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Exploring the Molecularity of the Odor and Taste Perceptions of "Brown": A Computational Approach

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ABSTRACT: We have developed a methodology that seeks to associate the molecularity of compounds with the perceptions of specific odor or taste. This methodology goes beyond gross structural features for a molecule: aromatic or aliphatic rings, lengths of the aliphatic straight chains, or the nature and variation in the functional groups. We target specific atom pairs–bonded or remote–within the smell and taste molecule that have structural-electronic features that are reproducible across molecules that elicit similar smell and taste responses. We represent the "structure" of the atom pair by its interatomic distance. The "electronic" aspects are represented by Nuclear Magnetic Resonance (NMR) chemical shifts that uniquely define the electronic environments of the atoms. We used quantum chemistry calculations and the density functional theory (DFT) to determine the chemical shifts and interatomic distances (through the Z-matrix). We used this methodology to process 19 molecules that elicited the smell of "brown," and 18 molecules that elicited the taste of "brown." These molecules were accessed through odor and taste indices from the GoodScentsCompany resource (https://www.thegoodscentscompany.com/). These "brown" odorants and tastants elicited other associated smells and tastes. We identified and illustrated specific bond pairs that elicited different smells and tastes. While smell and taste are intrinsically related, our studies also show atom pairs that are likely responsible exclusively for smell and taste, as well as pairs that elicit both. This work will be impactful in the domain of drug design in the pharmaceutical industry, in addition to enhancing our understanding of how a chemical catalyzes the process that results in chemosensory perception.

Key words: brown-odor, brown-taste, olfaction, gustation

INTRODUCTION

The QSAR (Quantitative Structure-Activity Relationship) methodology has evolved and been established to create comprehensive and large-scale high-throughput putative pharmaceutical products. (Tropsha, 2010; Verma, Khedkar, & Coutinho, 2010; Dudek, Arodz, & Gálvez, 2006) The SDAR (Structure Activity Relationship) methodology (Slavov, et al., 2014; Stoyanova-Slavova et al., 2017) was developed to identify toxicophoric aspects of pharmaceutical products and mapped to specific clinical adverse events like *Torsade de Pointe* from overuse of antimicrobials. (Sharifi, et al., 2017) The SDAR methodology was based on identifying intra-molecular features of pharmaceutical products such as atom pairs (bonded or remote) that were in similar electronic environments. The electronic environments were determined by chemical shifts of atoms with unpaired nuclei in NMR (Nuclear Magnetic Resonance) spectra of ^{1}H, ^{13}C, ^{15}N, and if necessary, ^{31}P atoms. One-dimensional SDAR was extended to three-dimensional SDAR by adding reproducible interatomic distances to the chemical shifts of these atom pairs.

We extend the application of SDAR notions through independently developed software and protocols to the research domain of the chemical senses–specifically smell and taste. We explored and provided a molecular basis for molecules of smell and taste, in conjunction with the visual perception of color–specifically, brown. An odor or taste "brown" does not exist. The smell or taste of brown is associated with visual stored memory or experience, that finds its neurological loci in the cortical regions of the brain. (Khamsi, 2022)

A study of this type is novel and impactful. Our approach is from the perspective of the odorant–the molecule that elicits the olfactory response, and the tastant–the molecule that elicits the gustatory response. These molecules are first captured by the olfactory or gustatory receptors, eventually resulting in the perceptions. These chemosensory receptors have come into prominence since the publication of the human genome. They belong to superfamilies of genes numbering in the several hundred. The discovery of the olfactory receptor (Buck & Axel, 1991) garnered the Nobel Prize in Medicine and Physiology to its discoverers. (Firestein, 2005) While several experimental (Sharma, et al., 2019) and computational studies (Crasto, 2009) have been carried out to assess the function of these genes, this study takes the olfactant- (or tastant-) driven approach.

