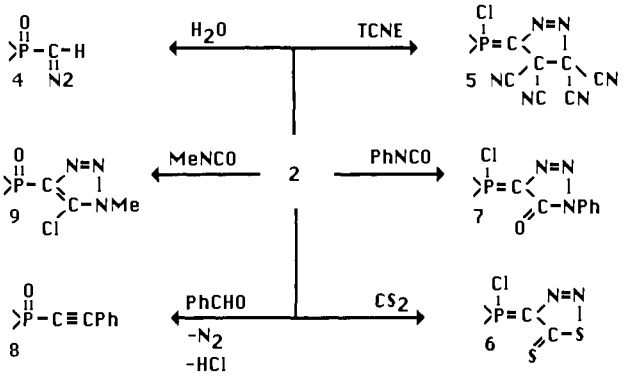
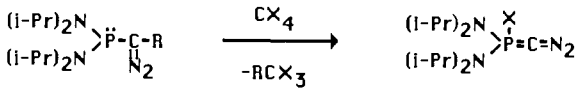
Scheme I



allows the synthesis of the *P*-bromo analogue **3**. Note that oxidative ylidation of methylphosphines is well documented.[7]

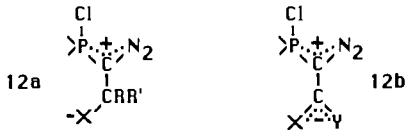


1a : R = H — **2** : X = Cl

1b : R = SiMe3 — **3** : X = Br

Compounds **2** and **3** are water-sensitive, red oily materials. They are stable in solution for several weeks but slowly decompose in the absence of solvent. The infrared (2035 cm^{-1} (2 and 3)), ^{13}C NMR (26.1 ppm, $^1J(PC)$ = 47 Hz (**2**)), and ^{31}P NMR spectra (+31 ppm (**2**), +15 ppm (**3**)) strongly support the proposed structure.[8]

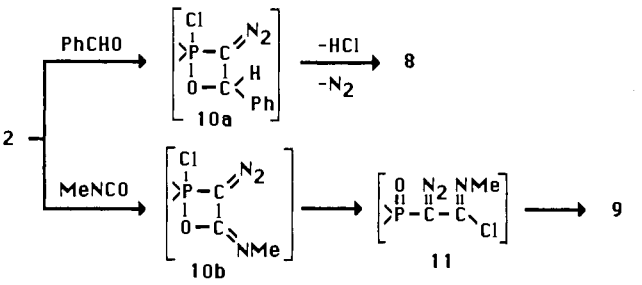
As expected, diazomethylenephosphoranes appear to be extremely versatile reagents as illustrated in Scheme I. Hydrolysis on silica gel leads to (diazomethyl)phosphine oxide **4**,[8] probably by nucleophilic substitution of the halogen atom followed by a classical 1,3 hydrogen shift. Tetracyanoethylene, carbon disulfide, and phenyl isocyanate afford derivatives **5**, **6**, and **7**,[8] respectively, which are the [2 + 3] adducts on the diazo moiety. We believe that benzaldehyde and methyl isocyanate react via a [2 + 2] cycloaddition on the phosphorus ylide center leading to transient oxaphosphetanes **10a,b** (Scheme II). Then, as is usual in the case of *P*-halogenophosphorus ylides, **10a,b** do not undergo a P–C bond cleavage but rearrange either with HCl elmination,[7f,e] leading to **8**, or via a 1,3 halogen shift,[7d,f] leading to α-diazoimine **11**, which subsequently[9] affords **9**[8] (Scheme II). The nucleophilicity of the ylidic carbon is certainly the driving force for all these reactions, inducing the primary formation of zwitterionic intermediates **12a** (or **12b**).[5] Then, depending on the affinity of X (or X and Y)



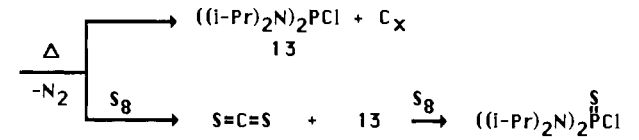
toward nitrogen and phosphorus, a 1,5 cyclization involving the diazo group, or alternatively a 1,4 ring closure involving the phosphorus ylide, occurs. This mechanistic hypothesis is strongly supported by the difference of reactivity observed between phenyl and methyl isocyanate.

