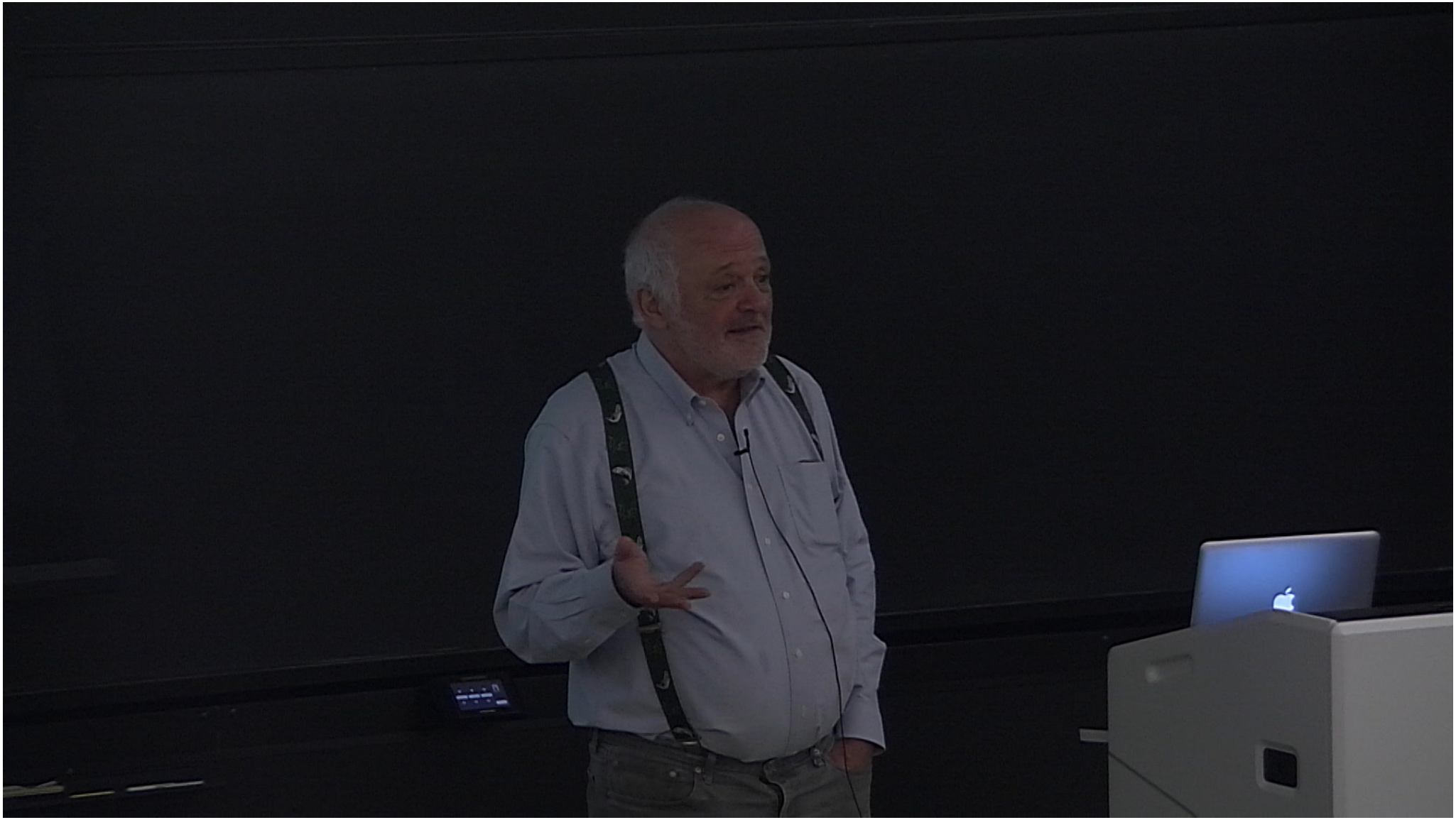
Title: Is smell a quantum phenomenon ?

Date: Nov 22, 2017 02:00 PM

URL: http://pirsa.org/17110043

Abstract: Our sense of smell is extraordinarily good at molecular recognition: we can identify tens of thousands of odorants unerringly over a wide concentration range. The mechanism by which this happens is still hotly debated. One view is that molecular shape governs smell, but this notion has turned out to have very little predictive power. Some years ago I revived a discredited theory that posits instead that the nose is a vibrational spectroscope, and proposed a possible underlying mechanism, inelastic electron tunneling. In my talk I will review the history and salient facts of this problem and describe some recent experiments, both on fruit flies and on humans, that go some way towards answering the question.



ADVANCES IN PHYSICS: X, 2017
VOL. 2, NO. 3, 937–977
https://doi.org/10.1080/23746149.2017.1378594

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Molecular recognition in olfaction

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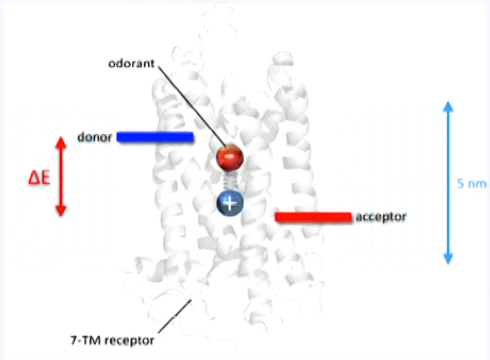
ABSTRACT

The mechanism by which the chemical identity of odourants is established by olfactory receptors is a matter of intense debate. Here we present an overview of recent ideas and data with a view to summarising what is known, and what has yet to be determined. We outline the competing theories, and summarise experimental results employing isotopes obtained for mammals, insects, and individual receptors that enable us to judge the relative correctness of the theories.



ARTICLE HISTORY
Received 17 May 2017
Accepted 4 September 2017

KEYWORDS
Olfaction; Turin vibrational theory; deuterium; flies; bees; humans

PACS
87.14.ep Membrane proteins; 87.15.ag Quantum calculations; 87.15.ap Molecular dynamics simulation; 87.15.ht Ultrafast dynamics; charge transfer; 87.80.Jg Patch clamping and other physiological measurements

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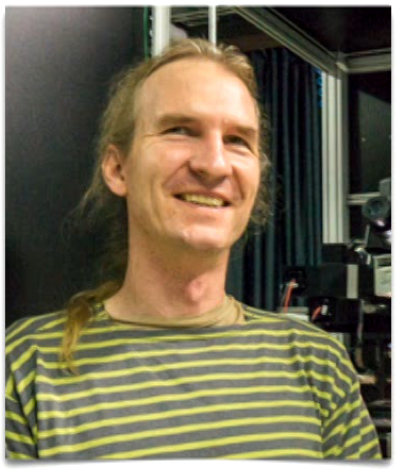

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Implausibility of the vibrational theory of olfaction

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Edited by Jerrold Meinwald, Cornell University, Ithaca, NY, and approved March 31, 2015 (received for review February 20, 2015)

The vibrational theory of olfaction assumes that electron transfer occurs across odorants at the active sites of odorant receptors (ORs), serving as a sensitive measure of odorant vibrational frequencies, ultimately leading to olfactory perception. A previous study reported that human subjects differentiated hydrogen/deuterium isotopomers (isomers with isotopic atoms) of the musk compound cyclopentadecanone as evidence supporting the theory. Here, we find no evidence for such differentiation at the molecular level. In fact, we find that the human musk-recognizing receptor, OR5AN1, identified using a heterologous OR expression system and robustly responding to cyclopentadecanone and muscone, fails to distinguish isotopomers of these compounds in vitro. Furthermore, the mouse (methylthio)methanethiol-recognizing receptor, MOR244-3, as well as other selected human and mouse ORs, responded similarly to normal, deuterated, and ^{13}C isotopomers of their respective ligands, paralleling our results with the musk receptor OR5AN1. These findings suggest that the proposed vibration theory does not apply to the human musk receptor OR5AN1, mouse thiol receptor MOR244-3, or other ORs examined. Also, contrary to the vibration theory predictions, muscone-d_{30} lacks the 1,380- to 1,550-cm^{-1} IR bands claimed to be essential for musk odor. Furthermore, our theoretical analysis shows that the proposed electron transfer mechanism of the vibrational frequencies of odorants could be easily suppressed by quantum effects of nonodorant molecular vibrational modes. These and other concerns about electron transfer at ORs, together with our extensive experimental data, argue against the plausibility of the vibration theory.

olfaction | isotopomers | cyclopentadecanone | muscone | electron transfer

In 1870, the British physician William Ogle wrote: "As in the eye and the ear the sensory impression is known to result not from the contact of material particles given off by the object seen or heard, but from waves or undulations of the ether or the air, one cannot but suspect that the same may be true in the remaining sense, and that the undulatory theory of smell… [may be] the true one" (1, 2). Of the 29 different "theories of odour" listed in the 1967 edition of *The Chemical Senses* (3), nine associate odor with vibrations, particularly those theories championed by Dyson (4, 5) and Wright (6–8). However, the premise that olfaction involves detection of vibrational frequencies of odorants remains highly speculative because neither the structures of the odorant receptors (ORs) nor the binding sites or the activation mechanisms triggered upon odorant binding to ORs have been established. In 1996–1997, Turin (9–12) elaborated on the undulatory theory of smell, as considered in more detail below, and suggested that a mechanism analogous to inelastic electron tunneling spectroscopy (13) may be involved, where tunneling electrons in the receptor probe the vibrational fre-

question" and that "a convenient way to address [this question] is to test for odor character differences between deuterated and nondeuterated odorant isotopomers since these have identical ground-state conformations but different vibrational modes." Gane et al. (14) also stated that a particularly appropriate test case would involve odorants containing "more CH group… [such as] musks [which] are among the largest odorants and typically contain 15–18 carbons and 28 or more hydrogens."

In judging the plausibility of the vibration theory, we use a multipronged approach:

i) We consider the concepts of shape vs. vibration theory and odorant perception vs. reception.

ii) As a test of the vibration theory, we have prepared a series of isotopomers of musks and other compounds, containing up to 30 C–H or C–D bonds as test odorants, which are evaluated using in vitro activation of receptors identified by us and other groups as being highly responsive to these isotopomers.

iii) We consider the confounding effects of impurities and isotope effects in interpreting odorant perception, as well as the validity of requirements for specific IR bands for recognition of musks by their receptors.

