Acetate 11 of (+)-Methyl 3,4-Anhydroshikimate. A solution of bromo acetate **7** (65 mg, 0.22 mmol) in benzene (2 mL) was treated with DBU (36 μL, 1.1 equiv) under Ar at room temperature. The solution turned cloudy, the CH_2Cl_2 was added dropwise to restore homogeneity. After 30 min, the reaction mixture was diluted with ether (3 mL), washed with 5% H_2SO_4 (2 × 3 mL), and dried over $MgSO_4$ and the solvent removed in vacuo to produce crude **8** (46 mg). Flash chromatography on SiO_2 (3:2 hexanes-ethyl acetate) gave pure **8**: 26 mg, 60% as a clear oil; R_f 0.57; $[\alpha]_D$ +233° (c = 0.39, EtOH); ^1H NMR ($CDCl_3$) 7.12 (t, 1 H, J = 3.7 Hz), 5.59 (m, 1 H), 3.75 (s, 3 H), 3.59 (m, 1 H), 3.48 (t, 1 H, J = 4.0 Hz), 2.80 (dt, 1 H, J = 18.1, 1.9 Hz), 2.33 (ddd, 1 H, J = 18.1, 5.4, 3.2 Hz) 2.02 (s, 3 H); IR (film) 2950, 1740, 1720, 1650 cm^{-1}; HRMS calcd for $C_{10}H_{13}O_5$ (M + 1) 213.0763, found 213.0763.

(−)-Methyl (3*S*,4*S*,5*R*)-3-Hydroxy-4,5-epoxy-1-cyclohexene-1-carboxylate (2) Directly from 7. A solution of $NaOCH_3$ in anhydrous CH_3OH (0.84 M, 1.86 mL, 1.56 mmol) was added dropwise under Ar to a 0 °C solution of bromo acetate **7** (0.435 g, 1.48 mmol) in CH_3OH (3.7 mL). The reaction mixture was stirred for 30 min at 0 °C and then placed in a 50 °C oil bath for 10 min and more $NaOCH_3$ solution added (1.86 mL). After it was stirred for 25 min at 50 °C, the reaction mixture was neutralized at that temperature with saturated NH_4Cl solution (1 mL) and the bulk of the solvent removed in vacuo. The aqueous residue was then extracted with ethyl acetate (6 × 5 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Crude product (0.278 g) containing the desired (−)-**2**, unisomerized (+)-**10**, and ring-opened product (+)-**12** was purified by flash chromatography (9:1 ether-hexanes) to isolate (+)-**12**. The epoxyol mixture (3:1 **2**-**10**, 0.165 g) was further purified by medium-pressure liquid chromatography (Prep-PAK 500 SiO_2 column, 3:7 ether-hexanes), and the products were eluted in that order.

(−)-**2**: 0.113 g, 46% yield; R_f 0.33 (9:1 ether-hexanes); mp 64-65.5 °C (lit.[4] mp 65-66.5°C); $[\alpha]_D$ −41° (c = 1.5, $CHCl_3$) (lit.[4] $[\alpha]_D$ −53.9°); ^1H NMR ($CDCl_3$) 6.78 (m, 1 H), 4.65 (m, 1 H), 3.74 (s, 3 H), 3.43 (m, 1 H), 3.28 (m, 1 H), 2.94 (dm, 1 H, J = 20.0 Hz), 2.65 (dq, 1 H, J = 20.0, 2.5 Hz); ^{13}C NMR ($CDCl_3$) 170.0, 133.8, 126.9, 63.1, 52.8, 52.1, 50.5, 24.4; IR 3250, 3000, 2960, 1720, 1660, 1250 cm^{-1}.

(+)-**12**: 85 mg, 28% yield; mp 66-67 °C; $[\alpha]_D$ +21° (c = 0.51, $CHCl_3$); ^1H NMR ($CDCl_3$) 6.80 (br s, 1 H), 3.83 (m, 2 H), 3.74 (s, 3 H), 3.58 (dd, 1 H, J = 9.9, 8.0 Hz), 3.49 (s, 3 H), 2.86 (dd, 1 H, J = 15.0, 5.7 Hz), 2.25 (m, 1 H); IR 3400, 2910, 1715, 1650, 1250, 1100 cm^{-1}; HRMS calcd for $C_9H_{14}O_5$ (M^+) 202.0841, found 202.0839.