All the reactions described in Scheme I occur in quantitative yield, demonstrating the potential synthetic interest of this new type of phosphacumulene ylide. Moreover, derivative **2** displays an intriguing thermal behavior. Attempted distillation under vacuum leads to the corresponding chlorophosphine **13** along with

Scheme II



Scheme III



carbon. In the presence of sulfur, an 88% yield of carbon disulfide is obtained, suggesting the transient formation of a diazocarbene ($:C{=}N_2$) or a naked carbon atom (Scheme III). Trapping of these small highly unsaturated species is under active investigation.

Acknowledgment. We thank the CNRS (GRECO basses coordinences) for support of this research.

Supplementary Material Available: Mass spectral, IR, and NMR (^1H, ^{13}C, ^{31}P) data for all new compounds (2 pages). Ordering information is given on any current masthead page.

A Model for the Sweet Taste of Stereoisomeric Retro-Inverso and Dipeptide Amides

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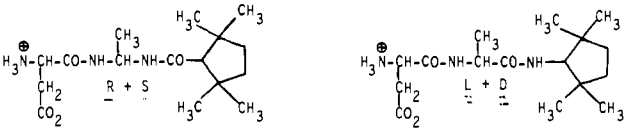
We have recently reported the synthesis of several *N*-(L-aspartyl)-1,1-diaminoalkanes, a class of sweeteners whose structure is based on a "retro-inverso" peptide modification.[1] Here we report the results from the conformational analysis, employing ^1H NMR spectroscopy and energy minimizations, of the L- and D-alanylamides[2] and the corresponding retro-inverso analogues incorporating a tetramethylcyclopentanyl group, *N*-(L-aspartyl)-*N'*-[(2,2,5,5-tetramethylcyclopentanyl)carbonyl]-(*R* or *S*)-1,1-diaminoethane (A) and L-aspartyl-(L or D)-alanyl-2,2,5,5-tetramethylcyclopentanylamide (B).



These four stereoisomeric compounds present a unique opportunity to study structure–taste relationships. Small changes in the overall topology affect the taste of these analogues (the L,L amide is bitter

(7) For examples, see: (a) Appel, R.; Waid, K. *Angew. Chem.* **1979**, *18*, 169. (b) Appel, R.; Peters, J.; Schmitz, R. *Z. Anorg. Allg. Chem.* **1981**, *475*, 18. (c) Kolodiaznhyi, O. I. *Zh. Obshch. Khim.* **1977**, *47*, 956. (d) Kolodiaznhyi, O. I.; Kukhar, V. P. *Phosphorus Sulfur* **1983**, *18*, 191. (e) Kolodiaznhyi, O. I. *Tetrahedron Lett.* **1980**, *21*, 3983. (f) Kolodiaznhyi, O. I. *Tetrahedron Lett.* **1985**, *26*, 439.

(8) Mass spectral, IR, and NMR data for each new compound are given in the supplementary material.

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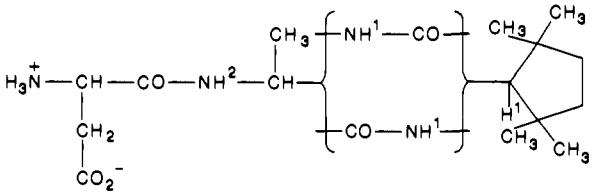
Table I. NMR Parameters[a] of Stereoisomeric Retro-Inverso and Dipeptide Amides



	dipeptide amides		retro-inverso amides	
	L,D	L,L	L,*R*	L,*S*
$J(NH^1\text{-}H^1)$, Hz	10.3	10.2		
$J(NH^1\text{-}AlaH_\alpha)$, Hz			7.6	7.2
$J(NH^2\text{-}AlaH_\alpha)$, Hz	<1	<1	<1	<1
NOE[b] $NH^1\text{-}H^1$, %			9.0	7.5
NOE $NH^2\text{-}AspH_\alpha$, %	8.4	absent	8.2	1.2
$\Delta\delta/\Delta T$[c] NH^1, ppb	5.5	4.9	5.9	7.5
$\Delta\delta/\Delta T$ NH^2, ppb	8.9	7.3	7.0	10.6

[a] Spectra were obtained as 2 mg/mL solutions in Me_2SO by using a home-built 360-MHz instrument. [b] NOE values were obtained from 1-D difference spectra. [c] Temperature coefficients were obtained from a best-fit plot of chemical shift values over the range 20–70 °C.

while the L,D amide and the two retro-inverso analogues are many hundreds of times sweeter than sucrose). In addition, the bulky acyl group greatly decreases the conformational mobility, allowing for an extensive conformational analysis by NMR. From these conformational results the differing tastes of the analogues can be explained.