MATERIALS AND METHODS

Identification Of Odorants and Tastants

We accessed TheGoodScents company's (thegoodscentscompany.com) odor and taste indices and searched the resource for molecules identified for having the smell and taste of "brown." Nineteen molecules that smelled brown and 18 molecules that tasted brown were identified. For this work, only molecules were identified. The GoodScentsCompany resource also returned odors or tastes–combinations of molecules or natural products that elicited the "brown" response. Given the nature of our studies, these were ignored.

Downloading The Data

The three-dimensional structures of molecules identified above were downloaded from the PubChem (https://pubchem.ncbi.nlm.nih.gov/) resource as SDF (Structure-Data Format) files. The OpenBabel (https://www.cheminfo.org/Chemistry/Cheminformatics/FormatConverter/index.html) resource where the files were converted to the MOL structure format.

Quantum Chemistry Calculations

GAUSSIAN quantum chemistry software (Frisch, et al., 2016) was used to determine the theoretical NMR shifts following geometry optimization. The Density Functional Theory calculations were used using the B3LYP (Becke, 3-parameter, Lee–Yang–Parr)) exchange-correlation functional is used to describe the electron density distribution around each atom. (Chermette, 1998) The Z-matrix which depicted the molecular geometries and the NMR chemical shifts were thus determined.

Identification Of Odors And Tastes Associated With "Brown"

For all the molecules returned to queries of "brown odor" and "brown taste" from the GoodScentsCompany resource, 18 tastes and 19 odors were identified as being associated with brown. These were cataloged in a recent publication. (Crasto, et al., 2023) Of these, the odors and tastes of baked, beefy, bready, brothy, burnt, buttery, caramelly, coffee, cooked, creamy, ethereal, fatty, fenugreek, herbal, maple, molasses, nutty, roasted, rummy, sugar, sweet, tequila, toffee, tropical, vanilla, and vegetable were common to both smells and tastes. In this work, we will identify atom pairs that have virtually identical electronic structural features and elicit the same smells.

Electronic-Structural Features Of Atom Pairs

We developed customized software, written using the Python scripting and programming language, that identified atom pairs in molecules that had elicited the same smell and taste that had virtually identical and reproducible electronic-structural features. Molecules were clustered by way of the elicited smells and tastes.

For each molecule, we comprehensively identified every atom pair and cataloged it in terms of chemical shift per atom and the interatomic distance for the atom pair. For every atom pair, our program scanned atom pairs in all the molecules (separately for smell and taste).

To be considered a reproducible structural-electronic feature, the interatomic distance between atom pairs would have to be equal to or less than 0.1 Å, and a chemical shift of 10 ppm (parts per million) or less. While a smaller chemical shift difference would also have yielded useful results, a scan of the tables of NMR shifts for ^{13}C, ^{15}N, and ^{31}P reveals that for atoms in the same environments, the chemical shift ranges vary over a range of ppm values. All the oxygen-oxygen and oxygen-sulfur bonds are ignored in these studies. While it is highly likely the O-O, S-O, and S-S pairs do contribute to specific odors and tastes, our methodology precludes

the use of atom pairs where the electronic environment through chemical shifts cannot be ascertained (both oxygen and sulfur have paired nuclei).

For every molecule, we identified the atom pairs that were potentially responsible, individually, or in conjunction with other pairs, for a specific odor or taste response. In the next section, figures representing molecules with the atom pairs highlighted by dotted lines, color-coded to represent a particular odor or taste are represented.

RESULTS AND FINDINGS

The figures illustrate the results of our methodology through three examples of molecules with the "brown" smell and taste.