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Crystal Structure of Two Retro-Inverso Sweeteners

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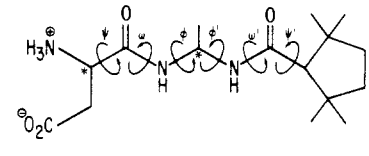
Abstract: We have solved the structure of a crystal composed of two diastereomers, *N*-L-aspartyl-*N'*-[(2,2,5,5-tetramethylcyclopentanyl)carbonyl]-(*R*)-1,1-diaminoethane (L,*R* isomer) and *N*-L-aspartyl-*N'*-[(2,2,5,5-tetramethylcyclopentanyl)carbonyl]-(*S*)-1,1-diaminoethane (L,*S* isomer). Both diastereomers are intensely sweet and are retro-inverso stereoisomers of dipeptides. We have related the crystal structure of these molecules to our model to explain the sweetness of peptide-based ligands. The "L shape" postulated on the basis of molecular mechanics and NMR spectroscopy is in full agreement with the crystal structures.

Introduction

As part of a program to relate structure of molecules to their taste, the conformations of four diastereomeric retro-inverso and dipeptide amides were recently reported.[1] The retro-inverso modification allows the examination of the effect of the backbone structure on taste and has led to many sweet-tasting compounds.[2] These molecules are sterically constrained as a result of the incorporation of a bulky substituent, the tetramethylcyclopentanyl group. The conformational preferences of the molecules were determined with use of high-resolution NMR and flexible geometry energy minimizations. The results from these experimental and theoretical approaches were found to be in good agreement. The favored conformations were then related to taste properties. From these results a model was developed to explain the sweet taste. In the molecular array of the sweet molecules the zwitterionic ring of the N-terminal L-aspartyl residue is coplanar and essentially perpendicular to the tetramethylcyclopentanyl ring leading to an "L shape" with the aspartyl moiety as the stem of the L and the tetramethylcyclopentanyl group the base of the L.

In this paper we present the X-ray diffraction analysis of a crystal composed of the following two diastereomeric retro-inverso amides: *N*-L-aspartyl-*N'*-[(2,2,5,5-tetramethylcyclopentanyl)carbonyl]-(*R*)-1,1-diaminoethane (Asp-R-gAlaTMCP) and *N*-L-aspartyl-*N'*[(2,2,5,5-tetramethylcyclopentanyl)carbonyl]-(*S*)-1,1-diaminoethane (Asp-S-gAlaTMCP). The similarities and differences of the solid-state structures are discussed and compared to the calculated conformations and those found in solution. The crystal structures are also compared to the solid-state conformation reported for aspartame.[3]



structure of Asp-(*R* and *S*)-gAla-TMCP

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Table I. Crystallographic Parameters of *N*-L-Aspartyl-*N'*-[(2,2,5,5-tetramethylcyclopentanyl)carbonyl]-(*R* and *S*)-1,1-diaminoethane[a]

mol formula	$2C_{16}H_{29}N_3O_4$
mol weight, amu	709.3
crystal system	monoclinic
space group	$P2_1$
Z, molecule/unit cell	2
a, Å	9.569 (8)
b, Å	9.621 (2)
c, Å	23.204 (3)
β, deg	92.57 (1)
V, Å^3	2134.2
d(calcd), g/cm^{-3}	1.017
d(exptl), g/cm^{-3}	1.10
radiation, Å	Cu Kα, 1.5418 (monochromated)
no. independent reflections	4327
reflections with $I > 3\sigma(I)$	3336
final *R* value	0.090
final weighted *R* value	0.104
esd of an observation of unit weight	1.47
temperature, °C	ambient
crystallization solvent	$H_2O/2$-C_3H_7OH (1:1)

[a] The estimated standard deviation of the least significant figure is given in parenthesis.