With the assumptions of a trans peptide bond and a nearly planar zwitterionic ring for the aspartyl moiety, the structure of the compounds can be determined from the NMR data. The coupling constants, nuclear Overhauser enhancement (NOE) values, and temperature coefficients used in defining the conformations of the four molecules are presented in Table I.

By use of a Karplus-type relationship,[3] the small $NH^2\text{-}AlaH_\alpha$ coupling constant results in a dihedral angle close to 90°. The amides have a large coupling constant, 10 Hz, between NH^1 and H^1 of the tetramethylcyclopentanyl ring, evidence for a trans (180° dihedral angle) orientation for these two hydrogens, while the NOE observed between NH^1 and H^1 of the tetramethylcyclopentanyl ring of the retro-inverso analogues is a strong indication that these two hydrogens are oriented in a cis arrangment (dihedral angle close to 0°). The largest difference between the four analogues is in the ϕ and ψ torsional angles of the aspartyl moiety. This difference is observed in the measured NOE values between NH^2 and the H_α of the aspartyl residue. Small, but reproducible, NOE values are measured for the L,D amide analogue and retro-inverso analogues, but none can be measured for the L,L amide analogue. The possibility of forming stable six-membered rings through hydrogen bonding can be eliminated because of the high temperature coefficients of the amide NH's, which indicate exposure to the solvent.[4]

The flexible geometry minimum energy calculations for these compounds result in several conformational minima for each compound.[5] Disregarding any minima with an energy 5 kcal/mol greater than the lowest energy found, only one minimum energy conformation can be matched with the NMR data for each of the analogues. These are shown in Figure 1.

The constrained nature of these molecules allows us to develop a model to explain their sweet and bitter tastes. From Figure 1, it can be seen that the three sweet analogues, the two retro-inverso isomers and the L,D amide, all have very similar conformations while the bitter tasting L,L amide is strikingly different. The major

