Why only four primary gustatory sensory paths?[1]

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Abstract –Finalize after final edit of text

[Abstract Version One, includes protein comment xxx]
The long-sought fundamental *dimension* underlying the gustatory modality is described. The four sensory receptors of mammalian gustation (GR) are identified specifically as diols of phospholipids frequently found associated with the outer bilayer of sensory neuron lemma. Transduction is shown to involve a two-step process, a selective stereochemical bonding followed by an electrostatic measurement of the dipole potential of the gustaphore (GU). Each diol is able to participate in a dual antiparallel coordinate bond (DACB) relationship with a very large number of gustaphores in the first step. Further differentiation/identification of the individual gustaphores is based on their individual dipole potentials as measured in the second step. The perpendicular distance between the two antiparallel bonds, the d-value, is the critical parameter in the selection step of the sensory mechanism. (117 words)

This analysis undertook to marry the available empirical data on taste stimulants and the recent description of the sensory neurons according to the Electrolytic Theory of the Neuron.

The working hypothesis based on this analysis is that (1) no chemical reaction takes place in olfactory transduction, only coordinate bonding, (2) only four gustatory sensory channels exist in humans (and probably most animals) and these channels rely upon electrolytic sensory neurons. (3) No proteins are involved in the transduction process. (4) Step one in transduction is carried out between four phospholipids associated with the external lemma of the neurons and four specific sets of gustaphores. (5) Step 2 in transduction (in the oral cavity) generates a graded (analog) voltage at the pedicle of the appropriate sensory receptor axon. Perception of the final taste (developed in the CNS) involves the interpretation of up to four orthogonal voltages.

The inorganic hydrated sodium ion plays a unique role in terrestrial chemical sensing. It forms a DACB with one organic sensory receptor. It will be shown that the putative umami gustant consists of multiple more fundamental gustaphores. A discussion of the "super-sweet" gustaphores of Shallenberger and their relationship to the artificial sweeteners is left to a separate paper. (203 words)

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[Optional based on space available for paper] More precise labels are provided for the four gustatory channels. Calibrated versions of both a gustation dendrogram and a three-dimensional perceived taste space are supported. (25 words)

[Optional to above versions if Sec 4.5 remains in paper] Umami is shown to be a perception derived from the stimulation of two distinct gustatory receptor channels. It does not relate to a unique gustaphore. (25 words)

Descriptors: coordinate chemistry, gustaphores, gustatory receptors, taste modality, tastants

1 Introduction

The external chemical senses of the mammals can be divided into two distinct groups; those serving a hedonistic purpose and those serving a nocent purpose. The hedonistic chemical senses can be divided into three modalities based on their mission, the gustatory, the olfactory and the oskonatory (formal designation for the modality associated with the vomeronasal region of the nasal cavity).

All of the hedonistic chemical sensory channels, and their respective sensory receptors can be described using a single

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unidimensional parameter. This parameter employs the same dual antiparallel coordinate bond (DACB) structure that Shallenberger and colleagues developed in the 1970s to explain the gustatory properties of the sugars. It is defined as the perpendicular distance (the d-value) between the two hydrogen bonds of the above DACB in Angstrom.

The review of the literature suggested that the gustatory modality might employ as many as six (but most likely four) independent sensory channels whereas the olfactory modality might employ as many as 23-30 independent sensory channels. The literature also suggested at least one functional channel might be replicated in each of the modalities. The term independent as used here implies orthogonality between the individual channels. The olfactory modality will not be addressed further in this paper as a separate detailed analysis is in preparation.

Henning has provided a simple assertive description of the basic requirements of chemoreception[1]. As he notes, "Most of the existing theories on odor and taste satisfy only part of these criteria." Rossiter, working in applied olfaction, has taken a different philosophical path and asked five different questions[2]. The Rossiter questions appear to be the more important. However, they are critically dependent on the context in which they are asked. It is a goal of this paper to particularize these questions with respect to gustation and present substantive first order answers to all of them.

The ***goals*** of this analysis are to provide a detailed framework, and define the specific methods and mechanisms of receptor excitation in gustation. This work applied the Scientific Method as espoused by Marmarelis to the question of how the chemical sensory modalities of the mammals, and specifically the human, were organized and performed[3]. Marmarelis stresses a two-part Scientific Method consisting of an inductive activity, allowing the available data to speak to the investigator, followed by a deductive activity where the investigator develops a working hypothesis that is capable of refutation (falsification) through subsequent experimentation.

Based on the long search for the physiological key to gustation, a very general *null* hypothesis was initially assumed. Up to six sensory channels and no specifics related to the transduction mechanism were assumed. The major elements of the *null* hypothesis were that (1) the facts known about the sensing of the sugars were relevant and (2), the previously discovered common form of the electrolytic mechanisms associated with the sensory neurons was retained. During the inductive activity, both the chemical theory of the neuron and the more recent and expansive electrolytic theory of the neuron were analyzed along with the relevant experimental literature.

The empirical data base of gustatory sensations and perceptions is large and well documented. It is this data that suggests gustatory stimulants are clustered in less than six main clusters. However, the database lacks any detailed description of a viable means of stimulant transduction and information extraction leading to the perception of taste within the central nervous system. The immense differences in perceived efficacy of gustaphores related to a specific sensory channel strongly suggest gustation involves a two-step transduction mechanism, selection followed by evaluation.

Recently, the Electrolytic Theory of the Neuron has shown that there is a common sensory neuron architecture within the neural system[4]. This commonality suggests gustatory transduction includes the ability of the sensory neurons to sense incremental changes in the electronic polarization of molecular structures, particularly when participating in coordinate bonding relationships with potential gustaphores. The chemical theory does not conceptualize any ability to sense incremental changes in electrical potential of a stimulant during transduction.

Most early investigations into the chemistry of taste have focused on the ionization chemistry of various stimulants. Shallenberger and associates discussed the unique structural features of sugars that appeared to account for their sweetness during the 1967-82 period. They focused on a unique configuration involving what was variously called London bonding and hydrogen bonding during that period. They were focusing on the coordinate chemistry of the sugars based on hydrogen bonding and a small unique set of ligands that are defined as "orbitals."

> The orbitals of interest in gustation include (in order of importance) oxygen, nitrogen, any carbon double bond of the alkenes, the electrophilic cloud of the aromatics, sulfur and phosphorous.

This paper focuses on the coordinate chemistry of the common natural stimulants eliciting perceptions of sweet, acid, salty and bitter, the selection step. Each of these perceptions is associated with a specific coordinate chemical bond arrangement between the gustaphore (GU) of the stimulant and the matching sensory receptor (GR) of the biological system. It will delay until a later paper perceptions elicited by inorganic materials other than the sodium complex, $Na^{+}(H_2O)_6$ in dilute solution. It will also focus on the experimental data obtained from closed-nose investigations in order to avoid contamination of the gustatory perceptions by olfactory perceptions.

The stereochemistry associated with coordination chemistry requires detailed knowledge of the conformation of the requisite chemicals. Verbal and text-based discussions of gustation based on Haworth, Mills, zig-zag, Fischer projections, etc. can only be used where the underlying detailed conformation has already been described. The recent

computerization of molecular modeling, culminating in the Jmol representation sponsored by the American Chemical Society, and now led by the Royal Society of Chemistry, has led to great strides in describing the 3D structure of complex molecules[5]. These representations can be used to describe the molecular electrostatic potentials (MEP) of individual molecules. These MEP's are useful in predicting the intensity of gustaphore stimulation and resultant perceptions, that will be addressed in subsequent papers.

It is important to note, the coordinate chemistry of a molecule is uniquely separate from its ionization chemistry. In general, they exist simultaneously. The application of coordinate chemistry to the facility of gustation leads to a demonstrable explanation for the perception of "salty" elicited by an inorganic moiety.

2 Methodology (Reserved)

3 Results

The parsimonious approach to taste sensing based on the architecture and histology of the neural system, provides a detailed description of the mechanisms and constituents of the gustatory modality. The detailed description is the result of (1)expanding the approach explored in the 1960's by Shallenberger & Acree and their colleagues, (2) mining the broad range of psychophysical data related to the taste perceptions elicited by a wide range of tastants, (3) and applying the Electrolytic Theory of the Neuron to the task.

The approach demonstrates there are only four types of gustatory receptors (GR), each based on a specific phospholipid molecule with one of four non-protein carbohydrates head groups (the combination generally described as a phosphoglyceride). The resulting four phosphoglyceride were isolated over 40 years ago but their function was unknown. The phospholipid is an integral part of the type 4 lemma forming a specialized portion of the dendritic tissue of each sensory neuron. The non-protein carbohydrate acts as the receptor site exposed on the surface of the lemma. Each GR site is capable of binding to a wide range of gustaphores (GU) meeting the selection criteria for that site, with the more complex tastants containing multiple gustaphores. The glutamates are an example of tastants exhibiting multiple gustaphores, rather than an example of a distinct class of gustaphores.

The *working* hypothesis resulting from this analysis is somewhat narrowed from the *null* hypothesis stated earlier;
- there are four specific chemical structures that act as sensory neuron receptors,
- the detailed character of these receptors are more specific than previously reported,
- these receptors are susceptible to coordinate bonding with an appropriate gustaphore as part of a stereo-chemical selection process,

The four simplest gustaphores, GU's, in gustation are ligands identifiable as the acidophore (Lewis acid), the glucophore (sweet), the natrophore (salty), the picrophore (bitter). They stimulate only four sensory receptors, GR's, that are simple modifications of normal neural lemma. A vast range of tastants are found in nature. They all exhibit or emulate one or more of the simplest gustaphores. The stimulants associated with the putative umami channel are found to contain two or more of the above individual gustaphores. Thus, umami is a complex perceived taste, and does not involve a distinct sensory receptor channel.