Significance

The vibrational theory of olfaction posits detection of odorants through their vibrational frequencies rather than solely through "hand-in-glove" substrate/enzyme-like odorant–odorant receptor (OR) interactions. To test the theory, we compare responses of different human and mouse ORs toward deuterated and undeuterated isotopomers (isotopic atom isomers) of receptor-responsive odorants because isotopomers should differ in their molecular vibrational frequencies. However, no differences in receptor response are seen with any tested labeled/unlabeled odorant/receptor pairs. Because published behavioral studies have shown that humans can distinguish isotopomers, peri-receptor events or impurities, rather than receptor-level vibrational effects, are suggested. Because theoretical aspects of the vibration theory are also found wanting, the vibration theory is deemed implausible in the absence of compelling receptor-level experimental evidence to the contrary.

Author contributions: E.B., S.J., H.M., V.S.B., and H.Z. designed research; E.B., S.J., H.M., S.S., B.D., M.Z.E., S.G., Y.P., S.L., Z.L., S.N.L., M.O., H.J., S.F.P., V.S.B., and H.Z. performed research; E.B. contributed new reagents/analytic tools; E.B., S.J., H.M., S.S., B.D., M.Z.E., S.G., Y.P., S.N.L., M.O., S.F.P., V.S.B., and H.Z. analyzed data; and E.B., S.J., H.M., V.S.B., and H.Z. wrote the paper.

The authors declare no conflict of interest.

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BIOPHYSICS AND COMPUTATIONAL BIOLOGY

CHEMISTRY

Professor Leslie Vosshall
Rockefeller University

"I like to think of the vibration theory of olfaction and its proponents as unicorns. The rest of us studying olfaction are horses"
BBC News Jan 28 2013

PNAS

COMMENTARY

Laying a controversial smell theory to rest

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[a]*Laboratory of Neurogenetics and Behavior* and [b]*Howard Hughes Medical Institute, The Rockefeller University, New York, NY 10065*

In the 50 y before the cloning of the odorant receptors (ORs) by Linda Buck and Richard Axel in 1991 (1), two competing mechanisms for odor detection were discussed, one chemical and one spectral. The chemical theory posited that "detectors" respond to physicochemical attributes of the odorant, including molecular size, molecular shape, and functional groups (2, 3). The alternative spectral theory hypothesized that the olfactory system detects molecular vibrations of the odor molecules (4, 5). This vibration theory was revived in 1996, along with a proposed mechanism of inelastic electron tunneling spectroscopy activated by ligand–receptor interactions (6). These early theories of how ORs detect odorants were developed using psychophysical experiments, in which human volunteers sniffed odor molecules and described what they perceived. In PNAS, Block et al. (7) shift the "shape vs. vibration" debate from olfactory psychophysics to the biophysics of the ORs themselves. The authors mount a sophisticated multidisciplinary attack on the central tenets of the vibration theory using synthetic organic chemistry, heterologous expression of ORs, and theoretical considerations to find no evidence to support the vibration theory of smell.

What are the predictions of the vibration theory of smell and how would one test it? Proponents of the theory argue that the answer lies in chemical stimuli that are considered "identical" in structure but are fully deuterated analogs in which hydrogen atoms are exchanged with deuterium atoms. The thinking is that such molecules, known as isotopomers, would have identical molecular shapes and functionality but very different vibrational spectra. Sniff-testing of isotopomers has yielded mixed results. Although acetophenone and fully deuterated acetophenone were said in the original 1996 theoretical paper to be readily discriminable by humans (6), this observation was not reproduced in a later study (8). These same isotopomers were tested in insects and shown confirmed that humans could not discriminate the acetophenone isotopomers after all, but offered new musk isotopomers that could be discriminated. Aside from being poorly reproducible, these psychophysical experiments are fraught with confounding variables. One cannot rule out that minute quantities of impurities in the isotopomers account for their discriminability or that the molecules are enzymatically transformed to novel odorants by nasal mucus long before they interact with their cognate OR, and subsequently yield a smell percept in the brain (12). Finally, it seems unlikely that fundamental subatomic mechanisms of OR ligand–receptor interactions can be inferred from human perceptual experiments alone.

Motivated by "disproving" the vibration theory, Block et al. bring us important insights into structure–activity relationships in olfaction, one of the most important problems facing the field.

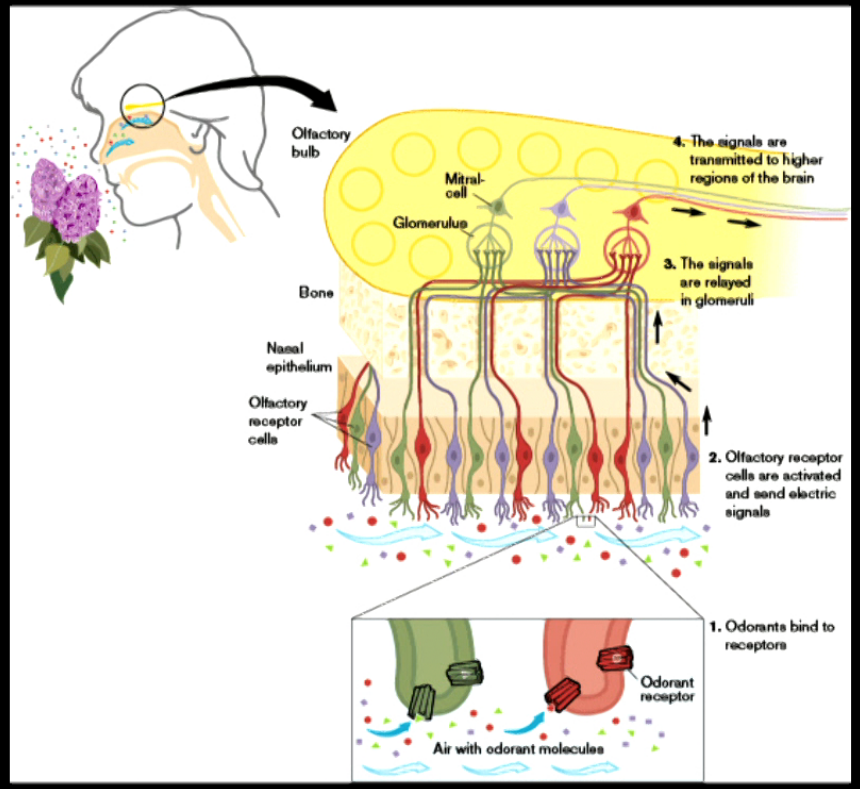
No Evidence for Vibration-Sensing Odorant Receptors. Block et al. (7) solve these problems by taking the theory to where it should have been all along: at the interface between odorant molecules and the receptor. They performed clean chemical deuterations of the three major classes of isotopomers used in previous work, acetophenone, benzaldehyde, and musks, for a total of over 15 different stimulus pairs. Taking advantage of recent advances in functional expression and deorphanization of ORs, they systematically screened 330 human receptors to identify a single receptor, OR5AN1, strongly activated by cyclopentadecanone and related ligand profiles and challenged them with many deuterated and nondeuterated isotopomer pairs. Again, no receptor was found that discriminates between isotopomers. The paper closes with a reexamination of the theoretical grounds supporting the vibration theory of olfaction (13), and finds them unrealistic in a biological milieu.

Precisely because this elegant and systematic study finds no evidence for the spectral theory, it suffers from the inevitable problem of being a series of persuasive negative results. Even having shown that the ORs profiled here are not the theoretical ones that can discriminate isotopomers, the authors cannot exclude the possibility that such an OR would eventually be found. Moreover, all of the work was carried out in tissue culture cells, not in native olfactory sensory neurons. Although such experiments are the gold standard for studying ligand–receptor interactions of all other G protein-coupled receptors, it is possible that heterologous expression does not reproduce the exact conditions in which the OR finds itself in the nasal epithelium. Perhaps the proposed inelastic electron tunneling mechanism fails to operate outside the nose. The ball is now in the court of the believers of the spectral theory, who need to produce experimental and not theoretical evidence that such problems are actually occurring in these experiments.

Why Should Odorant Receptors Be Exceptional? The paper by Block et al. (7) brings the field to an interesting juncture. Is this negative evidence sufficiently persuasive to lay the theory to rest, or should the screening of ORs and isotopomers continue until the absence of evidence passes the standard of reasonable doubt that would condemn the spectral theory? One interesting feature of the vibration theory is its exceptionalism. Vertebrate ORs are structurally and functionally related to the G protein-coupled receptor superfamily that senses hormones, neurotransmitters,

Author contributions: L.B.V. wrote the paper.
Conflict of interest statement: The author is a member of the Scientific Advisory Board of International Flavors & Fragrances, Inc.

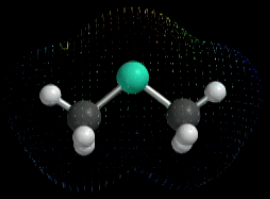
smell: a little anatomy



Source: EMBO reports (2007) 8, 629 - 633 doi:10.1038/sj.embor.7401029

odorants

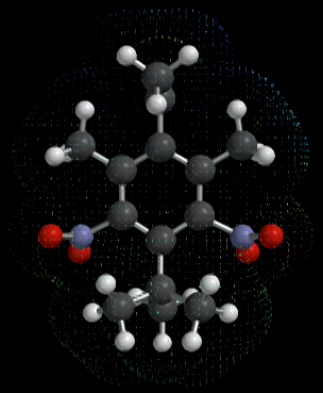
small



dimethyl sulfide

lasts for seconds

big



musk ketone

lasts for weeks

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Combinatorial Receptor Codes for Odors

Bettina Malnic,* Junzo Hirono,† Takaaki Sato,†‡
and Linda B. Buck*‡

odorants \ ORs	S 1	S 3	S 6	S 18	S 19	S 25	S 41	S 46	S 50	S 51	S 79	S 83	S 85	S 86
butanoic acid														
pentanoic acid														
hexanoic acid					●									
heptanoic acid	●			●	10		●c			●	●			
octanoic acid	●			●	10		●c	●		10	●	10		
nonanoic acid	10			10	1		●c	10		10		1		10
pentanol	a	●	a					b						
hexanol	b	●	a			●		b						
heptanol	b	●			●	●		b						
octanol	b			●	10		●c	b		●				
nonanol	b			●	1		●c	b		10		1		
bromobutanoic acid													●c	
bromopentanoic acid													●c	
bromohexanoic acid					●		●c						1	
bromooctanoic acid	10			●	1		●c	●		10		10	1	
hexanedioic acid													●c	
heptanedioic acid													●c	
octanedioic acid			●								●		●c	
nonanedioic acid			10d						10		1		●c	

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butanoic acid														
pentanoic acid														
hexanoic acid					●									
heptanoic acid	●			●	10		●c			●	●			
octanoic acid	●			●	10		●c	●		10	●	10		
nonanoic acid	10			10	1		●c	10		10		1		10
pentanol	a	●	a					b						
hexanol	b	●	a			●		b						
heptanol	b	●			●	●		b						
octanol	b			●	10		●c	b		●				
nonanol	b			●	1		●c	b		10		1		
bromobutanoic acid													●c	
bromopentanoic acid													●c	
bromohexanoic acid					●		●c						1	
bromooctanoic acid	10			●	1		●c	●		10		10	1	
hexanedioic acid													●c	
heptanedioic acid													●c	
octanedioic acid			●								●		●c	
nonanedioic acid			10d						10		1		●c	

$2^{400} \approx$ a lot

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1991

A Novel Multigene Family May Encode Odorant Receptors: A Molecular Basis for Odor Recognition

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New York, New York 10032

Summary

The mammalian olfactory system can recognize and discriminate a large number of different odorant molecules. The detection of chemically distinct odorants presumably results from the association of odorous ligands with specific receptors on olfactory sensory neurons. To address the problem of olfactory perception at a molecular level, we have cloned and characterized 18 different members of an extremely large multigene family that encodes seven transmembrane domain proteins whose expression is restricted to the olfactory epithelium. The members of this novel gene family are likely to encode a diverse family of odorant receptors.