Experimental Section

The two diastereomers, *N*-L-aspartyl-*N'*-[(2,2,5,5-tetramethylcyclopentanyl)carbonyl]-(*R*)-1,1-diaminoethane (L,*R* isomer) and *N*-L-aspartyl-*N'*-[(2,2,5,5-tetramethylcyclopentanyl)carbonyl]-(*S*)-1,1-diaminoethane (L,*S* isomer) ($C_{16}H_{29}N_3O_4$), were cocrystallized from a 1:1 mixture of $H_2O/2$-C_3H_7OH as colorless crystals. Preliminary oscillation and Weissenberg photographs were taken to establish the crystal symmetry and the space group. Determination of the cell constants and the collection of the X-ray intensity data were performed with use of Cu Kα monochromated radiation, on a CAD4 Enraf-Nonius diffractometer of the Centro Interdipartimentale di Metodologie Chimico-Fisiche at the University of Naples, equipped with a MicroVAX II Digital computer. Unit cell parameters were obtained by a least-squares procedure on the angular parameters of 25 reflections in the θ range of 17–25°. The analysis of the peak profiles suggested an $\omega - 2\theta$ scan mode with a scan angle equal to $(1.0 + 0.15\tan\theta)°$; background counts were taken in an additional area of $\Delta\omega/4$ on both sides of the main scan with the same scan speed for each reflection.

A crystal-to-counter distance of 368 mm was used with counter entrance aperture of 4 mm. The tube placed between the goniometer head and the detector was evacuated. Prescan runs were made at a speed of 3.5°/min. Reflections with a net intensity $I < 0.5\sigma(I)$ were flagged as "weak"; those having $I \geq 0.5\sigma(I)$ were measured at a lower speed ((1.0 - 3.5)°/min), depending on the value of the $\sigma(I)/I$. Two intensity control reflections were measured every 60 min of X-ray exposure time in order to monitor the crystal and electronic stability; no significant changes in intensity were observed during data collection. Orientation matrix checks were made with respect to the scattering vectors of four well-centered reflections every 200 reflections measured; reorientation was made by using 25 high angle reflections, if the displacements of the measured scattering vector exceeded the calculation value of 0.15°. The *h*, *k*, and *l* ranges were −11 to +11, 0 to +11, and 0 to +28, respectively. All reflections are corrected for Lorentz and polarization effects.

The structure was solved by direct methods and refined with the structure determination program (SDP) package. The full-matrix least-squares procedure was used, minimizing the quantity $\Sigma w(F_o - F_c)^2$ with weight $w = 1/[\sigma_1^2(F_0) + (\mathrm{PWT}\cdot F_0)^2 + \mathrm{QWT}]$, according to the Killean–Lawrence method, where $\sigma_1(F_0) = [F_0^2 + 2F_0\cdot\sigma(F_0)] - F_0$ and values of 0.02 and 1.00 are given to parameters PWT and QWT, respectively. All C, N, and O atoms were refined with anisotropic temperature factors. Hydrogens were introduced in structure factors calculation (but not refined) in their stereochemically expected positions with isotropic temperature factors equal to the equivalent B factor of the atom to which it is connected.

Refinements were deemed complete when the shifts in the atomic coordinates and temperature factors of the C, N, and O atoms were less than $^1/_5$ and $^1/_3$ of the corresponding standard deviations, respectively. The atomic scattering factors for all atomic species, with the real and imaginary dispersion corrections, were calculated according to Cromer and Waber. Crystallographic data are reported in Table I. Tables of final atomic parameters and equivalent isotropic thermal parameters for all non-hydrogen atoms, bond lengths and bond angles, coordinates for H atoms, and observed and calculated structure factors have been deposited in supplementary material and are also available from the Cambridge Crystallographic Data Centre.