All of the GR's associated with gustation are phospholipids (not proteins) commonly found associated with neurolemma. The cilia of the gustatory neurons are shown to exhibit a localized modification in the phospholipid of the bilayer of their outer lemma to facilitate gustatory sensing. The presence of such modified phospholipids was first documented in the literature during the 1960's without explanation as to their purpose.

The analysis associated with this paper suggests the actions of the inorganic (Lowry-Bronsted) acids and the majority of inorganic salts associated with astringency, are frequently associated with the nociceptor modality of the neural system and not the gustatory modality. Ultimately, the sensation of pain may be combined with that of taste in the ultimate perception.

No chemical reactions involving valence band electrons are involved in gustation; no residues are formed. Only temporary coordinate chemical bonds are involved. The binding process involves a dual antiparallel coordinate bond between the GR and a specific ligand (the functional-GU) associated with each gustaphore. The perpendicular distance between the two coordinate bonds (in 3D space) is the critical parameter in gustatory sensing. This distance determines the ability of the gustaphore to bind with a particular GR and its relative efficiency in stimulating the neural system. No requirement was uncovered in this study for an enzyme to aid binding, but the presence of such an enzyme supporting the process cannot be excluded.

To appreciate the binding process employed in cyclic molecules, it is necessary to expand the five potential molecular conformations shown in text books to include an *equatorial-trans-* and an *equatorial-cis-* conformation [xxx supplemental Figure S-1]. The designation glycophore, used since Shellenberger and colleagues featured it requires

further specification. Glycol, and various ligands based on it can exist in two forms. Glucophore is used here to define a *cis*– glycol and an *equat–trans*–glycol ligand, d–value = 2.6 Angstrom, that elicit a perception of sweetness. The alternate *trans*–glycol and the ligand, *axial–trans*–glycol, with a d–value ≈ 3.3 Angstrom elicit a perception of saltiness, and are identified as natrophores.

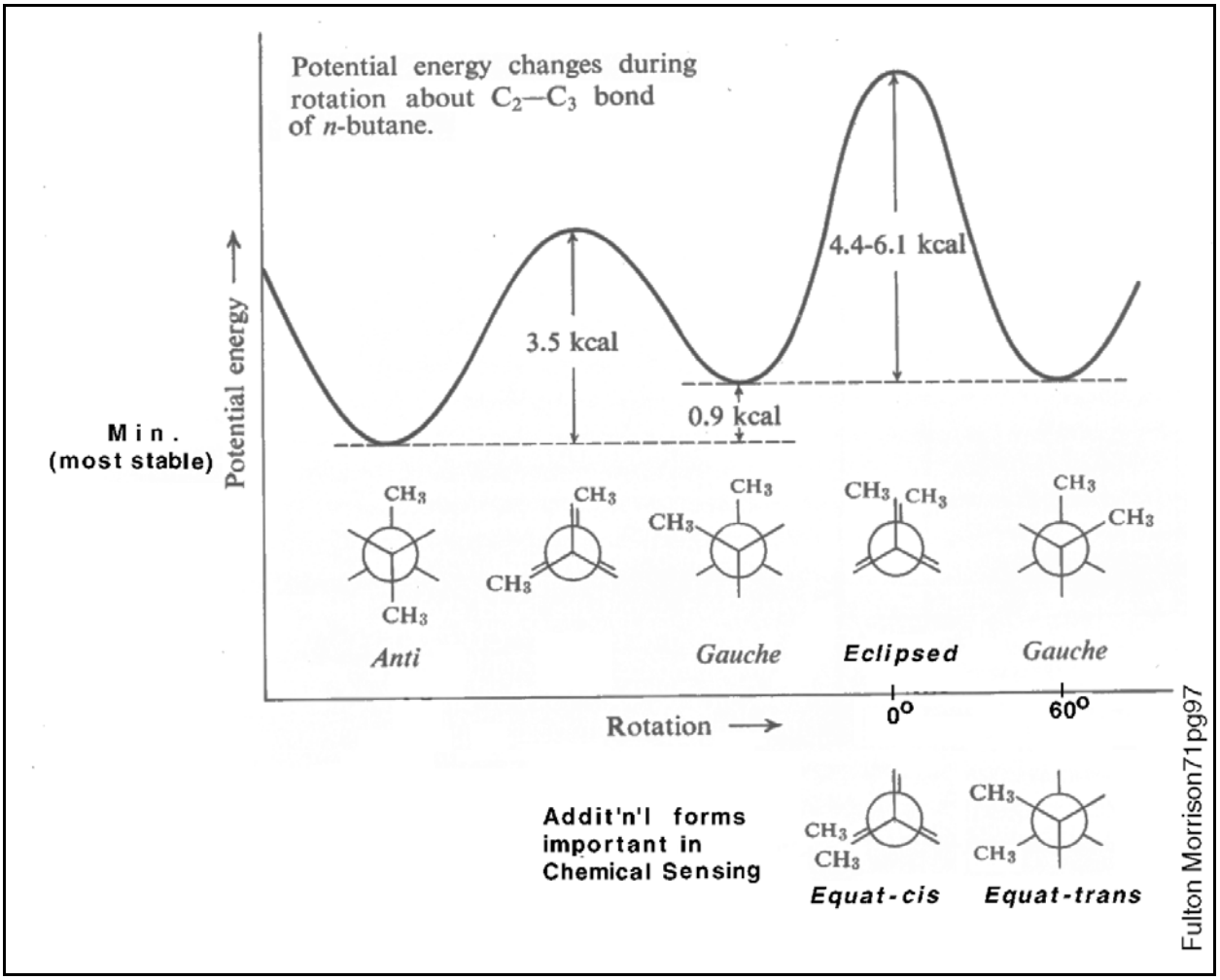


Figure S–1 Expanded set of Newman Representations required in discussing gustation. Top; conventional pedagogy based on *n*-butane. Bottom; additional forms. When used in cyclic molecules, the *Equatorial-cis*- conformation involves different distances between the methyl groups than does the *Eclipsed* conformation. The *Equatorial-trans*- conformation involves different distances between the methyl groups than the *Gauche* conformation. Expanded from Morrison & Boyd, 1971.

Figure 1 provides a useful conversion process if one is to transition from a behavioral to a more fundamental understanding of the gustatory modality (based on its neurology). The goal is to transition from a largely conceptual or semantic designation associated with a common perception or class of foods to a designation describing the chemical structures of sensory receptors and gustaphores eliciting a perception. As an example, the "acid" sensory channel does not sense a proton; it operates only in the Lewis acid sense in order to sense a carboxyl ligand. Thus, the expression H(ydrogen)–best is replaced by C(arboxyl)–Path.

Similarly, S–best, rather than suggesting sweet or sugar, is replaced by the G(lucol)–Path to address the fact that a very large number of nonsugars elicit a sweet, sugary perception. However, the simplest G–Path glucophere is an *equat-trans*-1,2 glycol (when embedded in a cyclic structure). The empirical term Q(uinine)–Best is replaced with the more precise P(icric)–Path since the simplest gustaphore exciting that path is present in a wide range of stimulants that are

frequently much simpler and totally unrelated to quinine. The umani sensation is the result of stimulating multiple sensory channels simultaneously, and does not involve a unique sensory process.

Historical or Behavioral Term	Simplest Neurological (Functional) Designation	Gustaphore (GU)	Gustatory receptor (GR)
H-Best (Bronsted Acid)	C–Path (Carboxyl)(Lewis acid)	Acidophore	PtdSer
S-Best (Sugar)	G–Path (1,2 *diequat-trans*–Glycol)	Glucophore	PtdGal
N-Best (NaCl)	N–Path (1,2 *diaxial-trans*–Glycol)	Natrophore	Ptd*muco*-Ins
Q-Best (bitter)	P–Path (Picric)(1,3 propanediol)	Picrophore	Ptd3'OagR'
U-Best (Umami)	Sum of N–, G– & C– Path signals	N/A	

Gustatory signal paths.ai

Figure 1. The transition from a behavioral to a neurological perspectives in gustation. All the gustaphores exhibit an AH,B molecular configuration and suitable stereographic configuration capable of forming a dual anti-parallel coordinate bond (a pair of hydrogen bonds) with a gustatory receptor. The N-path GR will bind with the fully hydrated sodium ion, and any other natrophore exhibiting a d-value ~3.3 Angstrom.

The term N-Best of behavioral investigations is replaced by the N-Path of the neurological system. The N-Path employs an organic molecule, phosphatidyl *muco*-inositol (PtdIns), to sense the hydrated sodium ion, rather than a more generalized "salt."

Figure 2 provides the first calibrated graph of the gustatory perception space. The vertical lines represent the nominal d-values of the sensory neuron receptors. The distributions about these vertical lines represent the probability that a given gustaphore can interact with the gustatory receptor (GR) associated with that d-value. Currently the widths of these distributions are not known. A subsequent paper will show this horizontal number line can be folded at each of the nominal d-values to form a three dimensional taste perception space.