Introduction

In vertebrate sensory systems, peripheral neurons respond to environmental stimuli and transmit these signals to higher sensory centers in the brain where they are processed to allow the discrimination of complex sensory information. The delineation of the peripheral mechanisms by which environmental stimuli are transduced into neural information can provide insight into the logic underlying sensory processing. Our understanding of color vision, for example, emerged only after the observation that the discrimination of hue results from the blending of information from only three classes of photoreceptors (Rushton, 1955, 1965; Wald et al., 1955; Nathans et al., 1986). The basic logic underlying olfactory sensory perception, however, has remained elusive. Mammals possess an olfactory system of enormous discriminatory power (for reviews see Lancet, 1986; Reed, 1990). Humans, for example, are thought to be capable of distinguishing among thousands of distinct odors. The specificity of odor recognition is emphasized by the observation that subtle alterations in the molecular structure of an odorant can lead to profound changes in perceived odor.

How are the diversity and specificity of olfactory perception accomplished? The detection of chemically distinct odorants presumably results from the association of odorous ligands with specific receptors on olfactory neurons, which reside in a specialized epithelium in the nose. Since these receptors have not been identified, it has been difficult to determine how odor discrimination might be achieved. It is possible that olfaction, by analogy with color vision, involves only a few odor receptors, each capable of interaction with multiple odorant molecules. Alternatively, the sense of smell may involve a large number of distinct receptors each capable of associating with one or a small number of odorants. In either case, the brain must distinguish which receptors or which neurons have been activated to allow the discrimination between different odorant stimuli. Insight into the mechanisms underlying olfactory perception is likely to depend upon the isolation of the odorant receptors and the characterization of their diversity, specificity, and patterns of expression.

The primary events in odor detection occur in a specialized olfactory neuroepithelium located in the posterior recesses of the nasal cavity. Three cell types dominate this epithelium (Figure 1A): the olfactory sensory neuron, the sustentacular or supporting cell, and the basal cell, which is a stem cell that generates olfactory neurons throughout life (Moulton and Beidler, 1967; Graziadei and Monti Graziadei, 1979). The olfactory sensory neuron is bipolar; a dendritic process extends to the mucosal surface, where it gives rise to a number of specialized cilia that provide an extensive, receptive surface for the interaction of odors with the cell. The olfactory neuron also gives rise to an axon that projects to the olfactory bulb of the brain, the first relay in the olfactory system. The axons of the olfactory bulb neurons, in turn, project to subcortical and cortical regions where higher-level processing of olfactory information allows the discrimination of odors by the brain.

The initial events in odor discrimination are thought to involve the association of odors with specific receptors on the cilia of olfactory neurons. Selective removal of the cilia results in the loss of olfactory responses (Bronshtein and Minor, 1977). Moreover, in fish, whose olfactory system senses amino acids as odors, the specific binding of amino acids to isolated cilia has been demonstrated (Rhein and Cagan, 1980, 1983). The cilia are also the site of olfactory signal transduction. Exposure of isolated cilia from rat olfactory epithelium to numerous odorants leads to the rapid stimulation of adenylyl cyclase and elevations in cyclic AMP (an elevation in inositol trisphosphate in response to one odorant has also been observed) (Pace et al., 1985; Sklar et al., 1986; Breer et al., 1990; Boekhoff et al., 1990). The activation of adenylyl cyclase is dependent on the presence of GTP and is therefore likely to be mediated by receptor-coupled GTP-binding proteins (G proteins) (Jones and Reed, 1989). Elevations in cyclic AMP, in turn, are thought to elicit depolarization of olfactory neurons by direct activation of a cyclic nucleotide–gated, cation-permeable channel (Nakamura and Gold, 1987; Dhallan et al., 1990). This channel is opened upon binding of cyclic nucleotides to its cytoplasmic domain, and can therefore transduce changes in intracellular levels of cyclic AMP into alterations in the membrane potential.

These observations suggest a pathway for olfactory signal transduction (Figure 1B) in which the binding of odors to specific surface receptors activates specific G proteins. The G proteins then initiate a cascade of intracellular signaling events leading to the generation of an action potential that is propagated along the olfactory sensory axon

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A Novel Multigene Family May Encode Odorant Receptors: A Molecular Basis for Odor Recognition

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2006

C. S. Sell

DOI: 10.1002/anie.200600782

Structure–Odor Relationships

On the Unpredictability of Odor

*C. S. Sell**

Keywords:
fragrances · olfaction · receptors · structure–activity relationships

The relationship between molecular structure and odor has fascinated and puzzled chemists for more than a century. Despite a great deal of research on structure–odor relationships, prediction of the odor of a novel molecule remains a statistical exercise and models only provide a probability of the character, threshold, and intensity. Surprises are still commonplace, and serendipity continues to be an important factor in the discovery of novel fragrant molecules. Recent advances in our understanding of the mechanism of olfaction provide an explanation for this and suggest that our ability to predict odor properties of molecules will not improve significantly in the near future.

1. Introduction

The search to correlate the molecular structure and the odor character of a chemical compound has a long recorded history. In ancient Greece, the proponents of Democritus' atomic theory proposed that the atoms of sweet-smelling substances had smooth surfaces whereas those of acidic materials had sharp points that pricked and irritated the nose. Since the development of synthetic organic chemistry in the 19th century, chemists have sought a clearer understanding of the relationship between molecular structure and the odor of a molecule, largely with the intention to design novel molecules with desirable odor properties.

However, this search for understanding has proved to be a very difficult task. There are many puzzling observations that often have no simple or obvious explanation. For example, on one hand, quite different molecules can have similar odors, whereas, on the other hand, similar molecules can have dissimilar odors. Thus, despite the significant differences in their structures, muscone (**1**),[1] musk ketone (**2**),[2] Traseolide (**3**),[3] and Helvetolide (**4**)[4] all have similar musk odors (Figure 1), whereas the two very similar structures **5** and **6** have very different organoleptic properties: **5** has an intense urinous character while **6** is odorless.[5]

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Sometimes, the functional group present in an odorant is all-important. For example, the ester group is often associated with a fruity character.[6] Thus, both Fruitate (**7**)[7] and Manzanate (**8**)[8] have distinctly fruity odors despite the differences in size and structural complexity between them (Figure 2). However, in other cases, the functional group seems unimportant: for example, structures **9**–**12** all have camphoraceous odors.[8]