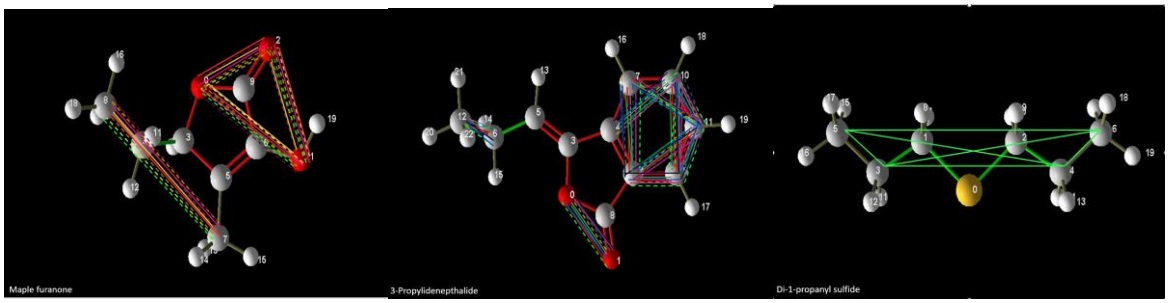

Figure 1. Molecules That Elicit The Smell Of Brown: A) Maple Furanone, B) 2-Propylidenepthalide, and C) Di-1-Propanyl Sulfide

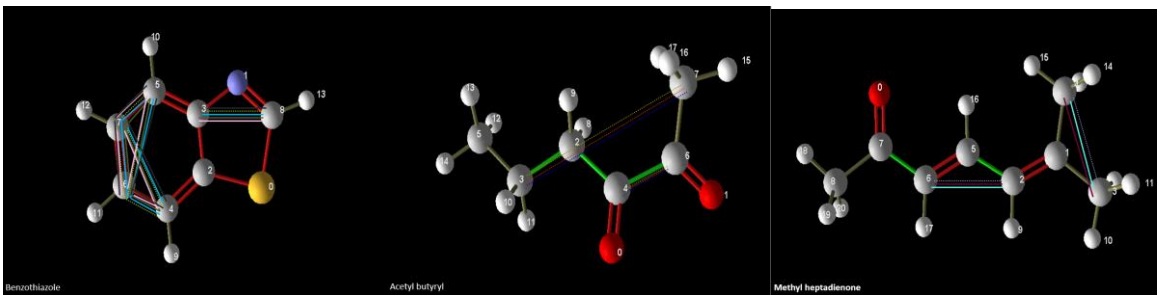

Figure 2: The Molecules That Elicit The Taste Of Brown: A) Benzothiazole, B) Acetyl butyryl, and C) Methyl heptadienone

Figures 1 and 2 represent six of the approximately 40 molecules tested using our methodology. In Figures 1 and 2, the solid lines are for atom pairs unique to a set of molecules that are exclusively associated with a specific odor or taste perception. The dashed lines (Figure 1 for odors) and dotted lines (Figure 2 for taste) represent perceptions that are not unique, but (see Discussion) fall under perceptions that are highly similar and likely not discernible from each other.

In Figure 1, the solid lines show atom pairs that are unique to a particular odor: light orange for praline, pink for chicory, light ochre for butterscotch (for A); blue for phenolic, dark blue for vegetable, purple for lovage, light green for brothy, dark gray for celery (for B), phosphorescent green for savory (for C). The dashed lines show atom pairs that contribute to the odors that are also present in other molecules: yellow-green for fruity, magenta for rummy, bright green for maple, ochre for caramel, red-brown for sugar, dark ochre for fenugreek (for A); bright green for maple, dark blue-green for herbal, dark ochre for fenugreek.

In Figure 2, the solid lines show atom pairs that are unique to a particular taste: light pink for meaty, dark gray for vegetable, light blue for coffee, dark olive green for beefy (for A); dark yellow green for creamy, royal blue for caramel, orange for fruity (for B) sky blue for green taste, magenta for herbal (for C). The dotted lines show atom pairs that contribute to the tastes that are also present in other molecules: yellow green for cooked (for A); dark yellow green for creamy, royal blue for caramel, orange for fruity (for B); light purple for sweet taste (for C).