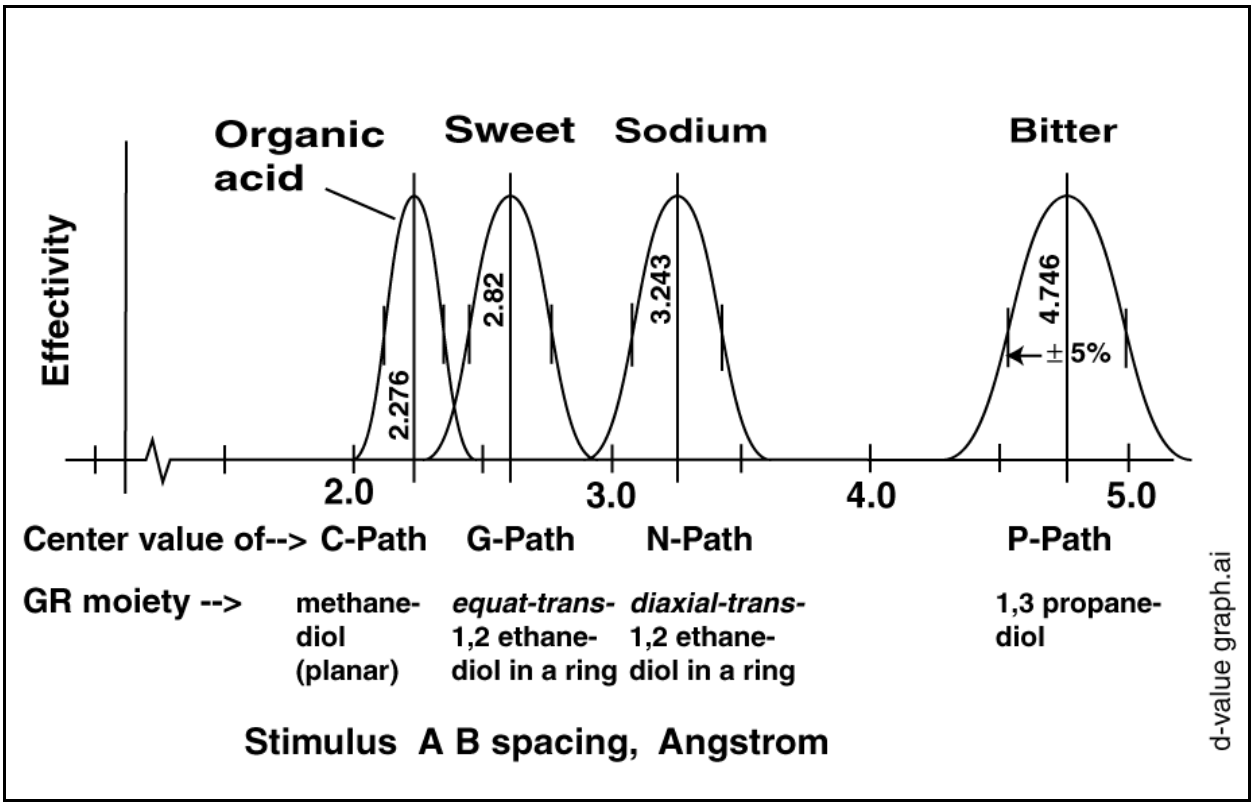


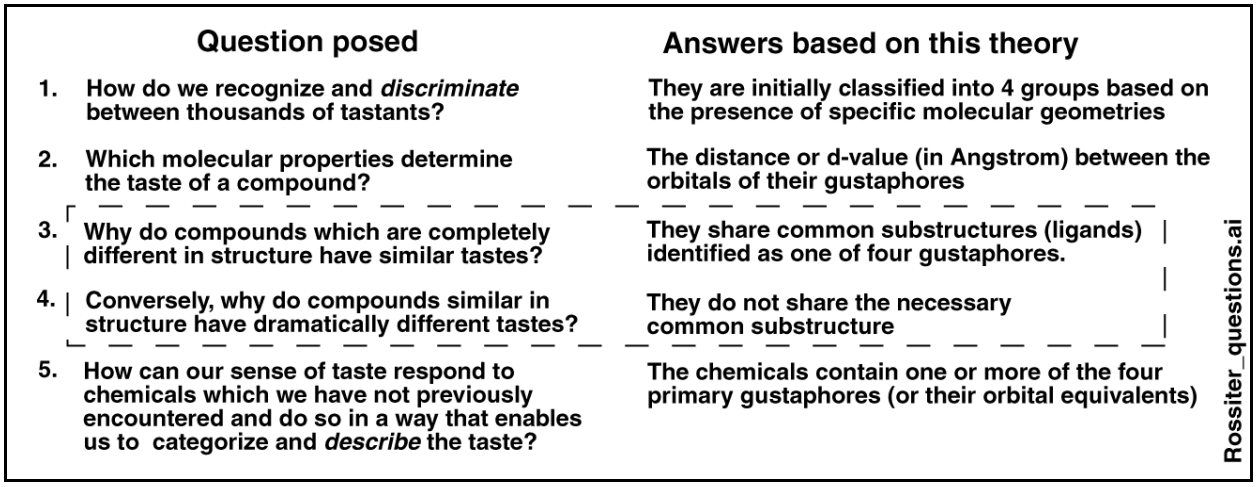
Figure 2. The one-dimensional effectivity graph of gustatory performance based only on the steric properties of the receptors and gustaphores. The term ring in the graph refers to a cyclic compound. Centroid values of each distribution are at nominals of 2.268, 2.82, 3.243 & 4.746 Angstrom.

The tastants and gustaphores defined in these contexts can be grouped into dendrograms (a.k.a. cladograms), and/or presented in a three-dimensional gustation space compatible with multi-dimensional scaling (MDS). An absolute scale is provided for both of these presentations for the first time. The scale greatly improves interpretability. The dendrograms are similar to those in the literature but omit the inorganic acids and the astringents, they are considered nocents in this hypothesis.

> It is hypothesized that the actions of hydrated hydrogen ions (inorganic acids) and various astringents (generally salts of the alkaline earth atoms) act on the nociceptor modality rather than the gustatory modality of the neural system.

In eliminating the hydrated hydrogen ion from the list of gustaphores, a new set of gustaphore class names is presented for consideration based on clearer functional roles. If the four sensory paths are recognized as independent within the neural system, they can be considered orthogonal in the mathematical sense. The above one-dimensional graph can be folded at the centroid values to form the corners of a three-dimensional gustation space.

The five questions of Rossiter as they relate to taste are answered succinctly in the following Table. The terms *describe* and *discriminate* are secondary after *recognize* and *categorize*. They will be addressed in a subsequent paper. The "global" structure of a molecule as typically developed in chemical texts has negligible impact on its taste. It is the distance in 3D space, or d-value, between specific orbitals that is important. Questions 3 and 4 were originally stated in the converse.



Many additional mechanisms can be described in detail (such as the super-sweet gustaphores) based on the approach documented here. However, they are outside the scope of this paper and are included in papers currently in preparation. The framework can also be expanded to describe the more complex olfactory environment and modality.

4 Discussion

The mechanism of gustatory transduction has long been an unsolved problem. The likelihood of four distinct perceived tastes, sweet, sour, salty & bitter have been proposes since ancient times and continue to be confirmed in modern times. Since about 1900, researchers, primarily in the Orient, have proposed a fifth gustaphore related to the perception labeled umami. This work will show that umami is actually a perception caused by the presence of multiple more fundamental gustaphores. Many, generally unsuccessful, efforts have been made to explain these perceived tastes based on the ionization chemistry (valence chemistry) of the stimulants or on their apparent structure. More recently Shallenberger and his colleagues have developed an approach based on the coordinate chemistry of the sugars[6,7]. This approach will be expanded beyond the sugars in this paper. Tancredi et al. began this expansion in 1979 into the bitter gustaphores but continued to consider the Fischer diagrams as relevant to their analyses rather than the more appropriate conformational representations[8]. They also focused on the putative stereochemical pocket required to select tastants and/or gustaphores. Such a pocket is not required for effective gustation according to the hypothesis of this work.

4.1 An extended nomenclature

The organic chemistry of the gustatory modality involves very complex chemical structures that are difficult to describe unequivocally using semantics and very difficult to illustrate using two dimensional drawings. Many different and frequently un-named, 2D representations have been used to highlight different aspects of the structural theory of 3D chemicals. Any reduced representation of a chemical (specifically the Fischer, Haworth and Newman representations) necessarily compromises the displayed attributes of that chemical. The actual distances and bond angles in 3D space associated with each overlay ligand are the critical feature. Both the angles and lengths vary with the character of the bonds involved. They also vary due to crowding in more complex molecules. Ultimately, the bond angles and lengths must correspond to those of the molecules when in solution and not their theoretical values when in the gaseous (or isolated) state.

The bond lengths and angles of interest are difficult to locate in the literature and many sources provide different values. For this work, the values given in the Jmol files of ChemSpider as interpreted by the Discovery Studio visualizer, vers. 3.5 are used exclusively.