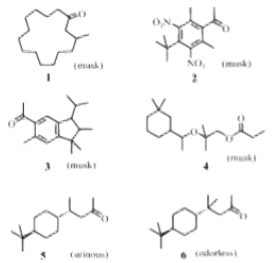
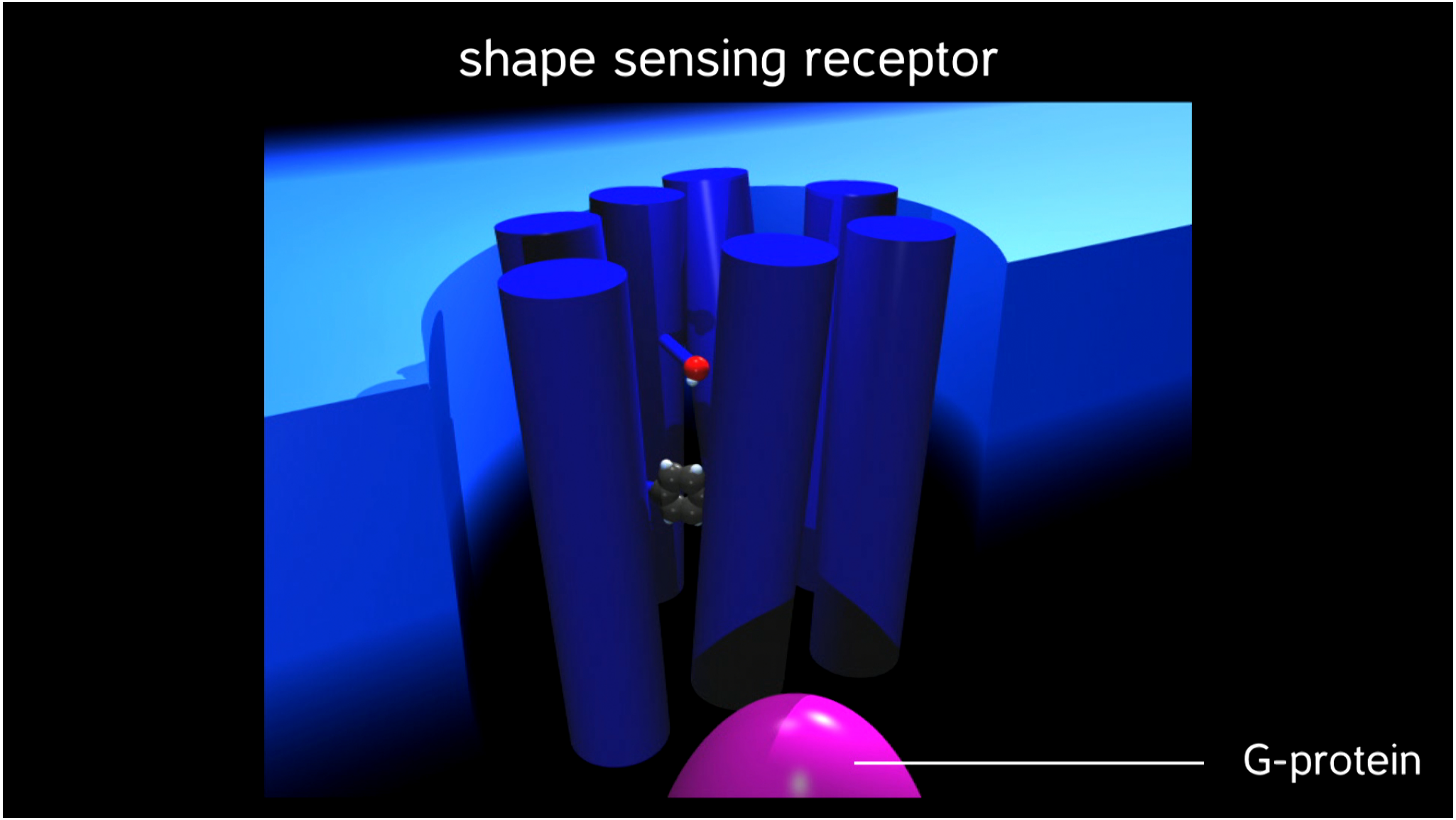
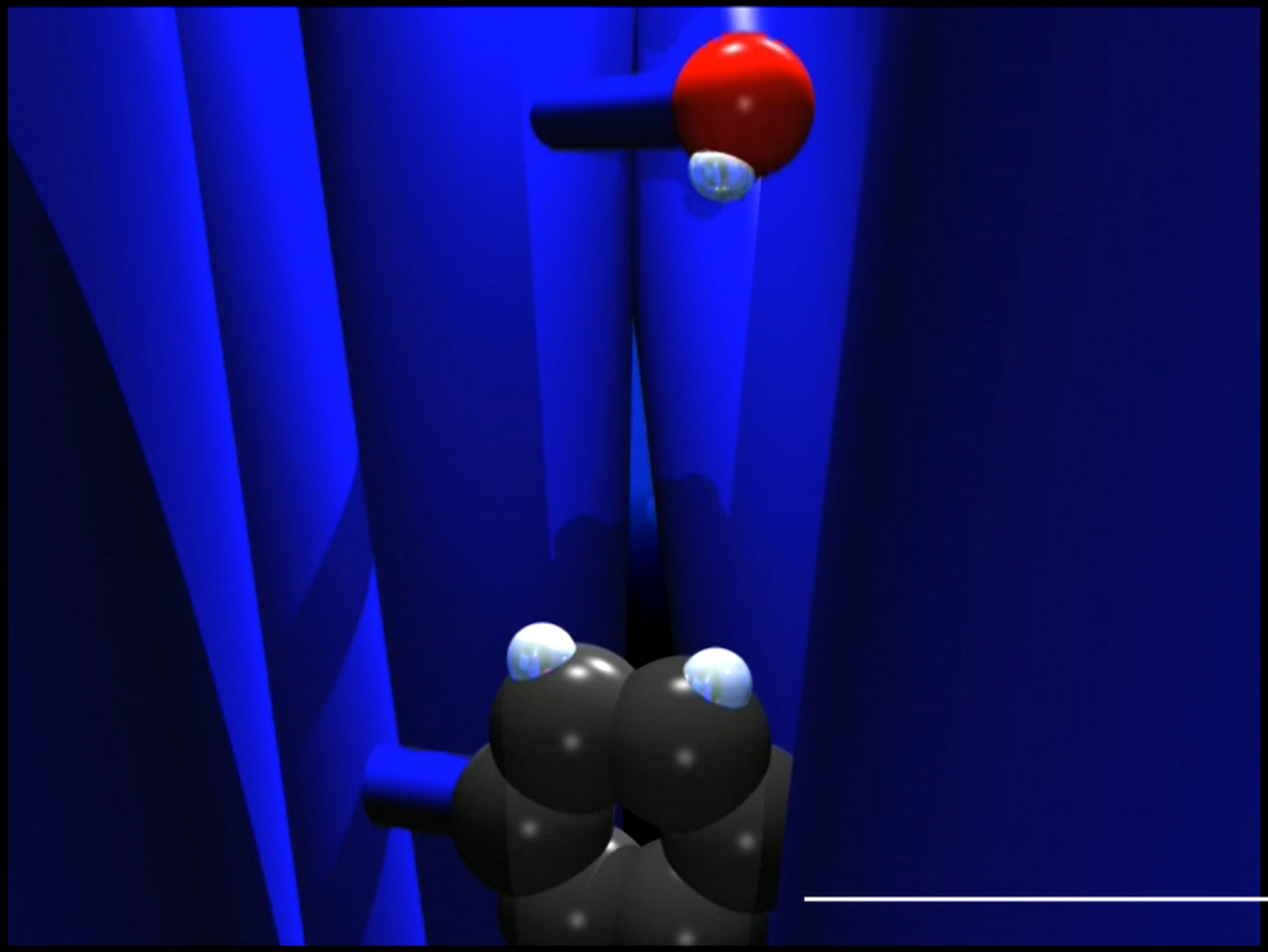


Figure 1. Different molecules, similar odors, and vice versa.

In many instances factors such as these can be brought together in triads, where the odd molecule out in structural terms is *not* the odd one out in odor. For example, of the structures **13**–**15** the last, **15**, is the odd one out in chemical terms as it is an alicyclic alcohol, whereas the other two, namely **13** and **14**, are both cinnamaldehyde derivatives (Figure 3). However, in terms of odor, it is α-methylcinna-


shape sensing receptor
G-protein

shape sensing receptor



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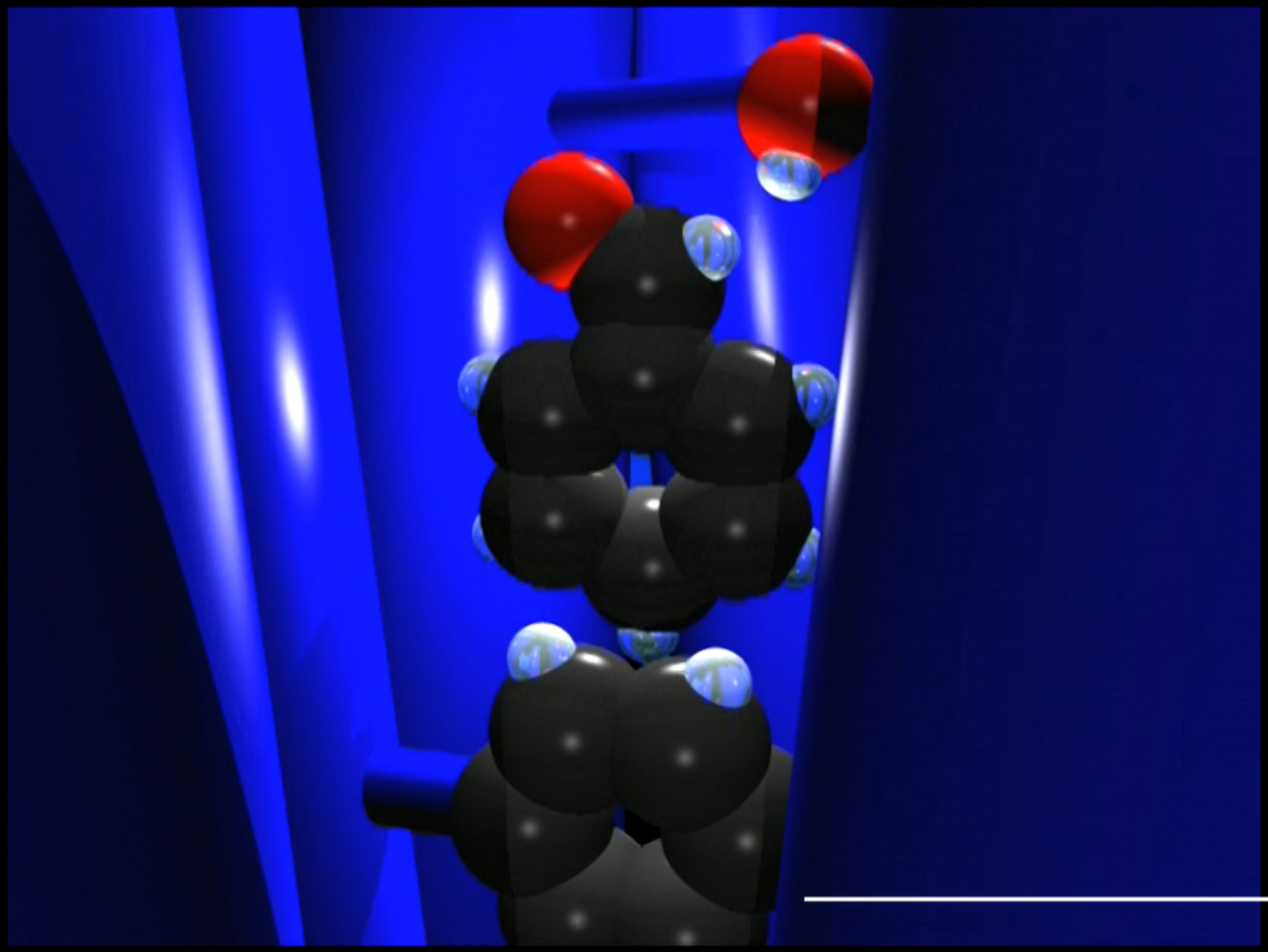
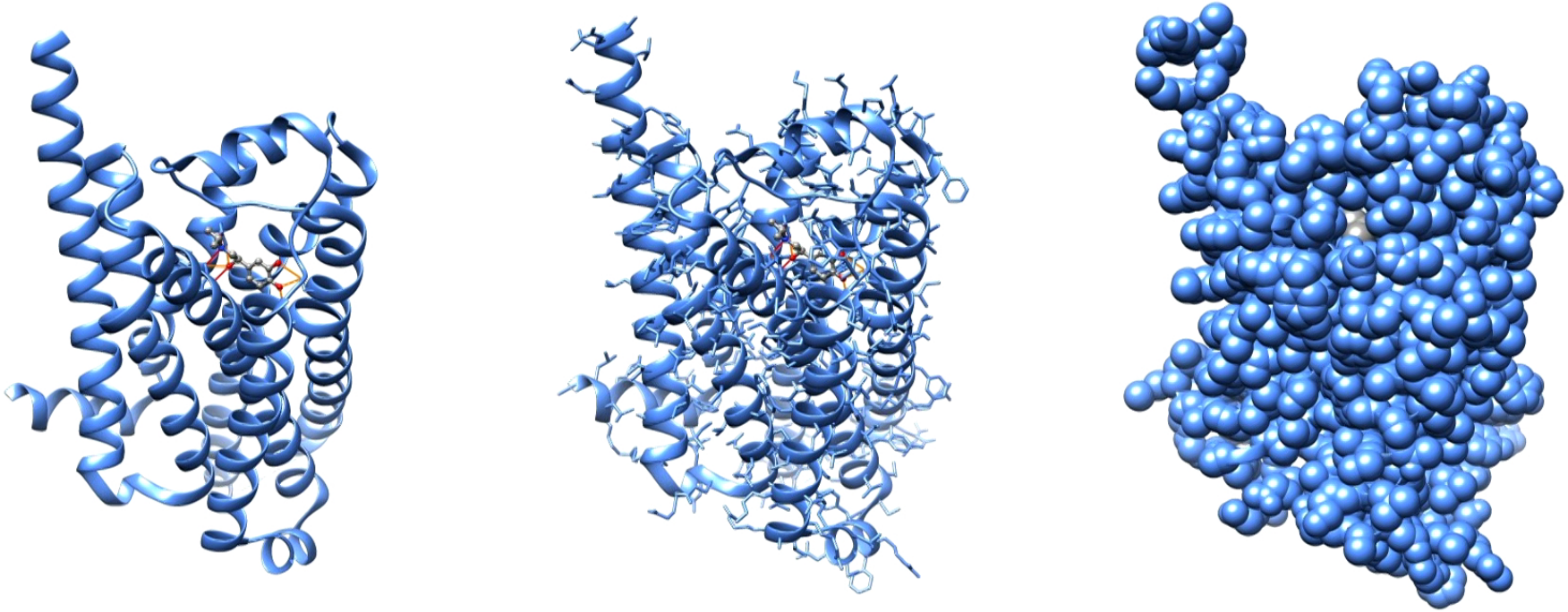
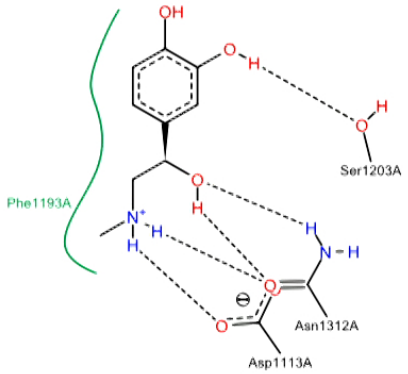


