication: *SHELXTL*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BK1453). Services for accessing these data are described at the back of the journal.

References

Bruker (1998). *SMART*. Version 5.054. Bruker AXS Inc., Madison, Wisconsin, USA.

Goodman, M., Mattern, R.-H., Gantzel, P., Santini, A., Iacovino, R., Saviano, M. & Benedetti, E. (1998). *J. Pept. Sci.* **4**, 229–238.

Hall, S. R., King, G. S. D. & Stewart, J. M. (1995). Editors. *Xtal3.4 Users Manual*. University of Western Australia, Australia.

Hatada, M., Jancarik, J., Graves, B. & Kim, S.-H. (1985). *J. Am. Chem. Soc.* **197**, 4279–4282.

Höltje, H. D. & Kier, L. B. (1974). *J. Pharm. Sci.* **63**, 1722–1725.

Mattern, R.-H., Amino, Y., Benedetti, E. & Goodman, M. (1997). *J. Pept. Res.* **50**, 286–299.

Nofre, C. & Tinti, J.-M. (1996). US Patent 5 480 668.

Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.

Sheldrick, G. M. (1997). *SHELXTL*. Version 5.10. Bruker AXS Inc., Madison, Wisconsin, USA.

Acta Cryst. (1999). C**55**, 1368–1369

An N···H—O intramolecular strong hydrogen bond in *N*-(2-aminophenyl)-naphthaldimine

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(*Received 3 November 1998; accepted 24 March 1999*)

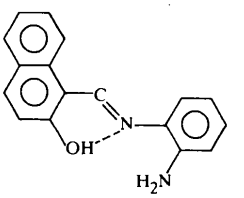
Abstract

The title compound, $C_{17}H_{14}N_2O$, contains a naphthaldimine and an *N*-(2-aminophenyl) group. There is a strong intramolecular N···H—O hydrogen bond between the imine and hydroxyl group [2.540 (2) Å].

Comment

Although many structures of transition metal complexes with Schiff bases have been determined, a relatively small number of free Schiff bases have been structurally characterized (Calligaris & Randaccio, 1987). Schiff bases are of interest because they are known to show photochromism and thermochromism in the solid state; this may involve reversible proton transfer from the hydroxyl-O atom to the imine-N atom (Cohen *et al.*, 1964; Kevran *et al.*, 1996; Hadjoudis *et al.*, 1987). Photochromism is produced by intramolecular proton transfer associated with a change in the π-electron configuration (Barbara *et al.*, 1980; Hadjoudis, 1981; Higelin & Sixl, 1983). Thermochromism is also due to a change in the π-electron configuration induced by a proton transfer which can occur in the ground state (Cohen *et al.*, 1964). Interest in studies on photochromic compounds has been increasing ever since the potential application of photochromic materials was realised in various areas such as the control and measurement of radiation intensity, optical computers and display systems (Durr, 1989; Durr & Bouas-Laurent, 1990).

Fig. 1 shows the molecular structure and atomic labelling scheme of the title compound. The title molecule has two almost planar moieties *A* [O1, C7–C17; planar with a maximum deviation of 0.034 (2) Å for



(I)

the O1 atom] and *B* [N1, N2, C1–C6; planar with a maximum deviation of 0.017 (1) Å for the C1 atom] which are inclined at an angle of 45.2 (1)° reflecting mainly the twist about C1—N2 [C2—C1—N2—C7 = 39.6 (3)°]. The conformation at the N2=C1 double bond is *trans* with the torsion angle C8—C7—N2—C1 = −174.9 (2)°.

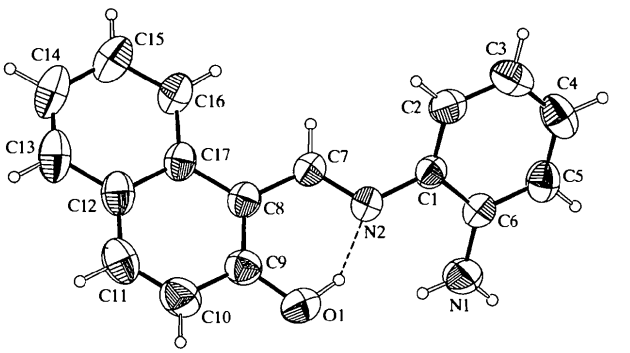


Fig. 1. The molecular structure showing 50% probability displacement ellipsoids with the atom-numbering scheme.

Two types of intramolecular hydrogen bond (either N—H···O or N···H—O) can exist in Schiff bases (Garnovskii *et al.*, 1993). The Schiff bases derived from salicylaldehyde always form the N···H—O type of hydrogen bond regardless of the nature of the substituent on N (aryl or alkyl) (Gavranic *et al.*, 1996). Both types of hydrogen bond were found in aldimine compounds derived from 2-hydroxy-1-naphthaldehyde (Elerman *et al.*, 1998). In the title compound, the N···O distance [2.540 (2) Å] indicates a