Adopting a sufficiently precise description of a group of chemicals with common characteristics is a recurring problem in chemistry. The IUPAC/IUB and its predecessors have always had difficulty in adopting terminology sufficiently quickly to meet the needs of the research community. Reading the literature frequently requires recognizing the variability of the notation standards promulgated at a given time. Describing the hydroxyls associated with a cyclic carbohydrate compound as either *cis*- or *trans*- highlights the current problem. Shallenberger & Acree discussed this situation in the 1970's. A more explicit matrix of terms is required. The critical distance, the d-value, between the parallel bonds of the dual coordinate bond employed in gustatory transduction requires the *cis*- form be expanded to indicate whether the elements are present as *equatorial-cis*- or *equatorial-trans*-. Similarly, the *trans*- designation needs

to be expanded to accommodate *axial-trans-* and *axial-cis-*. The required nomenclature must also recognize the actual distance in 3D space between non-adjacent carbon atoms.

Gustation is best understood by considering all of the GR's to contain a ligand of the diol family, beginning with methanediol, sometimes described as a hydrogenated form of formic acid. The homologous aliphatic series becomes $C_nH_{2n}(OH)_2$; 1,1 methanediol, 1,2 ethanediol, 1,3 propanediol. The hydrogen associated with the second hydroxyl group of a diol is not generally required in the dual coordinate bond employed in transduction. When present in a cyclic moiety, the 1,2 ethanediol and 1,3 propanediol can be present in multiple conformations with significant differences in the distance between the oxygen atoms. The difference in conformation is significant. The 1,2 ethanediol in a ring structure is associated with the perception of sweetness when its hydroxyl groups are present in the *equat-trans-* conformation. It is associated with the perception of saltiness when they are present in the *axial-trans-* conformation. The critical structural feature is that the two oxygen atoms be separated by the correct distance, their d-value, in order to dual coordinate bond optimally with their respective gustaphores.

4.2 The character of the gustaphores (GU) of taste

As documented by Lim & Lawless, it is extremely important to differentiate between data collected with the nose open and the nose closed[9]. By merely opening the nose, the nominal corners of their gustatory perception space changed from salty, sweet and acid to bitter, sweet and acid. When discussing gustation, it is important that steps be taken to avoid the transfer of volatile molecules of the stimulant to the olfactory tract. Only the closed nose condition is addressed in this work.

Many investigators have attempted to use a dendrogram or phylogenetic-like tree to organize the stimulants in gustation. In general, these are unsatisfactory for three reasons. First, because they require or assume all of the stimulants contain only one gustaphore. In fact, many stimulants involve multiple gustaphores. Second, all of the stimulants must be relatable to the substructures of the tree. Rogers et al. have offered a limited tree focused on bitter taste relationships[10,11]. They noted that "Seventy-five of the 833 bitter molecules, 9%, contain none of the tree's identified substructures and therefore these "singletons" have no node membership in the tree. Third, these trees are based on behavioral observations, documenting perceptions, and do not address the actual mechanisms involved in gustaphore sensing. As a result, there are a series of hidden variables not addressed in their analyses based on Fischer projections.

4.2.1 Background

Rogers et al. relied heavily on data mining of primarily psychophysical experiments. They did not consider the actual conformation of their candidate molecules, the propensity of those molecules to form dual coordinate bonds with their unspecified receptors, or the distance between the potential dual bonds.

> Rodgers et al (2005) and Rodgers et al. (2006) have developed a conceptual model based on the deductive approach. They described their method as "an alternative approach to the characterization of bitterness, . . . Bitter molecules are classified according to whether they produce a bitter taste; . . . most known bitter molecules have not been associated with a specific receptor." The approach used a "naive Bayes classifier" and employed a highly reduced interpretation of chemical structures based on Fischer diagrams to create a phylogenetic–like tree (PGLT). Their selection of candidate molecules relied upon the visual identification of "maximal common substructures" (MCS). Many of the adopted MCS were not recognized structural groups but apparent groups based on their examination of the appropriate Fischer diagrams. In the case of sufficiently complex molecules, multiple MCS were identified (five in their example– hesperidin) without indicating how these MCS reacted with a receptor site.
>
> No consideration was given to;
> • the conformation of their candidate, or selected bitter, molecules
> • the coordinate chemistry of selected elements of their bitter molecules
> • the diagonal distances between the oxygen or other orbitals known to participate in gustatory stimulation
> • how these selected MCS interfaced with a putative receptor structure.
>
> The above listed parameters constitute hidden variables in their analysis. They discussed but did not present cluster data to support their phylogenetic tree. No MDS analyses were offered.

It is noted that hesperidin, and their simpler variant prurin, contain at least one identifiable ligand consistent with the analysis of this work. The pair of oxygens separated by three carbons in the *ortho*-fused heterocyclic ring offers the potential of a d-value of 4.746 Angstrom. Many of the bitter tastants (particularly the first three of Table 3) described in Rodgers et al. (2006) exhibit a 1,3 diol structure. Many of the molecules in their figures 2 and 3 include the ortho-fused diol structure. The *ortho-f*used heterocyclic structure, but not the location of the oxygen atoms, is also shared with

the much simpler coumarin. Coumarin is considered sweet at low concentrations and bitter at high concentrations. Behrens et al. (2004) have identified a simple *ortho*-fused homocyclic structure with two hydroxyl groups that is bitter and deserves further study.

Pfaffman et al. provided some early electro-physical gustatory information using squirrel monkeys[12]. They recorded action potentials from the chorda tympani, a branch of the VII facial nerve. They introduced the concept of labeled lines, that will be adopted here, with little detail. They did note, "Two-thirds of our sample of taste units fall readily into one of the four classic taste categories with a peak at one basic taste stimulus. 'Side bands' around such peaks produce a certain degree of multiple sensitivity. One-third of the responsive fibers, however, cannot be classified by a single 'best stimulus' but appear to have broad multiple sensitivity."

Akabas noted a major problem related to assuming a protein-based chemistry for gustation in 1993, "In the absence of biochemical information on the proteins involved in taste transduction, one must use information based on homology[13]." As recently as 2003, Moller continues to use caricatures in the absence of adequate knowledge of the putative protein chemistry of the sensory receptors to support the chemical theory of the mechanism[14]. Recently Mattes has introduced data showing the gustatory modality of humans may also be sensitive to a series of free fatty acids[15]. His goal was to establish a relationship between these fatty acids and a variety of putative G-proteins, identified from genetic analyses, acting as sensory receptors. He used a very small sample size and noted the possibility that his data reflected somatosensory, rather than gustatory sensitivity. His conclusions were quite guarded. It is noted that his free fatty-acid stimulants involved six or more carbons and were all Lewis acids. While not compatible with an H-best designation, they do meet the C–Path criteria. His Lewis acids were intrinsically insoluble in water and two had to be heated above their melting point to place in solution to any reasonable level.

4.2.2 Expanding the AH,B framework of Shallenberger

Shallenberger, in cooperation with Acree and with Kier[16] described the unique coordinate chemistry exhibited by the natural sugars using the notation AH,B where initially A = an oxygen atom of a hydroxyl group, H = a hydrogen atom of the same hydroxyl group, and B = an oxygen atom. Beets (1978, pg 188) suggested this concept could be extended to include all of the organic taste stimulants[17]. Later, it was shown the AH,B notation could apply to a broader range of situations. In general,

- AH = a moiety capable of sharing additional pairs of electrons while closely associated with hydrogen. The AH moiety may be OH, NH, NH_2 or even CH in halogenated compounds.
- B = a moiety capable of sharing additional pairs of electrons. The B moiety may be O, N, an unsaturated center, or even the π-bonding cloud of a cyclic compound. All of the potential A's and B's were defined as orbitals by shallenberger & Acree.

This notation was later expanded to AH,B,X to account for the properties associated with a variety of artificial sweetners, some of very great potency. In 2000, Eggers, Acree & Shallenberger provided a review of their work over a 30 year span[18].

The AH,B.X notation and subject matter will be addressed in a subsequent paper. The ***goal*** of this paper is to follow Beets and expand the AH,B concept of coordinate chemistry to account for the gustatory properties of all stimulants leading to the perception of the four qualities listed above.

Figure 3(top) shows the basic coordination chemistry Shallenberger originally proposed as the mechanism resulting in excitation of the "sweet" sensory neuron. At the minimum, AH represents a hydroxyl group and B represents the oxygen of a neighboring hydroxyl group. Shallenberger initially focused on the distance between B and H, of about 3 Angstrom, rather than the perpendicular distance between the two hydrogen bonds, of about 2.6 Angstrom (both values within ±7%). For the situation to be symmetrical, the direction of the two bonds need to be antiparallel. It will be the distance in three-dimensional space, or the d-value in Angstrom, between the two bonds that is of primary interest in a particular instance.

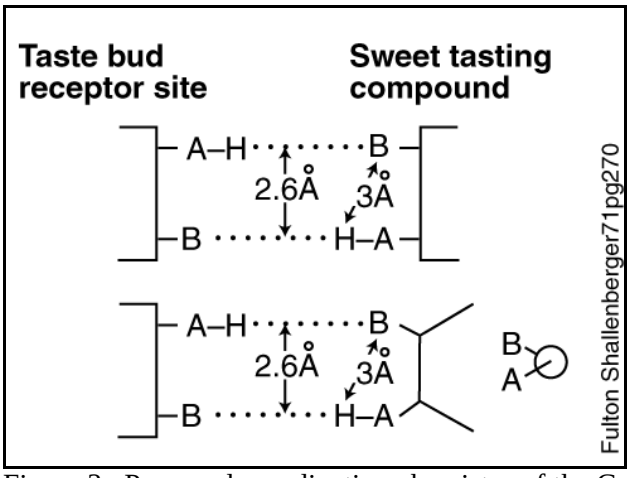


Figure 3. Proposed coordination chemistry of the G-Path sensory neurons clarifying the condition described by Shallenberger & Acree. Top; in the simplest case, all A's & B's are hydroxyl oxygen and H's are hydroxyl hydrogen. The original text did not differentiate between the distance between AH and B. Their later writings referred to the H,B distance as 3 Angstrom and the AH,B distance as 2.6 Angstrom. Both numerics are ±7%. Bottom; fundamental G-Path gustaphore shown as an *equatorial-trans-* form of glycol with angles appropriate to a cyclic compound. Modified from Shallenberger & Acree, 1971.