the beta-adrenergic receptor in various states of undress



sticky vs slippery ligands



noradrenalin in
beta-adrenergic receptor

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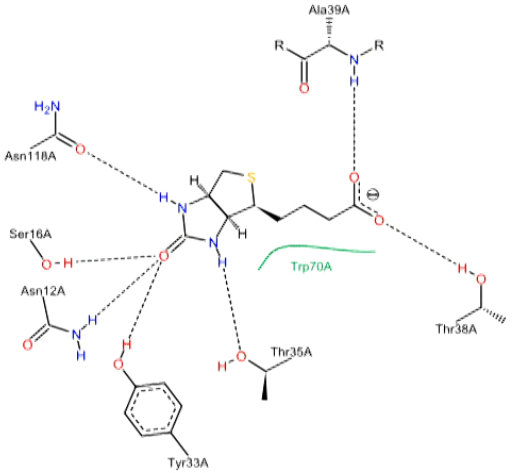
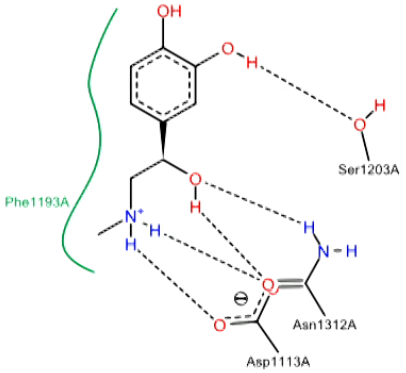
sticky vs slippery ligands



norbiotin in avidin



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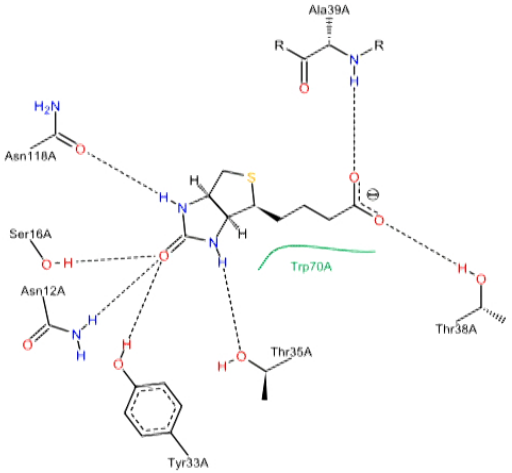

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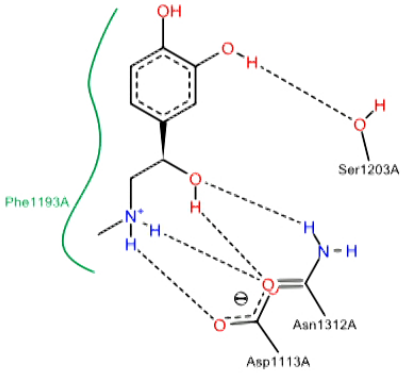

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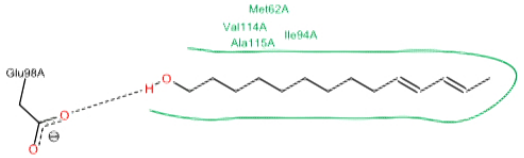

(10E,12Z)-tetradecadien-1-ol in
odorant binding protein

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then how is it that can we smell functional groups ?

Olfactory Theories and the Odors of Small Molecules

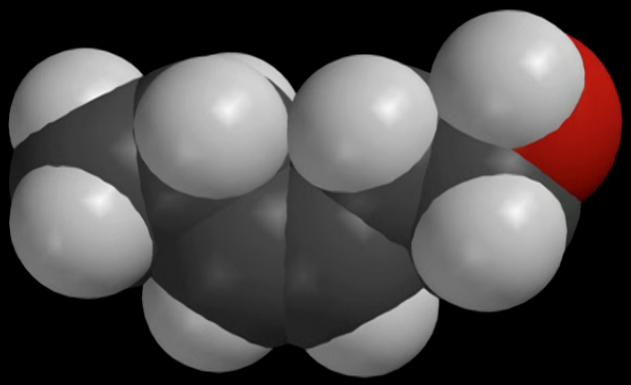
Hein L. Klopping

Industrial and Biochemicals Department, E.I. du Pont de Nemours & Co., Inc., Experimental Station, Wilmington, Delaware 19898

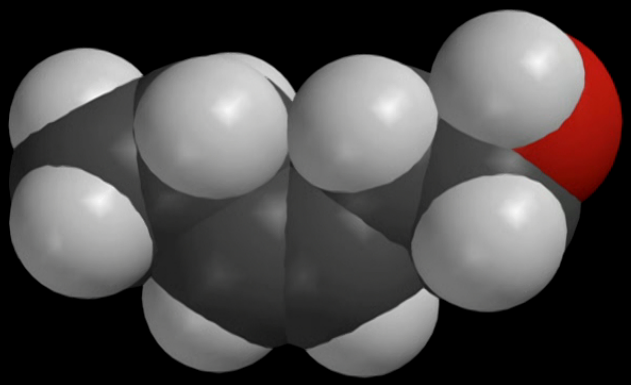
J. AGR. FOOD CHEM., VOL. 19, NO. 5, 1971

Table I. Monosubstituted Methane Odorants

Structure	Odor	Reference
CH_3-H	Odorless	
CH_3-Cl	Ethereal, nonirritating	Kirk-Othmer (1947)
CH_3-Br	Virtually odorless	Kirk-Othmer (1947)
CH_3-I	Pungent	Kirk-Othmer (1947)
CH_3-OH	Characteristic, pungent	Kirk-Othmer (1947)
CH_3-SH	Highly disagreeable	Kirk-Othmer (1947)
CH_3-SeH	Vile	Rodd (1951)
CH_3-TeH	Vile	Rodd (1951)
CH_3-NH_2	Characteristic, like NH_3	Kirk-Othmer (1947)
CH_3-PH_2	Characteristic, like PH_3 (stinking fish and garlic)	Kosolapoff (1950); Mellor (1929)
CH_3-AsH_2	Characteristic, like AsH_3 (garlic or rotten cabbage)	Rochow *et al.* (1957)
CH_3-NO_2	Pleasant	Kirk-Othmer (1947)
CH_3-CN	Pleasant, ethereal	Kirk-Othmer (1947)
CH_3-NC	Extraordinarily vile	Kirk-Othmer (1947)
CH_3-NCS	Characteristic (mustard)	Houben-Weyl (1955)
CH_3-HCO	Pungent, suffocating; somewhat fruity and pleasant in dilute solutions	Kirk-Othmer (1947)



cis-3-hexenol



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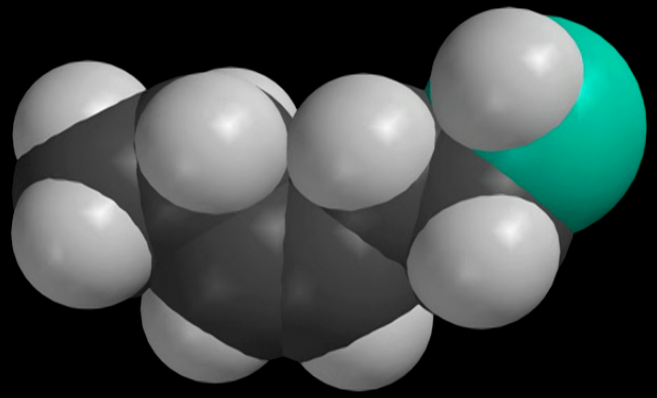
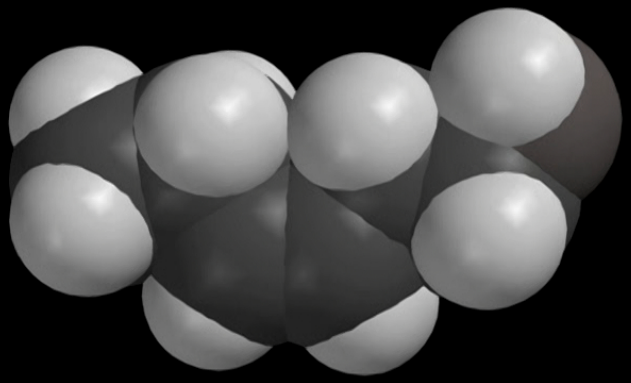