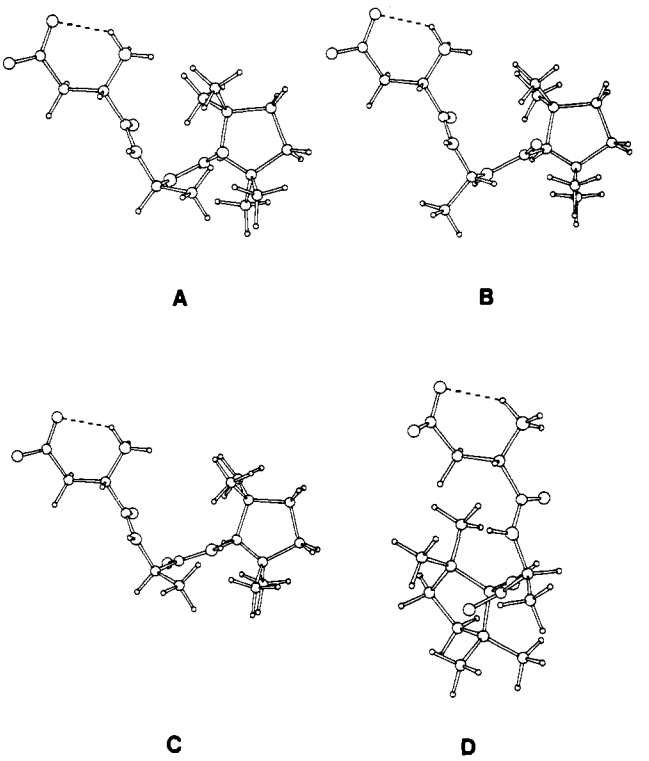


Figure 1. Preferred minimum energy conformations of (A) *N*-(L-aspartyl)-*N'*-[(2,2,5,5-tetramethylcyclopentanyl)carbonyl]-(*R*)-1,1-diaminoethane (L,*R* retro-inverso analogue), (B) *N*-(L-aspartyl)-*N'*-[(2,2,5,5-tetramethylcyclopentanyl)carbonyl]-(*S*)-1,1-diaminoethane (L,*S* retro-inverso analogue), (C) L-aspartyl-D-alanyl-2,2,5,5-tetramethylcyclopentanylamide (L,D amide), and (D) L-aspartyl-L-alanyl-2,2,5,5-tetramethylcyclopentanylamide (L,L amide).

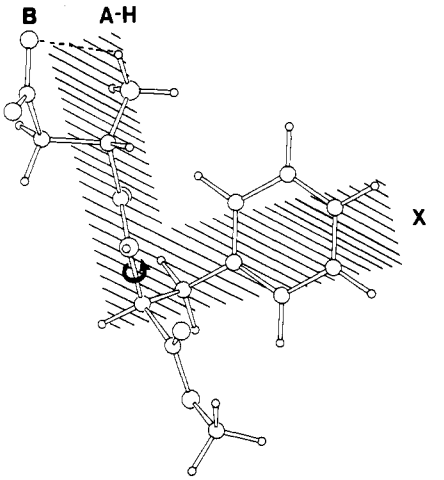


Figure 2. The model for the sweet taste with aspartame superimposed. The ϕ bond, shown by the arrow, has been rotated 40° from the X-ray diffraction structure.[6] In addition, the hydrogen atoms have been added, with standard bond lengths and angles.[5] The AH–B and X groups of the molecule are illustrated according to the Schallenberger–Kier suggestions.[11,12]

difference is the orientation of the tetramethylcyclopentanyl ring relative to the plane formed from the zwitterionic group of the aspartyl moiety. In the sweet compounds the two rings are essentially coplanar and are almost 90° from each other. This leads to a molecule with a small z-component. In the bitter L,L amide analogue the rings are almost aligned (nearly 0° from each other), but the tetramethylcyclopentanyl ring is out of the plane with respect to the aspartyl zwitterionic ring by more than 60°. The analogue thus has a large z-component.

The conformations of the sweet analogues found here are very similar to the structure reported for aspartame from X-ray crystallographic studies.[6] In that study the phenyl ring of as-

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(5) The minimizations were carried out by employing the valence force field program developed by Hagler and co-workers; see: Hagler, A. T.; Dauber, P.; Lifson, S. *J. Am. Chem. Soc.* **1979**, *101*, 5131–5141.

partame is close to 90° from the zwitterionic ring of the aspartic acid though the two rings are not coplanar as we find for the sweet compounds reported here. This slight twisting of the phenyl ring could be due to the packing forces within the crystal structure. The flexibility of aspartame in solution would easily allow for rotation about the ϕ bond to a conformation in which the rings are coplanar. Figure 2 shows our model with this structure of aspartame superimposed.

We are presently carrying out X-ray diffraction studies of the four analogues. The structure of the two retro-inverso analogues which cocrystallize has been solved and will be reported elsewhere.[7] The crystal structures have molecular topologies quite similar to those shown in Figure 1 for the retro-inverso analogues. There are slight conformational differences that can be obtained by rotations about ϕ and ϕ'.

In summary, low-energy conformations of the four constrained stereoisomeric analogues were chosen from several different minima generated from minimum energy calculations on the basis of agreement with NMR data. By utilizing these conformations we are able to generate a model to explain the differing tastes of the analogues. Our model, though similar to those proposed by Temussi[8,9] and van der Heijden,[10] employs a different orientation of the AH-B and X groups.[11,12] We are therefore able to correlate the structures of the stereoisomeric compounds with taste. We are now examining results from computer simulations, X-ray crystallographic structures, and NMR studies of a wide variety of amino acid- and peptide-based tastants to establish the generality of our model and to develop a model for the bitter taste.

Acknowledgment. We acknowledge the support of the National Institute of Dental Research (DE-05476). One of us (D.F.M.) would like to acknowledge a fellowship from the Upjohn Corp.