DISCUSSION

Our results illustrate specific atom pairs that bear similarly or virtually identical electronic-structural features for odors for over 40 molecules that elicit a response associated with the overall "brown" smell and taste. In

addition to the illustration of this concept in Figures 1 and 2, we have also clustered the compounds into groups that have similar smells and tastes.

The odors and tastes can be clustered in different groups. The lists of odors and tastes in the captions of the figures illustrate that. For the odors, four distinct groups emerge. 1. Cooked, roasted, meaty, savory, baked, bread, beefy, pungent, chicory, cocoa, coffee, fatty, lard, and brothy; 2. Sweet, sugar, caramelly, chocolate, fruity, toffee, vanilla, syrup, tropical, almond, butterscotch, creamy, praline, lactone, maple, molasses, nutty, whiskey, winey, tequila, burnt, burnt sugar, sugar, ethereal, rummy, buttermilk, buttery, cherry; 3. Vegetable, herbal, celery, phenolic, fenugreek, lovage; and, 4. Musty and dry. For the tastes associated with "brown", four groups emerge 1. sweet, creamy, caramel, sugar, maple, toffee, brown sugar, molasses, vanilla, fruity, tequila, tropical, strawberry, berry, apple, astringent, nut, nutty, ethereal, rummy, buttery, milky, alcohol, fermented; 2. Cooked, baked, roasted, brothy, bready, fatty, coffee, sulfurous, burnt, meaty, beefy, bloody, chicken, skin, shellfish, oily, sour; 3. Vegetable, green, herbal, fenugreek, potato; and, 4. Woody.

While the clusters are similar, not every molecule that invokes the smell perception invokes a similar perception is taste. A survey of our lists of 19 brown odor molecules and 18 brown taste molecules indicates that only five molecules belong to both groups: 2-oxobutyric acid, caramel dione, maple furanone, strawberry furanone acetate, and tetrahydrofurfuryl acetate. It is likely then that the atom pairs have some overlap for similar tastes and smells but with some differences. Research identifying these differences is currently ongoing.

In the cohort of molecules studied, there are several dashed and dotted lines and relatively few solid lines (Figures 1 and 2). Our reproducibility criteria are very stringent. We only allow interatomic distances that show a less than 0.1 A difference. We "bin" atoms with chemical shifts of 10 ppm or less. NMR chemical shifts of atoms of similar function groups often range up to 50 ppm. Every atom pair that did not meet these criteria was ignored as not being reproducibly representing a perception. The lists in the above paragraphs list include odors and tastes that are not necessarily discernible by the regular smeller and taster. It is likely that the perceptions in the GoodScentsCompany were performed by super smellers and super tasters.

This notion sets up an interesting discussion–how the visual senses, memory, and experience contribute to the chemical senses. For, example, if the perceptions of cooked, savory, and meaty point to the same atom pairs in a fixed set of molecules, it is unlikely that a vegetarian can have a perceived experience of a meaty odor or taste. Maple furanone has been identified by atom pairs, all of which are associated with the odors of praline, maple, butterscotch, and chicory. People who live in tropical countries do not have a chemosensory association with praline or maple; chicory is a coffee substitute used in the southern parts of the USA. When a molecule that has an atom pair associated with all these smells, an individual is likely to identify a smell with which he or she is familiar. These are largely not discernible odors–unless associated with specific memories.

This illustration of chemosensory responses to "brown," a non-smell and non-taste illustrates how the visual sense and stored memories direct our senses of smell and taste.

CONCLUSION

Our work is founded on the notion that we can explore the molecularity of molecules contributing to a specific response by identifying the electronic structural features of that molecule. Our work is in the domain of the chemical senses. However, it is founded on notions developed to identify molecular features that likely contribute to adverse clinical effects from certain pharmaceutical products. Conversely, the notions advanced here and in the development of the 1-D and 3-D SDAR methodologies can also be used to identify the molecularity of an efficacious response to a pharmaceutical product. Our work will likely be very impactful in the perfume and food industry in the development of novel products that will fulfill hedonistic as well as therapeutic needs.

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