cis-3-hexenethiol

cut grass vs. rotten eggs



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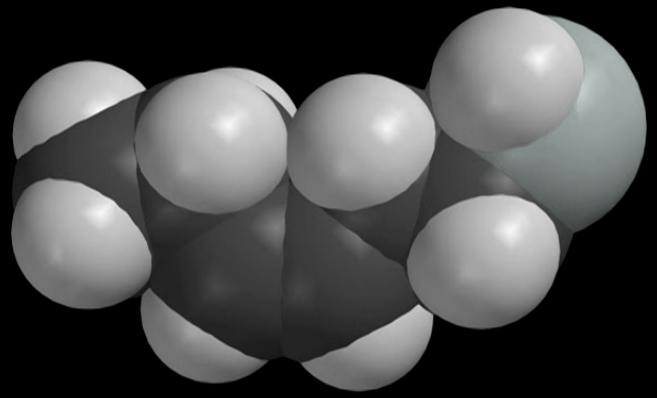
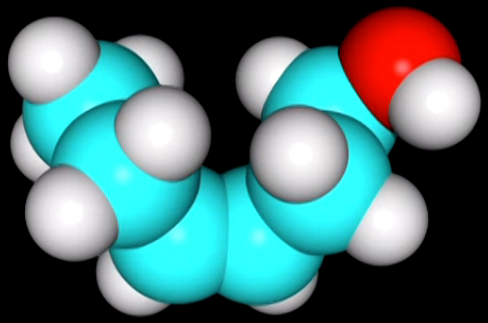


cis-3-hexenethiol

molecular dynamics in water @ 300K



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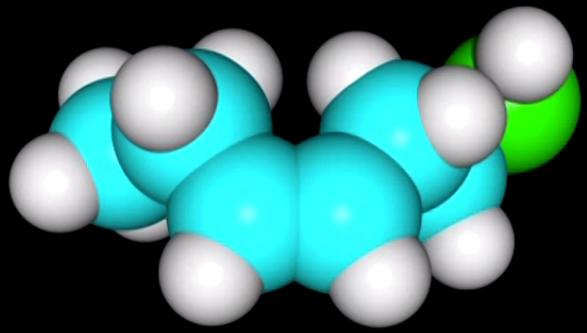

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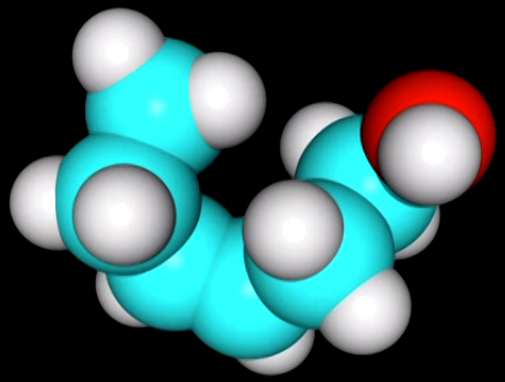

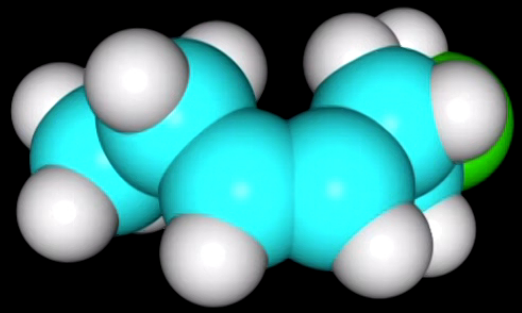

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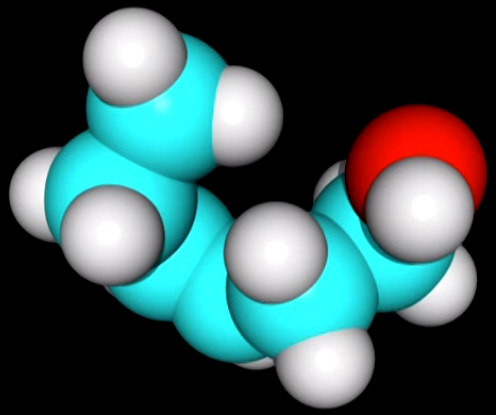

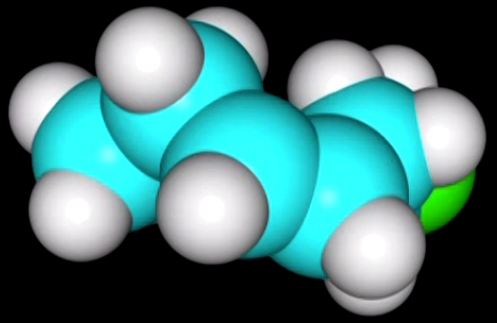

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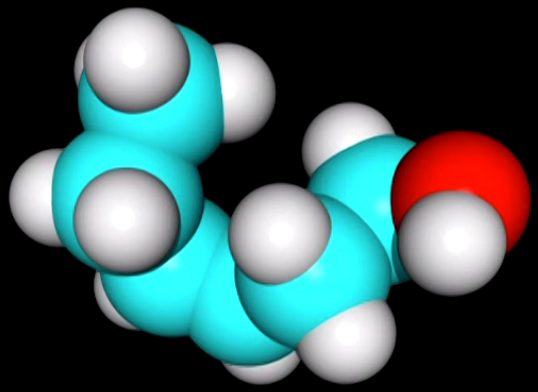

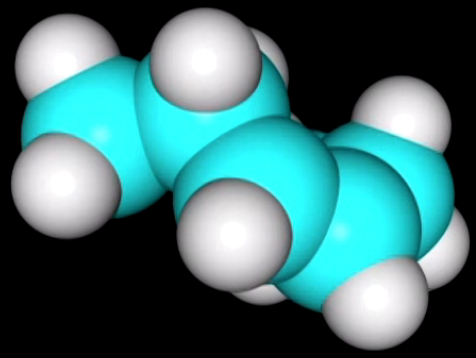

cis-3-hexenol

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ANOSMIA;

OR,

CASES ILLUSTRATING THE PHYSIOLOGY AND PATHOLOGY

OF THE

SENSE OF SMELL.

BY

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ASSISTANT-PHYSICIAN TO, AND LECTURER ON PHYSIOLOGY AT, ST. GEORGE'S HOSPITAL.

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THE SCIENTIFIC BASIS OF ODOUR

By DR. G. MALCOLM DYSON, F.I.C.

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(Paper read on behalf of Dr. Dyson before the London Section of the Society on March 7, 1938)

My problem tonight concerns the scientific basis of odour and for convenience the matter may be divided into the following sections:

1. The physiological basis of odour-perception.
2. The physical basis of the osmic stimulus.

I propose to deal in detail more with the latter section, but it will not, perhaps, be out of place to complete the picture as far as possible by a short description of the means by which smells are perceived.

The part of the nose associated with the perception of smell consists of a layer of cells, long and narrow, which are arranged with their length perpendicular to the plane of the nasal cavity. These cells are of two kinds, the sustentacular cells, the outer end of which is broad and blunt; these serve to support the more delicate olfactory cells associated with the actual process of perception. The olfactory cells are pigmented, the inner end being connected to the nervous system, the outer end being freely exposed to the air in the nostrils. This free end terminates in a small clear projection which passes through the cuticular membrane and is furnished with a number of stiff hair-like projections. These are kept moist by the mucus secretion of the nose, without which perception would be almost impossible. It may be added that the olfactory hairlets just described, are less prominent in man than in other animals, and appear to be most strongly developed in the amphibia.

pare; the lower ends of the taste cells are connected through the nervous system to the brain. Each taste-bud presents the picture of an almost spherical group of cells, the hairlets at the top coming together to project into the gustatory pore, the lower ends being collected together into a nerve fibre.

Certain substances have, even at ordinary temperatures, a tendency to evaporate, whilst others are comparatively permanent; the former part with their component molecules which pass off into the air, whilst the molecules of the latter have no tendency to pass off in this way. Camphor and turpentine are good examples of the former class, iron and glass of the latter; the former, tending to evaporate, show a vapour pressure, and the latter have either no vapour pressure or one which is insignificantly small. To be odorous, a substance must have a perceptible vapour pressure. It is, therefore, the invisible wandering particles of a substance which come to rest inside the nose, and having, so to speak, anchored themselves in the haven of the olfactory cells, proceed to stimulate the latter in their own peculiar way. The amount of material required before a sensation is registered at the olfactory cells is incredibly small, or incredibly large, according to the standard of measurement! It is almost unweighable; Newton exposed a grain or two of musk to the air of his study and observed that, after several years, it had not altered appreciably in weight, although it had perfumed the

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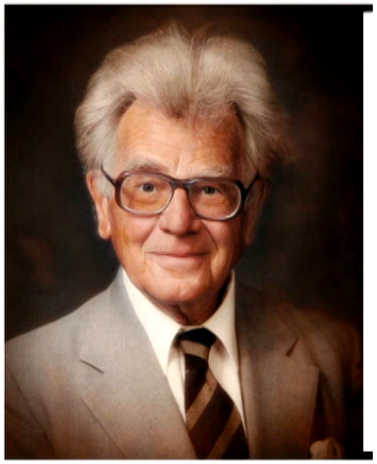

ODOR AND MOLECULAR VIBRATION: THE FAR INFRARED SPECTRA OF SOME PERFUME CHEMICALS

Robert Hamilton Wright

British Columbia Research Council, Vancouver, Canada

Introduction

The basic assumption of the vibrational theory is that the molecular quality which we perceive as odor lies in certain vibrational movements of the odorous molecules.[1] Such things as volatility, water- or lipid-solubility, adsorbability, and so on may affect the *strength* of an odor, but its essential *quality* will depend on what vibrational frequencies are present and in what relative proportions in any given assemblage of molecules. The shape or profile of a particular molecule may, however, help to determine which of the molecule's vibrational modes is most effective in triggering a sensation.

This working hypothesis can be considered quite separately from any particular theory of the process whereby the vibrations may initiate an olfactory sensation. For example, if the "olfactory pigment" should turn out to be unconnected with the triggering mechanism, it would not invalidate the vibrational hypothesis.