In relating their AH,B structure to the sugars, they noted the structure associated with the O-3 and O-4 oxygen atoms of a saccharide appeared in the vast majority of the sweeter sugars. This structure is best described as a 1-2 *equatorial trans*-glycol with bond angles as found in an aromatic ring (as shown at lower right). In the case of glucose, they showed that only OH-4 and OH-3 were the logical choice for a primary AH,B relationship. Using a galactose, they were able to further establish that OH-4 was AH and the only remaining possibility for B is O-3 (Shallenberger, 1982, pp 265-275). What they did not focus on were the number of carbon atoms in a cyclic ring separating the oxygen atoms.

The stereo-geometric complexity of the sugars is considerable and requires additional terminology to achieve the necessary precision in this discussion. The OH-3 and OH-4 ligands specified above were present as equatorial ligands relative to the notional plane of the aromatic molecule. These equatorial ligands were present in a *trans-* relationship to the intervening carbon-carbon bond. This configuration can be labeled *diequatorial-trans-* in comparison to an alternate configuration where the OH-3 and OH-4 ligands are present as axial ligands relative to the plane of the molecule and in the trans relationship relative to the intervening carbon-carbon bond. This latter configuration can then be labeled the *diaxial-trans-* configuration. Shallenberger & Acree have discuss this situation briefly.

Both the Haworth and Newman projections foreshorten the bond lengths to, and distort the bond angles between, the hydroxyl groups of the nonplanar molecules.

The bottom frame of the figure defines a gustaphore (GU) characteristic of what is labeled here the **G-Path** of the gustatory neural modality. This GU is characterized as a 1,2 *diequatorial trans*-glycol embedded in a cyclic aliphatic molecule. However, its primary characteristic is two orbitals separated by a distance of 2.6 Angstrom and capable of forming a dual coordinate bond with the equivalent structure associated with a G-Path gustatory receptor (GR). The dual coordinate bond can be further characterized as antiparallel due to the orientation of the two H–bonds. The focus on artificial sweeteners in the food industry since the 1970's has shown the importance of this dimensional parameter.

4.2.3 Extending the AH,B framework to other organic situations

> The term dimer is used variously by researchers in chemistry. For purposes of this work, a dimer will refer to a temporary chemical structure formed in solution by two simultaneous antiparallel coordinate bonds between two similar ligands or moieties of generally larger structures. The bonding is characterized by the perpendicular distance, d, between those two coordinate bonds expressed in Angstrom.

The dual coordinate bond structure associated with the 2-carbon diol, *equat-trans*-1,2 glycol acting as a gustaphore, suggests a similar bonding arrangement between other gustaphores.

In the case of the one-carbon diol, the carboxyl group is the foundation of all Lewis acids. The group is planar. The Lewis acids are well known for employing dual-coordinate bonds in the formation of dimers at their carboxyl groups.

The hydrogen bond in each leg of such a dimer typically has an energy of 2-10 kCal/mole. If used in a transduction process, this low energy illustrates the ease with which the coordinate bond can be broken.

A Lewis acid gustaphore (GU), or acidophore is characterized here by a simple carboxylic acid ligand. Such an acidophore is characteristic of the carboxylic acid path or **C-Path** of the gustatory neural modality. However, its primary characteristic is two orbitals separated by a nominal distance of 2.268 Angstrom and capable of forming a dual coordinate bond with the equivalent structure associated with a C-Path gustatory receptor (GR).

The natural environment contains few inorganic (Bronsted) acids, and these only in small amounts except in areas of volcanic activity. However, investigators have focused on them in evaluating the gustatory modality because of their ready availability in the laboratory and ease of calibration. The Electrolytic Theory of the Neuron clearly shows that it is the organic (Lewis) acids that are of primary interest to the gustatory modality of the neural system. The basic structure perceived as acidic is the carboxyl group, which in hydrated form is described chemically as a one-carbon diol.

This initial material will place the inorganic stimulants of gustation in a separate category in order to greatly simplify the description of the gustatory modality of terrestrial mammals. It appears the mammalian gustatory modality evolved based on the presence of various organic materials in the environment and the absolute need to replenish sodium ions lost within the terrestrial mammalian body.

Because of the carboxyl group in their intrinsic structure, all amino acids can coordinate with the proposed acid sensory receptor and stimulate the acid sensory channel to a degree. Boudreau reviewed the relative intensity of these sensations in several species[19].

The stimulants perceived as bitter have been associated with quinine since ancient times. However, quinine is not a simple form of the chemicals in this group. Research into a potentially fundamental picrophore ((a bitter tasting gustaphore) has had difficulty because of the great diversity of frequently complex compounds perceived as bitter. The preponderance of the research has sought a "valence chemistry" explanation for the operation of the picrophores. However, the pattern established by the fundamental acidophore (d = 2.268 Angstrom) and glucophore (d = 2.82 Angstrom) suggests the appearance of a three-carbon diol as a picrophore dual-coordinately bound to a sensory receptor. The simplest would be a 1,3 propanediol ligand with a bond structure influenced by its presence in a cyclic organic structure. This structure would exhibit a nominal d-value of 4.746 Angstrom based on a calculation assuming an *equatorial-cis-* configuration compatible with the nominally planar arrangement of the acyl group(s) but a bending of the backbone due to the presence of the NH_2 group.

As in the case of the potentially hydrated carboxyl groups, whether a hydrogen is associated with the B oxygen or not is irrelevant. The B oxygen is able to coordinate bond with a hydrogen of the other ligand in either case.

Looking at the conformations of a large group of known picrophores, it appears such a 1,3 diol ligand with two orbitals separated by a distance of 4.746 Angstrom is present. In fact, many candidate picrophores exhibit more than one set of orbitals with the specified distance between them.

A bitter gustaphore (GU), or picrophore is characterized here by a simple 1,3 propanediol ligand. However, the primary characteristic of a picrophore is two orbitals separated by a distance of 4.746 Angstrom and capable of forming a dual coordinate bond with the equivalent structure associated with a P-Path gustatory receptor (GR).

4.2.4 Extending the AH,B framework to specific inorganic complexes

While the perception of sodium in solution has been recognized as a primary stimulant of gustation since ancient times, its means of stimulating the gustatory modality has not. Two critical facts are important. First, a salt of low molecular weight does not exist when dissolved in water, it is ionized almost completely. Second, the sodium ion does not exist alone when in solution, it only exists as a hydrated sodium ion, normally in a coordinate chemistry relationship with six water molecules, $Na^+(H2O)_6$. This structure exhibits many of the properties of a diol with a single sodium ion separating pairs of oxygen atoms. Each $Na^+(H_2O)_6$ complex exhibits multiple diol ligands. **Figure 4** illustrates the two most common states of hydration of the sodium ion. In dilute solution, it is believed to form $Na^+(H_20)_6$ with the water molecules arranged at the vertices of an octahedron. The distance between the pairs of oxygen atoms of this hydrate is 3.3 Angstrom. In more concentrated solutions, it is believed to form $Na^+(H_20)_2$ The distance between the water molecules, that can act as AH,B coordinate structures, are nominally 4.7 Angstrom. Other hydration states may exhibit a d-value closer to d = 2.82 and be more amenable to causing a perception of sweetness.

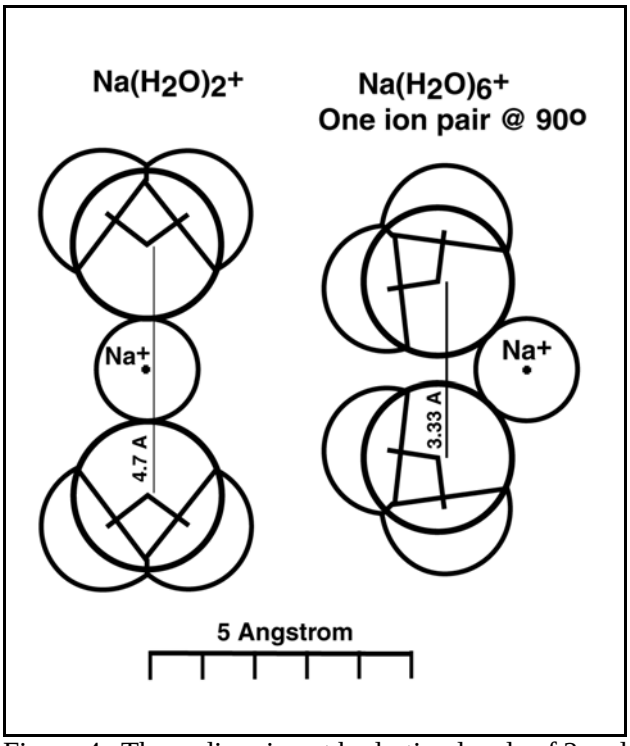


Figure 4. The sodium ion at hydration levels of 2 and 6. Only one of the three pairs of water molecules are shown on the right. See text.