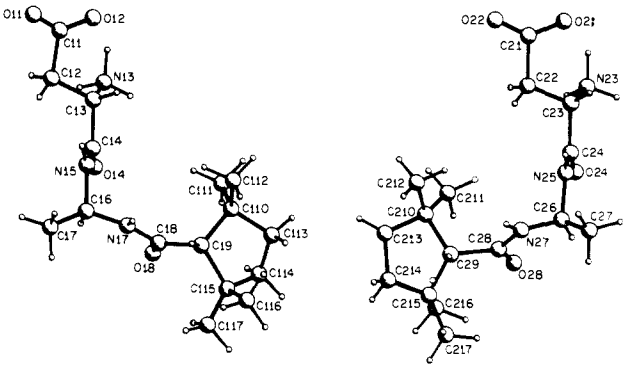

Figure 1. Molecular structure of *N*-L-aspartyl-*N'*-[(2,2,5,5-tetramethylcyclopentanyl)carbonyl]-(*R*)-1,1-diaminoethane (L,*R* diastereomer) (left) and the *N*-L-aspartyl-*N'*-[(2,2,5,5-tetramethylcyclopentanyl)carbonyl]-(*S*)-1,1-diaminoethane (L,*S* diastereomer) (right).

Table II. Torsion Angles from X-ray Crystallographic Structures[a]

L,*R* isomer		L,*S* isomer	
O_{11}–C_{11}–C_{12}–C_{13}	−168.9 (8)	O_{21}–C_{21}–C_{22}–C_{23}	177.8 (6)
O_{12}–C_{11}–C_{12}–C_{13}	−1.3 (11)	O_{22}–C_{21}–C_{22}–C_{23}	−1.9 (9)
C_{11}–C_{12}–C_{13}–N_{13}	−82.6 (7)	C_{21}–C_{22}–C_{23}–N_{23}	−75.4 (7)
C_{11}–C_{12}–C_{13}–C_{14}	156.2 (6)	C_{21}–C_{22}–C_{23}–C_{24}	163.6 (5)
C_{12}–C_{13}–C_{14}–N_{15}	−66.7 (7)	C_{22}–C_{23}–C_{24}–N_{25}	−71.4 (8)
C_{12}–C_{13}–C_{14}–O_{14}	114.3 (7)	C_{22}–C_{23}–C_{24}–O_{24}	109.5 (7)
N_{13}–C_{13}–C_{14}–O_{14}	−7.0 (9)	N_{23}–C_{23}–C_{24}–O_{24}	−12.7 (10)
N_{13}–C_{13}–C_{14}–N_{15}	172.0 (5)	N_{23}–C_{23}–C_{24}–N_{25}	166.4 (7)
C_{13}–C_{14}–N_{15}–C_{16}	−175.4 (5)	C_{23}–C_{24}–N_{25}–C_{26}	177.5 (6)
O_{14}–C_{14}–N_{15}–C_{16}	3.6 (9)	O_{24}–C_{24}–N_{25}–C_{26}	−3.5 (11)
C_{14}–N_{15}–C_{16}–C_{17}	−134.4 (5)	C_{24}–N_{25}–C_{26}–C_{27}	137.2 (6)
C_{14}–N_{15}–C_{16}–N_{17}	104.4 (5)	C_{24}–N_{25}–C_{26}–N_{27}	−99.7 (6)
N_{15}–C_{16}–N_{17}–C_{18}	−97.3 (6)	N_{25}–C_{26}–N_{27}–C_{28}	104.8 (6)
C_{17}–C_{16}–N_{17}–C_{18}	141.2 (6)	C_{27}–C_{26}–N_{27}–C_{28}	−132.8 (6)
C_{16}–N_{17}–C_{18}–O_{18}	−14.1 (2)	C_{26}–N_{27}–C_{28}–O_{28}	7.6 (9)
C_{16}–N_{17}–C_{18}–C_{19}	166.8 (5)	C_{26}–N_{27}–C_{28}–C_{29}	−169.4 (5)
N_{17}–C_{18}–C_{19}–C_{110}	−100.4 (6)	N_{27}–C_{28}–C_{29}–C_{210}	92.8 (6)
N_{17}–C_{18}–C_{19}–C_{115}	138.0 (6)	N_{27}–C_{28}–C_{29}–C_{215}	−142.2 (6)
O_{18}–C_{18}–C_{19}–C_{110}	80.5 (7)	O_{28}–C_{28}–C_{29}–C_{210}	−84.1 (7)
O_{18}–C_{18}–C_{19}–C_{115}	−41.1 (9)	O_{28}–C_{28}–C_{29}–C_{215}	40.9 (9)

[a] Values in degrees. The estimated standard deviation of the least significant figure is given in parenthesis.