However, the vibrational theory does presuppose some kind of direct interaction between the vibration of the odorous molecules and the receptor organs. It is necessary to mention this because it has been suggested, for example, that the vibrational theory requires that we should perceive an odor if infrared light

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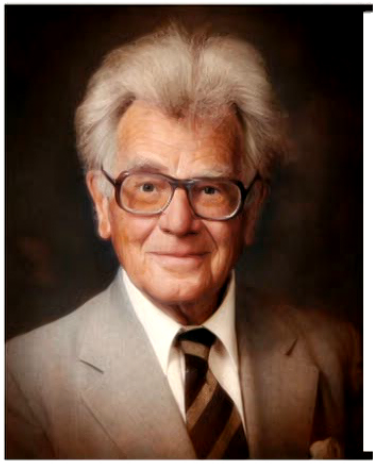

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 0030-0950/84/0003-0085 $2.00/0

DETERMINING THE ACTIVE COMPONENT IN 1,3,3-TRIMETHYL-2-OXABICYCLO [2,2,2] OCTANE (CINEOLE) THAT REPELS THE AMERICAN COCKROACH, *PERIPLANETA AMERICANA*[1]

RORY SCRIVEN and CLIFTON E. MELOAN, Department of Chemistry, Kansas State University, Manhattan, KS 66506

ABSTRACT. The compound 1,3,3-trimethyl-2-oxabicyclo [2,2,2] octane, more commonly known as cineole or eucalyptol, present in bay leaves, is a natural repellent to the American cockroach, *Periplaneta americana* L. It was found that the isopropyl-oxygen-isopropyl fragment of the compound is the smallest effective portion, and that the cyclohexane plus oxygen subgroup has the greatest effectiveness.

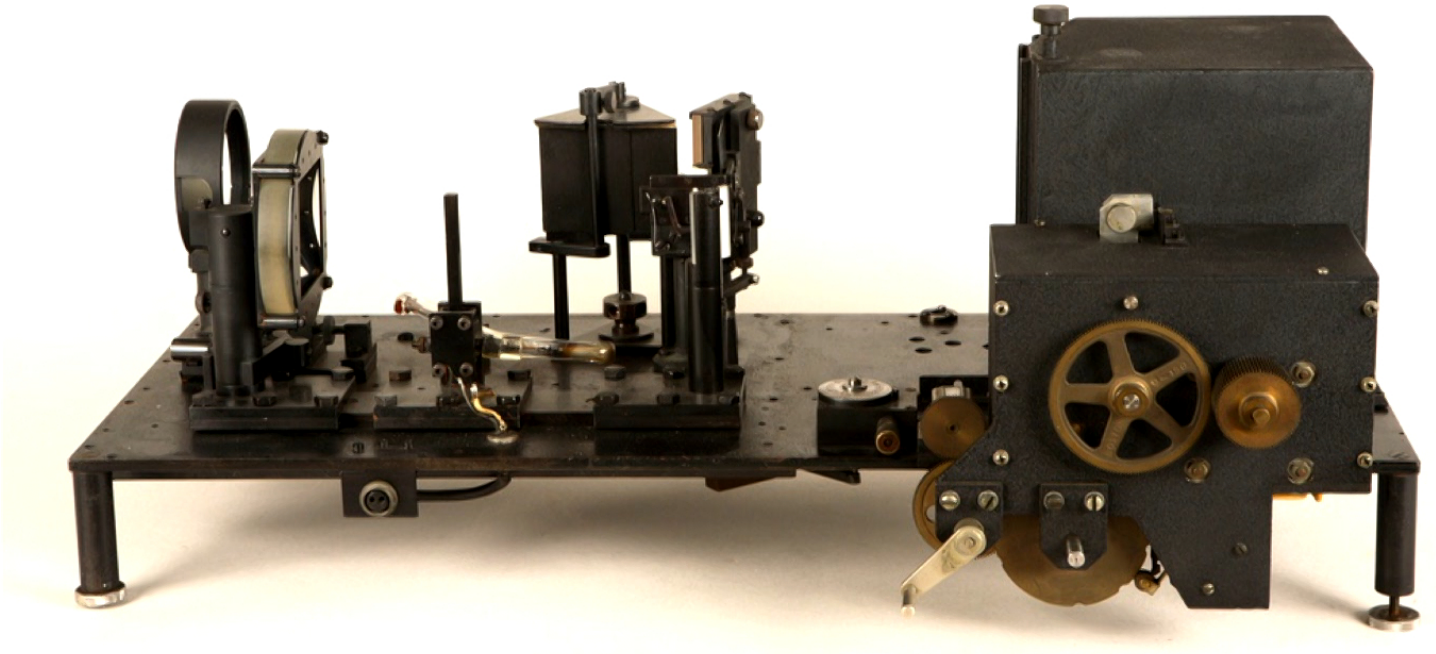
OHIO J. SCI. 84 (3): 85-88, 1984

INTRODUCTION

Work by Verma and Meloan (1981) isolated 6 compounds from the bay leaf (cineole, geraniol, linalool, alpha phellandrene, piperazine and phenyl hydrazine) that repelled the American cockroach (*Periplaneta americana*, Linneus), to various degrees. Of those compounds, clearly the most effective was 1,3,3-trimethyl-2-oxabicyclo [2,2,2] octane (cineole). The structure and numbering system of this compound is shown in fig. 1. If this compound is to be used to help understand the basic mechanism of the olfactory process then it is important to know if the entire molecule is needed for the repellent effect. It was the purpose of this project to determine if smaller portions of the molecule could be effective. It was found only a small portion of the molecule was necessary for activation in previous work (Scriven and Meloan 1984), and therefore it was

[1]Manuscript received 28 July 1983 and in revised form 16 March 1984 (#83-27)

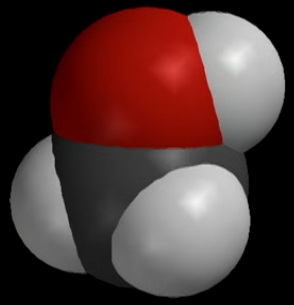
the main problem with vibration theories of smell



Prototype for the Perkin-Elmer Model 12 Infrared Spectrophotometer www.chemheritage.org

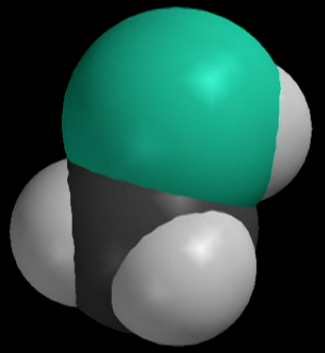
hooch vs. rotten eggs

methyl alcohol



3643 wavenumbers
364 Hz

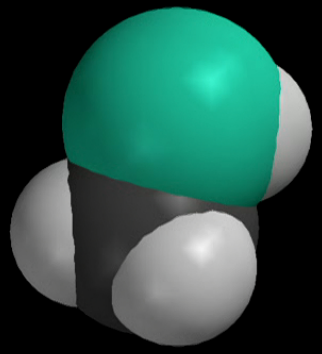
methyl sulfide



2650 wavenumbers
265 Hz

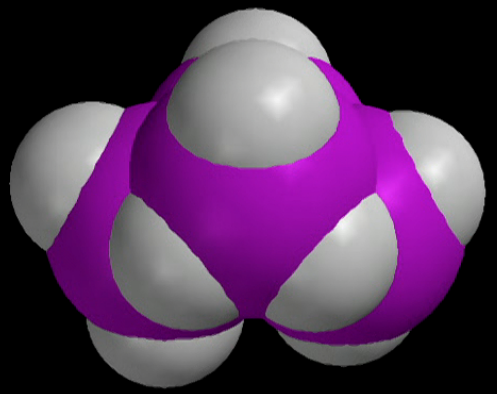
rotten eggs vs. rocket fuel

methyl sulfide



2650 wavenumbers
265 Hz

tetraborane



2668 wavenumbers
267 Hz

the odor of boranes

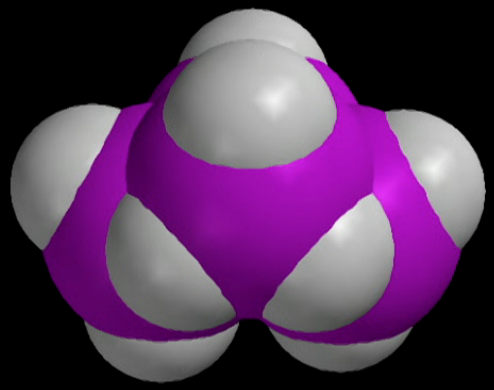
Alfred Stock, 1912

Borwasserstoffe
Alfred Stock, Carl Massenez

Berichte der deutschen chemischen Gesellschaft
Volume 45, Issue 3, pages 3539–3568,
Oktober–Dezember 1912

B_6H_{12} ist eine farblose, an der Luft sofort Feuer fangende Flüssigkeit von höchst widerlichem Geruch, der demjenigen des B_4H_{10} ähnelt, aber zugleich etwas an Schwefelwasserstoff erinnert.

2668 wavenumbers
267 Hz



tetraborane

Easily realized inelastic electron tunneling spectrometer

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Department of Physics, University of Akron, Akron, Ohio 44325-4001

(Received 5 October 1992; accepted for publication 19 November 1992)

An easily realized inelastic electron tunneling spectrometer (IETS) controlled by computer through an IEEE-488 interface bus is described. Components and circuits of the system are described in detail in order to help newcomers to IETS build a research quality spectrometer on a relatively low budget. The system design is much simpler and easier to implement than others reported in the literature, and experimental results indicate that the spectrometer has comparable resolution and signal-to-noise ratio. Additionally, in-house software routines offer the system considerable flexibility in spectral data manipulation, for example, background correction, numerical differentiation, and subtraction of one spectrum from another may be performed.

I. INTRODUCTION

Inelastic electron tunneling spectroscopy (IETS), discovered in 1966 by Jacklevic and Lambe,[1] is a very sensitive spectroscopic technique which can be used for the study of various compounds, and complexes of adsorbates, at the interfaces of metal/insulator/metal tunnel junctions by the observation of vibrational and electronic spectra. In fact, IETS has been very successful in the area of adhesion, biological molecules and polymers, catalysis, corrosion and lubrication.

Various kinds of IET spectrometer have been described in the literature.[2–6] However, for new workers in the field, these may appear to be rather complicated. The purpose of this paper is to provide a simpler and less expensive design for IETS beginners. We have developed a system which consists primarily of off-the-shelf components, and a relatively simple in-house built analogue circuit; the cost of the entire system is under $10 000. We will present spectra obtained from benzoic acid adsorbed on alumina (at approximately monolayer coverage) which demonstrate that the spectrometer is of research quality.