It is proposed that the salty stimulant of antiquity is described more precisely as the fully hydrated sodium ion in solution. It exhibits multiple natrophores (gustaphores), each consisting of two oxygen orbitals separated by a distance of 3.3 Angstrom. Such a natrophore is characteristic of the chemical exciting the **N-Path** of the gustatory neural modality. Its primary characteristic is its ability to form a dual coordinate bond with the equivalent structure associated with a N-Path gustatory receptor (GR).

The fact that the positive sodium ion, Na^+, does not exist alone in aqueous solution also applies to the positive hydrogen ion, H^+. The ion only exists in association with one or more water molecules. There are multiple hydration states of the hydrogen ion. The d-values associated with these structures vary and may be functions of time as well. It appears the d-values range from 2.3 to 2.55 angstrom, suggesting the H^+ complexes can form the necessary dual coordinate bonds with the Lewis acid GR but does do not exhibit d-values closely matching those of other glucophores or natrophores.

The complexes of sodium and hydrogen with the host solvent suggests similar structures might also be present for the other alkali and alkali earth salts frequently used as stimulants in gustatory research. However, because of their greater radius, hydration of the positive ions of these salts tends to place their molecular "orbitals" at greater distance than the d-values of interest in gustation.

4.2.5 The proposed family of primary gustaphores

Figure 5 shows the first-order or primary form of the four gustaphores of taste. All are diols in the sense used here (where the second oxygen may also be associated with a hydrogen atom as long as an appropriate d-value is maintained. The titles are arbitrary but designed to emphasize the character of the gustaphore. Acidophore suggests the Lewis acid character of the acidophore, as opposed to a simple hydrogen ion. The first order acidophore is invariably derived from a carboxyl group and could be labeled a carboxylophore. A d-value of 2.268 has been determined for this gustaphore by averaging a wide range of reported data. There are a number of factors related to a specific gustaphore that can affect its d-value in solution. Even the angle between the two oxygen atoms has been reported variously by investigators.

As noted earlier, many other chemical formulations with a d-value of 2.82 can exist. In the extended world of sweetness, the oxygen orbital can be replaced by nitrogen, sulfur or an electronegative feature such as an unsaturated carbon bond or the π-bonding system of a cyclic structure. The controlling feature is the dimension, d, between the two orbitals. There are suggestions in the literature that the oxygen orbital can be replaced by sulfur or potentially phosphorous if their parent molecule is sufficiently strained to provide the necessary d-value of 2.82.

The natrophore describes the configuration of the hydrated sodium ion giving what is commonly called the salty sensation. The anion of the salt plays no role in this sensation. The natrophore exhibits a 90 degree angle between the two orbitals due to the octahedral form of the hydrated sodium ion. As a result, its d-value is 3.3 Angstrom. Dual coordinate bonding only involves one of the hydrogens present on one of the water molecules. The presence of the other hydrogen atoms is irrelevant.

The gustaphore contributing to the bitter taste, d = 4.746 Angstrom, has been labeled a picrophore to suggest its bitter taste. It could be described as the propophore to suggest the three carbon backbone of the minimum structure.

The structures shown are the minimal structure needed to achieve the required d-value. Especially in the case of the higher d-values, many different structural paths between the orbitals can achieve the desired d-value. It is only necessary for one of the pair of orbitals to provide a hydrogen atom. Excess hydrogen atoms are ignored and do not participate in the dual coordinate bond AH,B relationship.

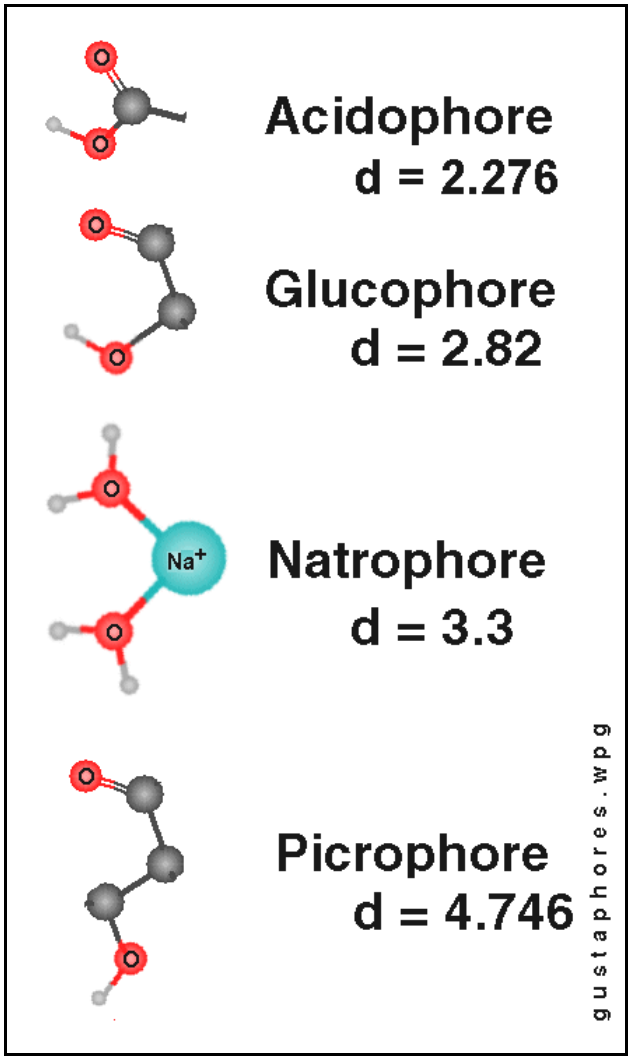


Figure 5. The first-order (simplest) gustaphores of taste. The spacing, d, between the oxygen atoms (or alternate orbitals) is the critical dimension in determining the effectiveness of the gustaphore. See text.

4.3 The matching stereo-chemistry of the sensory receptors (GR) of taste

With the gustaphores defined as above, along with their respective dual coordinate bond spacing, d-values, it is now possible to describe the gustatory receptors (GR's) within the Electrolytic Theory of the Neuron.

The chemical structure of the gustaphores strongly suggest the receptors of the gustatory modality sensory neurons might rely upon a similar structure. It has been known since the 1960's that there is great variation in the head structure of the phospholipids of the neurolemma[20]. However, the reason for the variation was unknown. Lehninger, and others, unknowingly documented the phospholipids forming the four gustatory receptors at that time, including the correct conformation based on a Haworth projection.

The coordinate bonding between the various stimulants and receptors on the external lemma of the sensory neurons involves a very low energy (5kcal/mole) and does not constitute a chemical reaction in the conventional sense. No reaction products are formed and the original species reappear when the hydrogen bonds are disrupted. No stimulants or residues of stimulants pass through the lemma of the sensory neuron.

As noted in Chapter 8 of "The Neuron and the Neural System," [1] other orbitals can participate in the gustatory process besides oxygen, specifically nitrogen. The challenge is to identify a set of GR's that can dual coordinate bond with the gustaphores defined above. The parsimonious method of satisfying these requirements is to identify receptor ligands similar to the gustaphore ligands.

C-Path GR–When PtdEtn is modified to form, or is replaced by, PtdSer, the PtdSer exhibits a planar one-carbon diol

(with or without the second hydrogen ion). It exhibits a carboxyl group and is most appropriate for forming the C-Path gustatory receptor (GR) of the sensory neurons. This GR can coordinate bond with a wide variety of Lewis acids.

It is proposed that this formation of a dimer between the carboxylic acid ligand of PtdSer and a carboxylic acid ligand of a stimulus constitutes the major transduction process in the (organic) acid or C-Path of the gustatory modality. The d-value of this dimer in solution is about 2.268 Angstrom.
PtdSer is therefore defined as the receptor (GR) of the sensory neuron initiating the sourness, or acidic, channel of gustation.

G-Path GR–One of the identified lipids of the lemma, phosphatidyl galactose has an oxygen and a hydroxyl group separated by two carbons with a d-value of 2.82 Angstrom due to its *equat-trans*-1,2 glycol configuration involving O-3 and O-4 of an aromatic structure. As a result, it exhibits the geometry necessary to form a dual coordinate bond between a wide variety of glucophores (including the common sugars) and is defined here as the "sweet" or G-Path GR. This structure was also known earlier as a *cis*-1,2 glycol ligand, when implicitly embedded in a cyclic structure. An earlier designation was galactocerebroside (CerGal). It can be described as a 2-carbon *equat-trans*-diol.

N-Path GR--One of the historically identified lipids of the lemma occurs in many conformations. Phosphatidyl *muco*-inositol (Ptd*muco*-Ins and not to be confused with Ptd*mylo-I*ns) has an oxygen and a hydroxyl group separated by a d-value of 3.243 Angstrom due to its 1,2 *axial- trans*-glycol configuration involving O-3 and O-4 of an aromatic structure. It can be described as a 2-carbon *axial-trans*-diol. This *organic* structure is unique. It exhibits the geometry necessary to form a dual coordinate bond with an *inorganic* structure, the fully hydrated sodium ion.