Results and Discussion

The diastereomeric pair of *N*-L-aspartyl-*N'*-[(2,2,5,5-tetramethylcyclopentanyl)carbonyl]-(*R* and *S*)-1,1-diaminoethane, abbreviated as L,*R* and L,*S*, were crystallized by the slow evaporation of a mixture of water/2-propanol at controlled temperatures. The diastereomeric pair crystallizes in the acentric $P2_1$ monoclinic space group with three water molecules in the independent unit.

The molecular structures of the two diastereomers and the numbering of the atoms are shown in Figure 1. A list of the torsion angles defined by non-hydrogen atoms of the two molecules is given in Table II. In Table III, the intermolecular hydrogen bonds of the diastereomeric pair and water molecules are listed. The geometric parameters (including bond length and bond angles) have been deposited in supplementary material and with the Cambridge Crystallographic Data Centre. The values of these parameters as far as the aspartyl terminal end and the peptide groups are concerned are in good agreement with literature values. The tetramethylcyclopentanyl terminal end in both diastereomers presents greater deviations from commonly accepted values for C–C bond distances and C–C–C bond angles. This result must be ascribed to the "loose" packing in which these hydrophobic terminal ends are involved in the crystal. The atoms of this portion of both diastereomers have much larger thermal parameters than

Table III. Intermolecular H Bond in the Structure of (L,*R*)(L,*S*) Diastereoisomeric Pairs

donor	acceptor	distance, Å	angle, deg N···O=C (O_w···O—C)	symmetry operation[a]
N_{15}	O_{24}*	3.05	159	$x, {}^1/_2 + y - 1, z + 1$
N_{17}	O_{28}*	2.83	169	$x, {}^1/_2 + y - 1, z + 1$
N_{25}*	O_{14}*	2.90	164	$x + 1, {}^1/_2 + y - 1, z + 1$
N_{27}*	O_{18}	2.82	166	$x + 1, {}^1/_2 + y - 1, z + 1$
N_{13}	O_{21}*	2.76	121	x, y, z
N_{13}	O_{w1}*	2.89	-	$x + 1, y, z$
N_{13}	O_{w2}*	2.82	-	$x + 1, {}^1/_2 + y - 1, z + 1$
N_{23}*	O_{11}	2.58	115	$x, {}^1/_2 + y - 1, z + 1$
N_{23}	O_{12}	2.85	104	x, y, z
N_{23}	O_{w3}*	2.59	-	x, y, z
O_{w1}*	O_{21}	2.76	142	$x, {}^1/_2 + y, z + 1$
O_{w1}*	O_{22}	2.69	120	$x + 1, y, z$
O_{w2}*	O_{22}	2.68	132	x, y, z
O_{w3}*	O_{11}	2.85	121	x, y, z
O_{w3}*	O_{w1}	2.84	-	x, y, z

[a] The symmetry operation refers to the "starred" atoms.

the atoms in the rest of the molecule.

The L-aspartyl residue is very similar in conformation in both of the diastereomers. The pertinent torsion angles differ on the average by less than 10°. The rest of the molecules, containing a chiral carbon atom of opposite configuration in the L,*R* and L,*S* diastereomers (C_{16} and C_{26}, respectively), have torsion angles with opposite signs, but their absolute values do not differ by more than 10° if the thermally disordered tetramethylcyclopentanyl group is not considered. The C^{α}–C^{β} bond of the aspartyl residue (C_{11}–C_{12} and C_{21}–C_{22} in L,*R* and L,*S*, respectively) is almost coplanar with the side-chain carboxylate group: the x_1 and x_2 have values close to 0 and 180°. The terminal amino group of the aspartyl residue lies in the plane of the amide group linking the aspartyl residue with the N′-substituted diaminoethane moiety: the torsion angles around the C_{13}–C_{14} bond (L,*R* isomer) and C_{23}–C_{24} bond (L,*S* isomer) are 172.0° and 166.4°, respectively.