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Multidentate Lewis Acids. Complex of a Macrocyclic Tetradentate Organomercuric Perfluoroglutarate†

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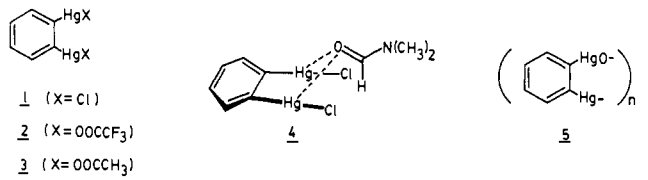
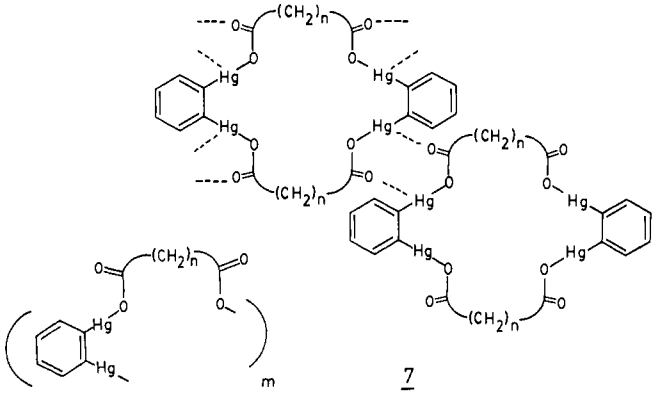
Well-designed bidentate Lewis acids can recognize and bind simple anions and basic sites in organic molecules.[1,2] For example, 1,2-phenylenedichlorodimercury (**1**) forms a 2:1 complex with chloride in which the added chloride occupies an electrophilic cavity created by four atoms of mercury.[1b,d] In addition, structure **4** shows how the mercury atoms of dichloride **1** can cooperate to bind dimethylformamide.[1a] Similar complexation of thiocarbonyl compounds by bis(trifluoroacetate) **2** leads to useful chemical



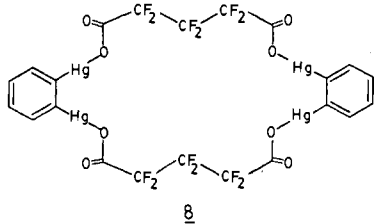
activation of the carbon-sulfur double bond.[1c] The unusual coordination chemistry of simple bidentate Lewis acids like compounds **1** and **2** made us eager to study complex, cyclic Lewis acids containing a larger number of well-oriented electrophilic sites.[3] This communication describes the first synthesis and structural characterization of a complex of a macrocyclic multidentate Lewis acid.

Treatment of dichloride **1** with aqueous NaOH produces (μ-1,2-phenylene-μ-oxo)dimercury (**5**), a polymeric oxide that can be converted into carboxylates like bis(trifluoroacetate) **2** and diacetate **3** by treatment with 2 equiv of the appropriate carboxylic acid.[1c] We therefore hoped that similar reactions with α,ω-di-



carboxylic acids would yield macrocycles containing 1,2-phenylenedimercury units linked by dicarboxylate bridges. Treatment of suspensions of oxide **5** in THF with dilute solutions (0.007 M) of a wide variety of dicarboxylic acids produced a series of dicarboxylates that showed low crystallinity and negligible solubility in THF, CH_3CN, and Me_2SO. Although these intractable materials could not be characterized in detail, we believe that they are linear polymers **6** or polymeric aggregates of multidentate macrocyclic oligomers represented arbitrarily by the cyclic dimers of structure **7**. The large number of potential intermolecular carboxylate bridges in the aggregates would account for their extremely low solubility, which is characteristic even of simple bidentate carboxylates like diacetate **3**.

Since bis(trifluoroacetate) **2** is significantly more soluble and more Lewis acidic than diacetate **3**, we treated oxide **5** with an equimolar amount of perfluorosuccinic acid. Unfortunately, the extremely low solubility of the final product in THF, CH_3CN, and Me_2SO suggested that it was a linear polymer. In contrast, the reaction of oxide **5** in THF with an equimolar amount of perfluoroglutaric acid produced a crystalline THF complex of tetradentate macrocycle **8** in 81% yield.[4]



† This paper is dedicated to Professor Henry G. Kuivila on the occasion of his 70th birthday.

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