Thus, Ptd*muco*-Ins is defined here as the hydrated sodium GR, of the sensory neuron initiating the sodium-path (previously the "salty" channel) of gustation. This terminology avoids confusion regarding the role of salts in gustation. It is the initial element in the N-path of gustation. The anions of the majority of salts play no recognized role in eliciting the "salty" sensation. An exception is the inosinates. As noted below, selected *muco*- conformations of these anions readily form a dimer with the inosinate of Pdt*muco*-Ins.
The conformation of the *muco*-inositol is that of Simperler et al[21].

Simperler et al. document the ability of *muco*-inositol to form dual "antiparallel" coordinate bonds between axial and equatorial hydroxyl groups to form a dimer in their figure 6. They also note the fact that *muco*-inositol can form ring crystalline motifs between equatorial hydroxyl groups where each OH is involved in two distinct hydrogen bond links. This suggests each phospholipid sensory receptor of *muco*-inositol can form an *axial-trans*-dual coordinate bond with two gustaphores at once by having the middle *axial*- hydroxyl participate in two pairings.

The correct representation of *muco*-inositol as it is esterfied to the phosphatidyl moiety is critically important to understanding the dimension, d, between various pairs of hydroxyls. The calculated distance between the oxygens alternating between above and below the molecule (3.243 Angstrom) is in good agreement with the distance between the oxygens of the hydrated sodium ion. **Figure 6** shows the proposed bonding between the hydrated sodium ion and Ptd*muco*-Ins.

The numbering of the carbons of *muco*-inositol is arbitrary and seldom described in the literature. There is a plane of symmetry associated with the left most oxygen and that opposite to it. Here, the carbon supporting the equatorial hydroxyl opposite the single (up) axial hydroxyl between the two (down) axial hydroxyls is taken as C-1. The figure can represent the natrophore bonding with the sensory receptor at O-3 and O-4 or O-4 and O-5. The out of plane length of the carbon bond is foreshortened in this 2D figure.

The literature of the inositols is very conflicted due to the number of changes in numbering and labeling mandated by the IUPAC and the subsequent IUB between 1968 and 1989. These changes are well documented in Majumder & Biswas[22]. In 1996, Dowd et al. produced two papers in which they note they used different IUPAC numbering nomenclature[23]. The focus in this paper is on any inositol with one or more adjacent hydroxyls that are

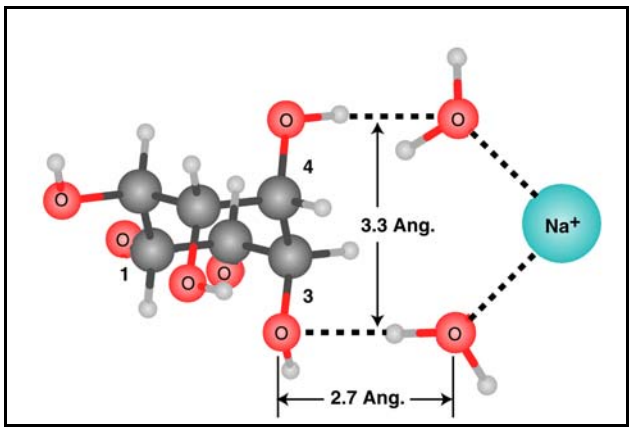


Figure 6. A hydrated sodium natraphore in a dual antiparallel bond with the *muco*-inositol receptor. The sodium ligand is planar. The lengths of the bonds associated with the gustatory receptor are foreshortened in this two-dimensional projection.

axial and *trans*-. There are three; *muco*-inositol and the enantomiers, D-*chiro*- and L-*chiro*-inositol. The prefix *muco*- is suggestive of the presence of this variant in the mucus of the nose (where it was apparently first found) and potentially the saliva of the mouth. The more common *myo*-inositol found in muscle is of little interest here. *Muco*-inositol is best described as CAS # 488-55-1 and the Jmol image attached to that number. It should not be confused with the generic or myo-inositol, CAS # 87-89-8 or with CAS # 41546-34-3.

Dowd et al. have presented a scatter diagram to show that *ab initio* calculations related to the conformation of the inositols and similarly complex molecules are not adequate for defining the dual coordinate bonding character of the mechanism of gustation[24].

P-Path GR–One of the identified lipids of the lemma from the 1970's, phosphatidyl 3'-O-aminoacyl glycerol (Ptd3'Oag) has an oxygen and an amine separated by 2 carbons in an aliphatic configuration. It also exhibited an unspecified R group representing a variety of ligands. In their experiments, Silvius et al. found R to be mostly in the form of alanine[25]. With further acylation as described below, it can become a 3-carbon diol exhibiting the geometry necessary to form a dual coordinate bond with the defined picrophores.

The most probable phospholipid of the outer bilayer membrane of the microvilli capable of operating as the picric sensory receptor is an acylated form of Ptd3'Oag. The result is a 3-carbon diol ligand (1,3 propanediol) describable as acylated phosphatidyl 3'-O-aminoacyl glycerol (Ptd3'OagR'). It is hypothesized that this species, shown in **Figure 7** with an R' group remaining undetermined, is the fourth unique phospholipid-based GR of the gustatory modality. The amine group is not functional if present in the ultimate molecule but may introduce crowding. Ptd3'OagR' exhibits a spacing of 4.746 Angstrom between the doubly bonded oxygen and the hydroxyl group. This spacing is compatible with a very large group of chemicals that can coordinate bond with it and elicit a sensation of bitterness.

This broad spacing suggests this sensory receptor is positioned as shown in the lower frame of the figure, achieving a sensation space with minimum overlap with the other sensory channels. As noted earlier, the mean values of each distribution is calculable but the distributions are shown only conceptually.

The right side of the figure shows a very complex molecule known for its bitterness, a quassin. Quassinoids are highly oxygenated triterpenes. The most prevalent quassinoids have C-20 picrasane skeletons. The Quassins have a bitterness threshold of 1:60,000. The complexity of this molecule suggests it could form an AH,B bond with a d-value of 4.746 Angstrom AH,B in multiple ways. Thus, each molecule of the stimulant is likely to exhibit multiple picrophores.

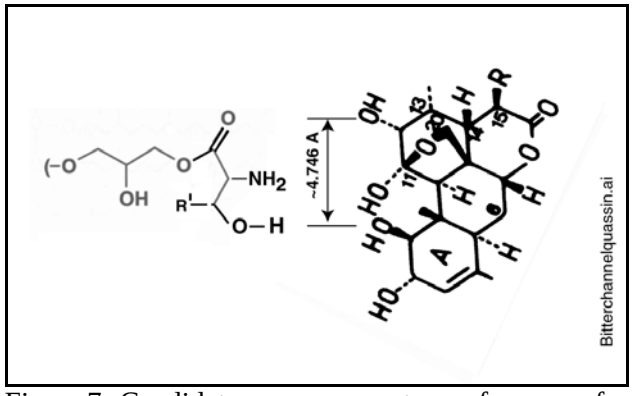


Figure 7. Candidate sensory receptor performance for the picric channel, or "bitter" channel (using mixed representations as an expedient). Left, active ligand of bitter sensory receptor, acylated Ptd3'Oag or Ptd3'OagR'. Right; a quassin shown oriented so as to form an AH,B coordinate bond with the sensory receptor. The nominal d-value of the picric channel is an A,B spacing of 4.746 Angstrom. Modified from O'Neill et al., 1986. See text.

4.3.1 The gustatory receptors--features of the sensory neuron lemma

Figure 8 summarizes the GR's of terrestrial mammals in relation to the other molecular structures associated with the dendrites of the sensory neurons of gustation.

The figure is complex. However, by following the logic of Dowhan[26], it provides a variety of answers. It begins at upper left describing the chemical structure of a typical phospholipid and its ability to bond with a variety of terminal groups through esterification. The ligand in the box is labeled on the right with the trivial name choline, or formally phosphatidylcholine (PtdCho). This ligand plus the next one below it, ethanolamine (PtdEtn), are the principle phospholipids of the lemma of all cells. The electrical properties of the long lipid chains on the left are conventionally ignored. However, they can exhibit adequate though small electrical conductivity when in the liquid crystalline state. When the structures on the right below the horizontal line are substituted into the box, the accompanying lipid chains are hypothesized to be electrically conductive. The ligands shown below the line are those commonly found in the lemma of neurons and particularly sensory neurons of the gustatory system. They each support a separate sensory channel of gustation leading to a sensation of sourness (presence of an organic acid or acidophore), sweetness (presence of a glucophore), saltiness (presence of a hydrated ion of sodium or natrophore) or bitterness (presence of a picrophore). The discrimination between gustaphores (GU's) is based on the distance, d-value, between the orbitals of the GR's as suggested by the brackets and given numerically to the right of the structures. The brackets indicate the points of dual antiparallel coordinate bonding between the GR's