The terminal amino group and side-chain carboxylate of the aspartyl residue are in the ionic form so that this portion of the molecule should be considered as a zwitterion. In both diastereomers the nitrogen atom and C–O atoms of the carboxylate are separated by short distances, (L,*R* isomer, 3.2 and 3.1 Å for N_{13}···C_{11} and N_{13}···O_{12}, respectively; L,*S* isomer, 3.1 and 3.1 Å for N_{23}···C_{21} and N_{23}···O_{21}, respectively).

Both of the amide hydrogens are antiplanar to their vicinal carboxyl oxygens as well as to the hydrogen of the chiral C_{16} or C_{26} carbon atoms. This leads in both diastereomers to a conformation where both amide hydrogens are directed toward the same side of the molecule. Actually the plane of the two amide groups lies perpendicular to the rest of the molecule which is rather flat with the cyclopentanyl and the carboxylate group almost coplanar with only the methyl groups and the protonated N-terminal amino group projecting out of the plane.

The conformation adopted allows for the formation of intermolecular hydrogen bonds between the amide of one diastereomer and carbonyl of the other diastereomer in the unit cell (along the *a* direction). The molecular packing is shown in Figure 2. Both diastereomers are connected by hydrogen bonds between their amide moieties forming molecular ribbons along a noncrystallographic pseudoglide plane. The distances between the atoms involved in the hydrogen bonds are in good agreement with literature values (3.05, 2.83, 2.90, and 2.82 Å for N_{15}···O_{24}, N_{17}···O_{28}, N_{25}···O_{14}, and N_{27}···O_{18}, respectively). The diastereomeric pair are then packed one on top of the other in a ribbon-like structure in a direction parallel to the (*ab*) plane of the unit cell. In the *c* direction, these ribbons pack with each other by means of hydrophobic interactions (the tetramethyl moiety) and hydrophilic interactions (zwitterion of the aspartyl group and the three water molecules). In the resulting hydrogen-bonding scheme, each protonated amino group forms three hydrogen bonds with either the oxygen atoms of the carboxylate group or the water molecules: N_{13} forms H bonds with O_{21}, O_{w1}, and O_{w2} with distances of 2.76, 2.89, and 2.82 Å, respectively, while N_{23} forms H bonds with O_{11}, O_{12}, and O_{w3} with distances of 2.58, 2.85, and 2.58 Å, respectively. The O_{w1} water molecule is hydrogen bonded to two donors and two acceptors in a tetrahedral array. The O_{w2} water molecule is involved in only two hydrogen bonds, once as a donor and once as an acceptor. The O_{w3} water forms three hydrogen bonds, twice as a donor and once as an acceptor. The geometry of these bonds is in general agreement with expected values. Finally it is worth noting that both of the two carboxylate oxygens of the L,*S* molecule are acceptors in two hydrogen bonds, while for the L,*R* molecule, O_{11} is the acceptor of two hydrogen bonds and O_{12} the acceptor of one hydrogen bond.

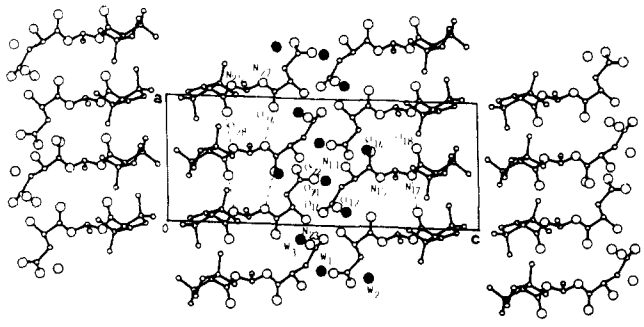

Figure 2. Molecular-packing diagram for the crystal of *N*-L-aspartyl-*N*′-[(2,2,5,5-tetramethylcyclopentanyl)carbonyl]-(*R*)-1,1-diaminoethane (L,*R*) and *N*-(L-aspartyl)-*N*′-[(2,2,5,5-tetramethylcyclopentanyl)-carbonyl]-(*S*)-1,1-diaminoethane (L,*S*). The unit cell is enclosed in the rectangle shown. Water molecules are indicated as filled circles. Intermolecular hydrogen bonds of the N—H···O=C type are shown as dashed lines. The N, O, and W atoms involved in hydrogen bonding are appropriately labeled.