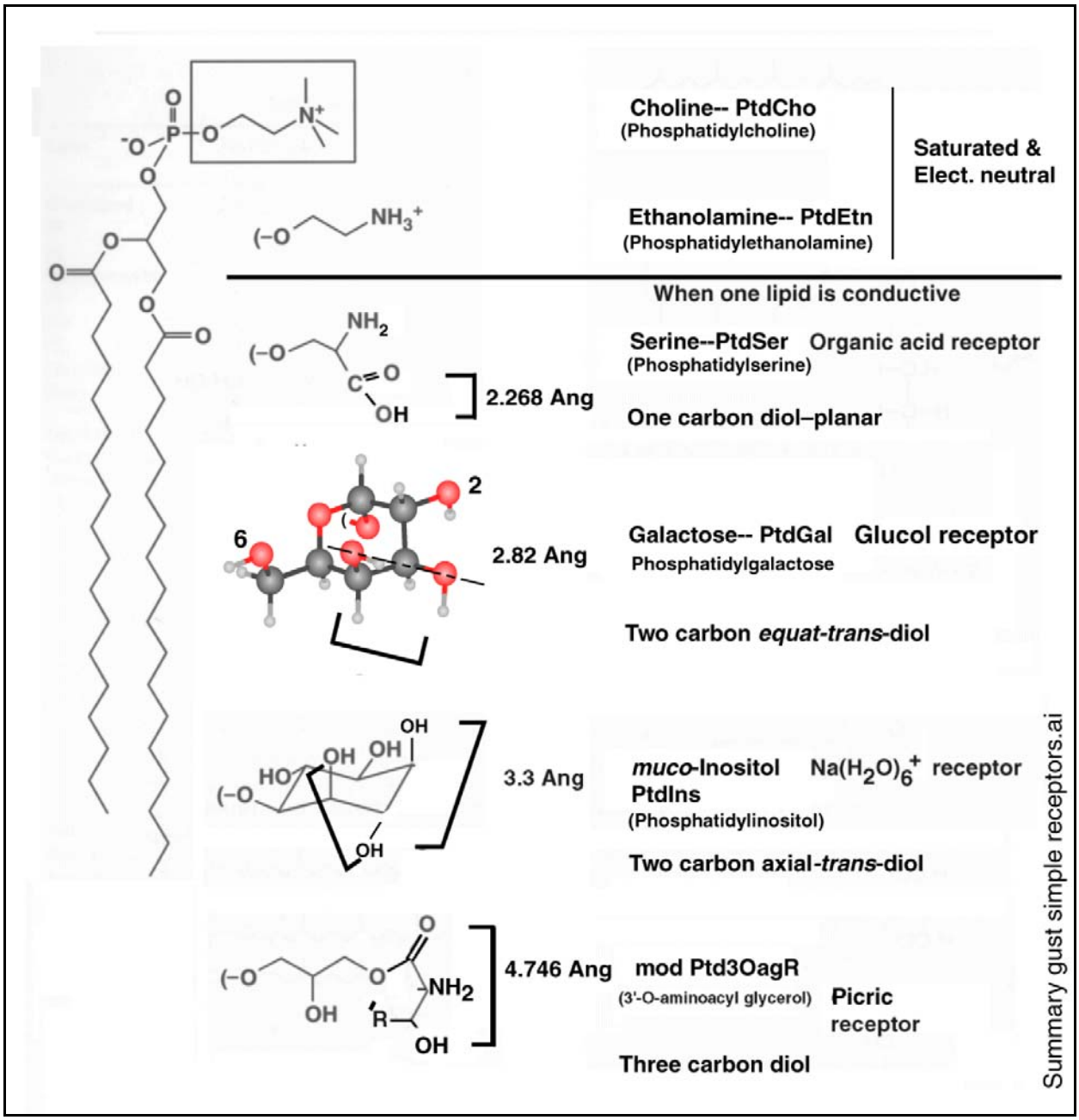


Figure 8. Summary: fundamental sensory receptors of gustatory modality based on the Electrolytic Theory of the Neuron and a coordinate chemistry mechanism. Phospholipid is shown stylized. See text. Built using the style of Dowhan, 2002.

and the GU's.

Ptd*muco*-inositol is the only inositol with three axial hydroxyl groups. The three form two adjacent diaxial hydroxyl pairs by sharing the central hydroxyl group. This conformation could support an enhanced sensitivity to hydrated sodium.

The text on the right includes other characteristics associated with each channel and condensed into Figure 1.

4.4 Summarizing the framework of gustation

The goal of this work is to provide a set of designations describing the chemical structures of sensory receptors and gustaphores eliciting a perception. The right hand columns of Figure 1 summarizes those designations. As developed here, the conventional "acid" sensory channel does not sense a proton; it operates only in the Lewis acid sense in order to sense a carboxyl ligand. Thus, the expression H(ydrogen)–best of the first column is replaced by C(arboxyl)–Path in the second column.

> The theoretical chemistry literature is quite clear that a hydrogen ion, H^+, does not exist in the aqueous state. It only exists in a complex such as H_3O^+, $H_5O_2^+$ or $H_9O_4^+$. Agmon has provided invaluable data on the spacing between the elements of these molecules in explaining the Grotthuss Effect[27].

Similarly, S–best, rather than suggesting sweet or sugar, is replaced by the G(lucol)–Path to address the fact that a very large number of nonsugars elicit a sweet, sugary perception. However, the simplest G–Path glucophere within a cyclic structure is an *equat-trans*-1,2 glycol. The empirical term Q(uinine)–Best is replaced with the more precise P(icric)–Path since the simplest gustaphore exciting that path is present in a wide range of stimulants. These stimulants are frequently much simpler and totally unrelated structurally to quinine. The umani sensation is the result of stimulating multiple sensory channels simultaneously, and does not involve a unique sensory process.

The term N-Best of behavioral investigations is replaced by the N-Path of the neurological system.

In the context of this figure, an acidophore, glucophore, etc. excites the appropriate gustatory receptor, creating a signal in the appropriate neural path. All of the gustatory receptors are phospholipids known to be present on the outer bilayer of sensory neuron lemma.

PtdSer–phosphatidyl Serine	1-carbon diol
PtdGal–phosphatidyl Galactose	2-carbon diol, *equat-trans*-
Ptd*muco*-Ins–phosphatidyl muco-Inositol	2-carbon diol, *axial-trans*-
Ptd3'OagR'–phosphatidyl 3'–O–amino acyl glycerol acylated further	3-carbon diol

Figure 2 provides the first calibrated graph of the gustatory perception space. The vertical lines represent the nominal d-values of the sensory neuron receptors. The distributions about these vertical lines represent the probability that a given gustaphore can interact with the gustatory receptor (GR) associated with that d-value. Currently the precise widths of these distributions are not known. Half-widths of ±5% are shown for discussion. A subsequent paper will show this horizontal number line can be folded at each of the nominal d-values to form a three dimensional taste perception space.

4.5 The character of related stimulants–Umami

The Japanese, beginning in 1908, have suggested a fifth fundamental taste sensation called umami. The term appears to have been derived from their word, umai (delicious). The common word, and possibly the designation, appears to have a strong representation in their culture. The theory developed here provides a definitive explanation for the source of the perception labeled umami.

Yamaguchi has been the leading investigator of umami in recent times[28]. Yamaguch & Ninomiya have addressed the question of whether chemicals inducing the perception of umami are gustaphores or only taste enhancers., by asserting, "Umami makes a variety of food palatable, although it is not palatable by itself[29]." The naturally occurring L-glutamate is reported to be tasteless while D-glutamate is sometimes reported to be sweet. The perceptions elicited by mono-sodium glutamate are primarily those of salty, with a slightly acidic, and to some individuals a slightly sweet taste.

In 1987, Yamaguchi & Komata presented some results of multi-dimensional analyses and asserted that umami is represented by a different dimension than the other four historical sensations[30]. However, the printed record of this poster presentation does not include any graphical material and speaks of dimensions and vertices of the taste sensation space that may suffer in translation. It does comment on, but not cite the 1979 Yamaguchi paper. That paper did not include a full multi-dimensional analysis. It specifically did not include the basis factors demonstrating a unique node or vertex associated with umami. In 1991, Yamaguchi reported a large scale test comparing the sensations of Orientals and Caucasians of European origin[31]. No significant differences were found.

Schlichtherle-Cerny et al. have provided a "selected list" of the broad range of chemicals claimed to be associated with the perception of umami based on purely psychophysical tests[32]. They illustrate these chemicals using only Haworth diagrams.

The behavioral evidence favoring an independent umami sensory channel is weak. The chemical evidence is strong that

the materials associated with the umami perception contain multiple gustaphores associated with the four identified GR's of gustation. These conclusions are consistent with Belitz et al[33]. Kurihara & Kashiwayanagi addressed umami in 1998 and described the principle chemicals associated with it as mono-sodium glutamate, disodium inosinate and disodium guanylate[34]. These chemicals, when in solution, all create multiple gustaphores as defined in this work.

• Monosodium glutamate incorporates the N-Path GU, the C-Path GU and potentially the G-Path GU. [figure S-4] In the absence of crowding, the spacing of the glutamate atoms is probably not close to the nominal 2.82 Angstrom.

•Disodium guanylate incorporates two N-Path GU's, and a G-Path GU.

•Disodium inosinate is unique in that it includes two N-Path GU's and the inosinate can act as both a G-Path GU and an additional N-Path GU.

> ***If an inosinate that does not include a sodium ion is pereceived as "salty," it would be strong support for the hypothesis of this work.*** That hypothesis suggests an inosinate alone is a natrophore and can form a dimer with the "salty" phospholipid receptor, phosphatidylinositol, d-value = 3.3 Angstrom.

Most of the chemicals identified by Schlichtherle-Cerny et al., beginning with monosodium glutamate are also seen to contain the fundamental GU's defined above, with some clearly involving the replacement of an oxygen atom by one of the other identified orbitals associated with the gustaphores. The most common replacement is nitrogen. The presence of the C-Path GU in all of the chemicals on their select list, except for the family 5'-()MP is noted. That family offers multiple opportunities to exhibit GU's identified in this paper but more analysis is needed.

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