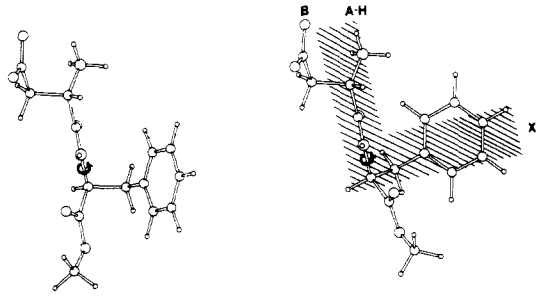

Figure 3. X-ray structure of an isolated aspartame molecule from the Kim X-ray structure and with the rotation about the ϕ torsion illustrating the ease of obtaining a coplanar "L-shape" consistent with our model for sweet taste.[3] The terms A-H, B, and X refer to hydrogen-bond donating group, hydrogen-bond accepting group, and a hydrophobic-dispersive group, respectively. These terms were originally developed by Shallenberger and Acree[4] and extended by Kier.[5]

The diastereomeric pair, as shown in Figure 1, can be described topologically as having an "L shape" (L,*R* isomer) and a backward "L shape" (L,*S* isomer). The structure found for the L,*R* diastereomer has many similar features to that reported for the solid-state structure of aspartame, L-aspartyl-L-phenylalanine methyl ester (see Figure 3).[3] The reported structure of aspartame has the same overall topology, the "L shape" with a 90° angle at the second chiral center, despite differences in the packing of the molecules within the crystal. In the crystal of aspartame, the packing is dominated by the stacking of the aromatic rings which forces this part of the molecule out of the plane of the rest of the structure. In the diastereomers studied here, the saturated tetramethylcyclopentanyl groups have lower hydrophobic interactions and greater steric hindrance than the phenylalanine aromatic rings which lead to a coplanarity of the cyclopentanyl rings with the zwitterionic L-aspartyl groups. It should be noted that a rotation of approximately 40° about the ϕ torsion of the isolated aspartame molecule from the X-ray structure leads to a coplanar structure fully consistent with our proposed "L shape".

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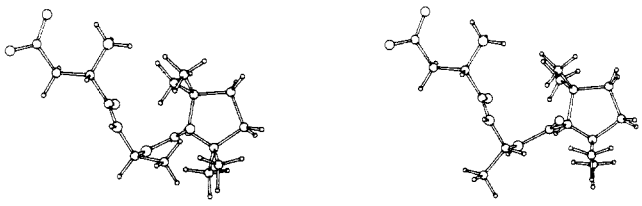

A B

Figure 4. The low-energy structures of the L,*R* (A) and L,*S* (B) isomers as formulated by NMR studies and computer simulations.[1] There is close agreement between these structures and those from X-ray shown in Figure 1.

Table IV. Backbone Torsion Angles from X-ray Crystallographic Analysis and Conformation Studies[a]

torsion angle	crystal structure		structure in solution	
	L,*R*	L,*S*	L,*R*	L,*S*
ψ	172.0 (5)	166.4 (7)	118	123
ω	-175.4 (5)	177.5 (6)	179	180
ϕ	104.4 (5)	-99.7 (6)	8	21
ϕ'	-97.3 (6)	104.8 (6)	88	81
ω	166.8 (5)	-169.4 (5)	179	176
ψ'	-100.4 (6)	92.8 (6)	116	131

[a] Values in degrees. The estimated standard deviation of the least significant figure is given in parenthesis for the torsions of the X-ray structure.

The conformations of the L,*R* and L,*S* isomers determined from NMR and computer simulations are shown in Figure 4. A comparison of the torsions of the isomers in solution and in the solid state is given in Table IV. The differences observed in the torsions arise from the packing forces present within the crystal. A comparison of the isomers in Figures 1 and 4 indicates a difference in the orientation of the amide NH's; an anti array in solution and a syn array in the solid state. In the crystal structure the ϕ and ϕ' torsions arise from the complementarity of structures within the unit cell. In solution without the formation of the intermolecular hydrogen-bonding pattern this complementarity of conformations is not retained and the ϕ and ϕ' torsions are very similar for the two diastereomers.

Despite these minor differences in the conformations found in solution and solid state, largely derived from forces within the crystal, the overall topologies of the isomers are quite similar. The L,*R* diastereomer adopts the "L shape" both in the crystal structure and in solution. The "reverse L" found for the L,*S* diastereomer in the crystal can be converted to the "L shape" simply by a 180° rotation about ϕ (Figure 1) which accounts for the preferred structure in solution.

The results found from the three techniques used in the conformational analysis of the two diastereomers, X-ray crystallography, NMR, and computer simulations, provide strong support for the value of the unified approach employed in the study of structure–taste relationships. The solid-state structures reported here only require facile rotations about one or two of the backbone torsions to obtain the structures found in solution which explains the fact that both diastereomers are sweet.

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Supplementary Material Available: Tables of positional parameters and their estimated standard deviations, refined displacement parameter expression, general displacement parameter expressions, root-mean-square amplitudes of thermal vibrations, bond distances and angles and torsion angles (12 pages); listing of observed and calculated structure factors (17 pages). Ordering information is given on any current masthead page.

The Structure of Cyclopropylcarbinyl Cations: The Crystal Structures of Protonated Cyclopropyl Ketones[1]

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Abstract: The structures of 1-cyclopropyl-1-hydroxyethylium hexafluoroantimonate, **9**, 1-(1′-methylcyclopropyl)-1-hydroxyethylium hexafluoroantimonate, **10**, and 2-hydroxybicyclo[4.1.0]heptan-2-ylium hexachloroantimonate, **11**, have been determined by single-crystal X-ray diffraction methods. The structures of these cations show major differences in their bond distances as compared to those of the neutral cyclopropyl ketones with the distal bonds in the cyclopropyl ring being shortened, the vicinal bonds lengthened, and the C(=O)—C(apex) bonds shortened. The cations adopt a conformation which is either bisected (**9**) or close to this (**10**, **11**). The bond distances and conformation of these ions are fully consistent with those expected for a bisected cyclopropylcarbinyl cation. Comparison of the structures of these cations with those of other protonated cyclopropyl ketones reveals systematic changes in bond distances that can be related to the degree of charge delocalization into the cyclopropyl ring. Details of the structures of these cations and their crystal packing are discussed.

The cyclopropylcarbinyl cation is one of a series of closely related isomeric $C_4H_7^+$ cations.[2] Entry into this series can be achieved by ionization of cyclopropylcarbinyl, cyclobutyl, or homoallyl derivatives. In the parent system the product distributions arising from ionization of each of these different materials are remarkably similar suggesting the existence of common intermediates.

A long standing and continuing question is that pertaining to the structure of the $C_4H_7^+$ cation(s). This has been investigated by a large variety of methods including isotopic tracer experiments,[3] solvolytic studies,[4] detailed NMR studies on solutions of

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(2) For reviews, see: Tidwell, T. *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley-Interscience: New York, 1987; Chapter 10. Friedrich, E. C. *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley-Interscience: New York, 1987; Chapter 11. Brown, H. C. (with comments by Schleyer, P. v. R.) *The Nonclassical Ion Problem*; Plenum: New York, 1977; Chapter 5. Richey, G. *Carbonium Ions* **1972**, *III*, 1201–1294. Wiberg, K. B.; Hess, B. A.; Ashe, A. J. *Carbonium Ions* **1972**, *3*, 1295–1345. Bartlett, P. D. *Nonclassical Ions*; W. A. Benjamin Inc.: New York, 1965.

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