The components of the system and circuit details are described herein, and a flowchart of the computer program is also provided.

II. EXPERIMENT

A. Basic principles of IETS

The quantum mechanical phenomenon of electron tunneling through a potential barrier is used in IETS[7–10] to elicit information regarding the molecular nature of the insulating barrier. As shown in Figs. 1(a) and 1(b), by placing a sufficiently thin insulating layer (of the order of 1–3 nm thick) between two metal electrodes and applying a small voltage, V_0, across this structure the Fermi levels, E_{F1} and E_{F2}, of the two metals become offset by an amount eV_0, and electrons may tunnel through the potential barrier from filled states in metal 1 to empty states in metal 2.

Elastic tunneling is that accomplished without energy loss, shown in Fig. 1(b), which is the case for most electrons. When the voltage across the junction is sufficiently large, tunneling electrons may excite vibrational modes of the barrier material and lose a quantum of energy. In this case the condition $V \geq h\omega_0/e$ is satisfied, where $h\omega_0$ is the energy associated with a particular excited vibrational mode of the barrier. This inelastic tunneling process, which is the case for about 1% of electrons, provides another channel for current flow in addition to the elastic tunneling channel. An incremental change in the slope of the current-voltage (I-V) curve occurs at this voltage point which is shown schematically in Fig. 2(a) for a junction at 0 K, and a peak will appear on the second derivative of the I-V curve [see Fig. 2(c)]. Actual IETS peaks are broadened due to thermal smearing of the Fermi edge. An IET spectrum consists of a series of such peaks, each at a voltage corresponding to a particular vibrational mode of the barrier in question.

Experimentally, modulation techniques are often employed to obtain the derivatives of the I-V curve. Either the current or the voltage applied across the junction may be modulated because the line shapes of d^2V/dI^2 and d^2I/dV^2 versus the dc bias voltage are proportional through the relationship $d^2V/dI^2 = -(1/G^3)d^2I/dV^2$, where the dynamic conductance, $G = dI/dV$, is slowly varying over the desired voltage range. The current across the junction can be written as Taylor series expansion

$$\begin{aligned} I(V) &= I(V_0 + \delta\cos\omega t) \\ &= I(V_0) + (dI/dV)_{V_0}\delta\cos\omega t \\ &\quad + (1/2)(d^2I/dV^2)_{V_0}\delta^2\cos^2\omega t + \cdots \\ &= I(V_0) + (dI/dV)_{V_0}\delta\cos\omega t \\ &\quad + (1/4)(d^2I/dV^2)_{V_0}\delta^2[1+\cos(2\omega t)] + \cdots . \end{aligned} \tag{1}$$

MOLECULAR VIBRATION SPECTRA BY ELECTRON TUNNELING

R. C. Jaklevic and J. Lambe
Scientific Laboratory, Ford Motor Company, Dearborn, Michigan
(Received 18 October 1966)

The conductance of metal–metal oxide–metal tunneling junctions has been observed to increase at certain characteristic bias voltages. These voltages are identified with vibrational frequencies of molecules contained in the barrier.

In an experimental study of a number of metal-oxide-metal tunneling junctions a new phenomenon has been identified. Tunneling electrons are found to interact with vibrational states of molecules included at a metal-oxide interface. There are increases in the conductance G of the junction occurring at various characteristic voltages V. These voltages correspond to vibrational frequencies ν of molecules contained in the junction, i.e., $eV=h\nu$. These increases represent changes in G of about 1% and correspond to the onset of new tunneling channels paralleling the bulk of the tunneling current. The characteristic voltages occur when molecular impurities are introduced in the junction, usually after formation of the oxide insulating barrier and before deposition of the top metal film. Coverage is estimated to be of the order of one monolayer.

The majority of the junctions were Al–Al oxide–Pb. These were made entirely in an oil-free ultrahigh-vacuum system (10^{-9} Torr ultimate pressure) so equipped that air was not admitted to the system until all steps in fabrication were completed. These steps include an initial pumpdown and degassing of evaporation sources, a $\frac{1}{2}$-h cleanup in a high-purity O_2 discharge (5×10^{-2} Torr, 500 V), second pumpdown, and evaporation of the 2000-Å Al film. This film was oxidized to approximately 30 Å in the gas discharge with a one-volt potential.[1] At this point, when desired, the oxide was exposed to the vapor of an organic material. After a short pumpdown the Pb overlay cross strip was deposited (~1 μ thickness) and the junctions were removed. Nominal resistance ranged from 10 to 10^4 Ω. Measurements were made with the sample in a liquid-helium Dewar so that temperatures from 0.9 to 300°K were possible. The derivative $\Delta G/\Delta V$ was measured by a second-harmonic detection infrared (IR) region from 25 to 2.5 μ.

In Fig. 1 a number of recording traces of $\Delta G/\Delta V$ are reproduced. These were taken at 4.2°K. Each peak represents an increase of conductance of the Al–Al oxide–Pb junction. Not shown is the low-voltage region below 50 mV, where structure due to the Pb superconducting density of states was prominent. Curve A is for a junction fabricated without any deliberate addition of molecular impurities. This "clean" spectrum shows prominent peaks due to OH bending and stretching modes, respectively, as identified by comparison with IR spectra.[2] These possibly arise from OH groups present either chemically in the oxide, or as

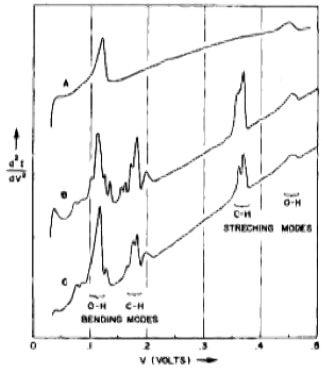

FIG. 1. Recorder traces of d^2I/dV^2 versus applied voltage for three Al–Al oxide–Pb junctions taken at 4.2°K. The zero of the vertical scale is shifted for each curve, and all three are normalized to the same arbitrary units. The largest peaks represent increases of 1% in G. Also indicated are intervals associated with the energy of IR-active molecular vibrational

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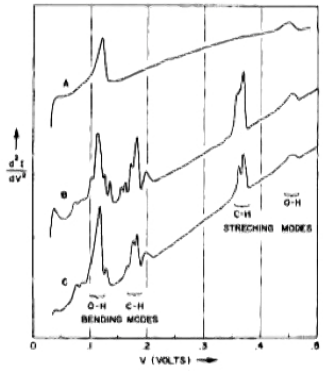

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ORIGINAL RESEARCH PAPER

A Spectroscopic Mechanism for Primary Olfactory Reception

Luca Turin

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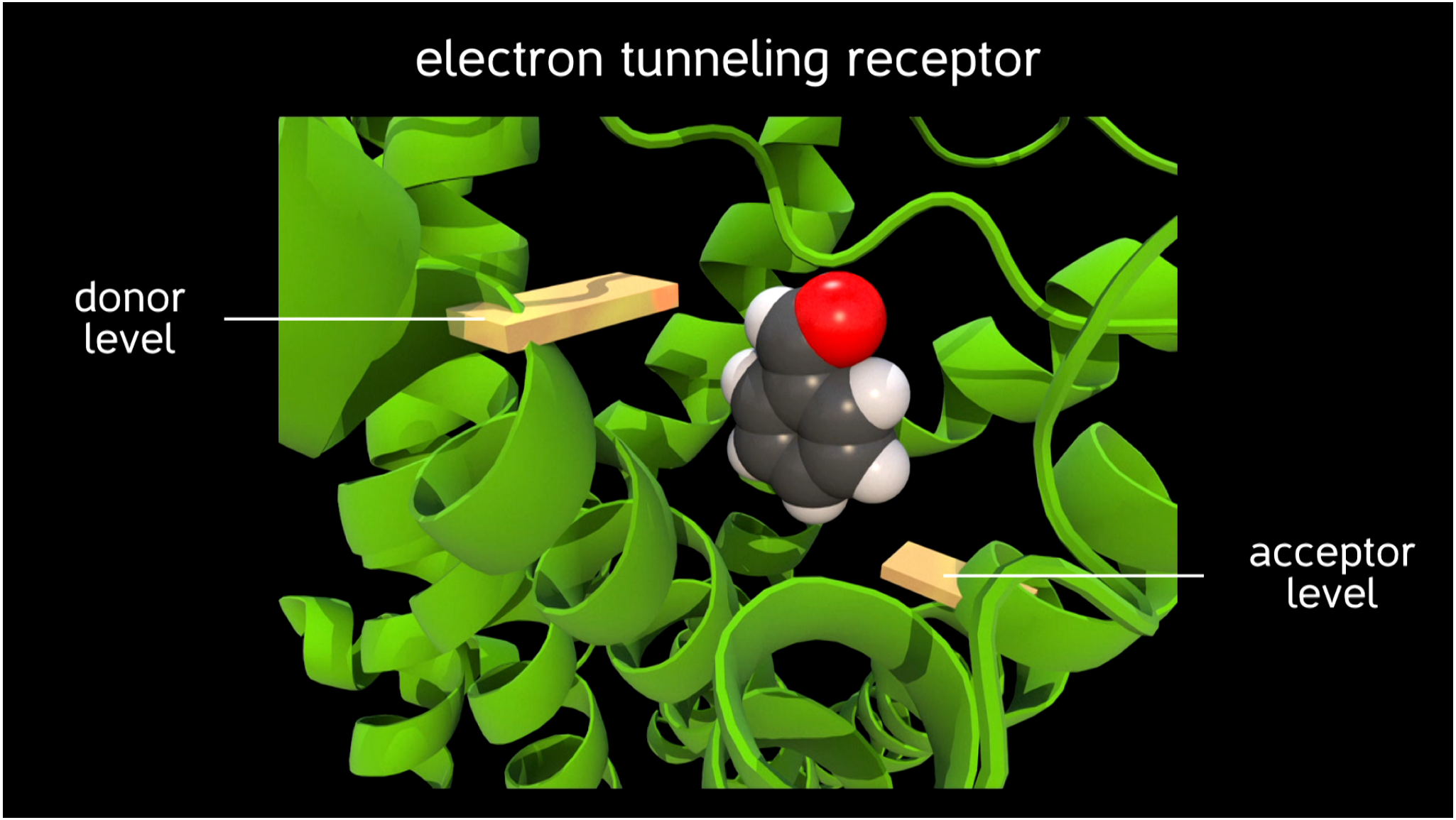
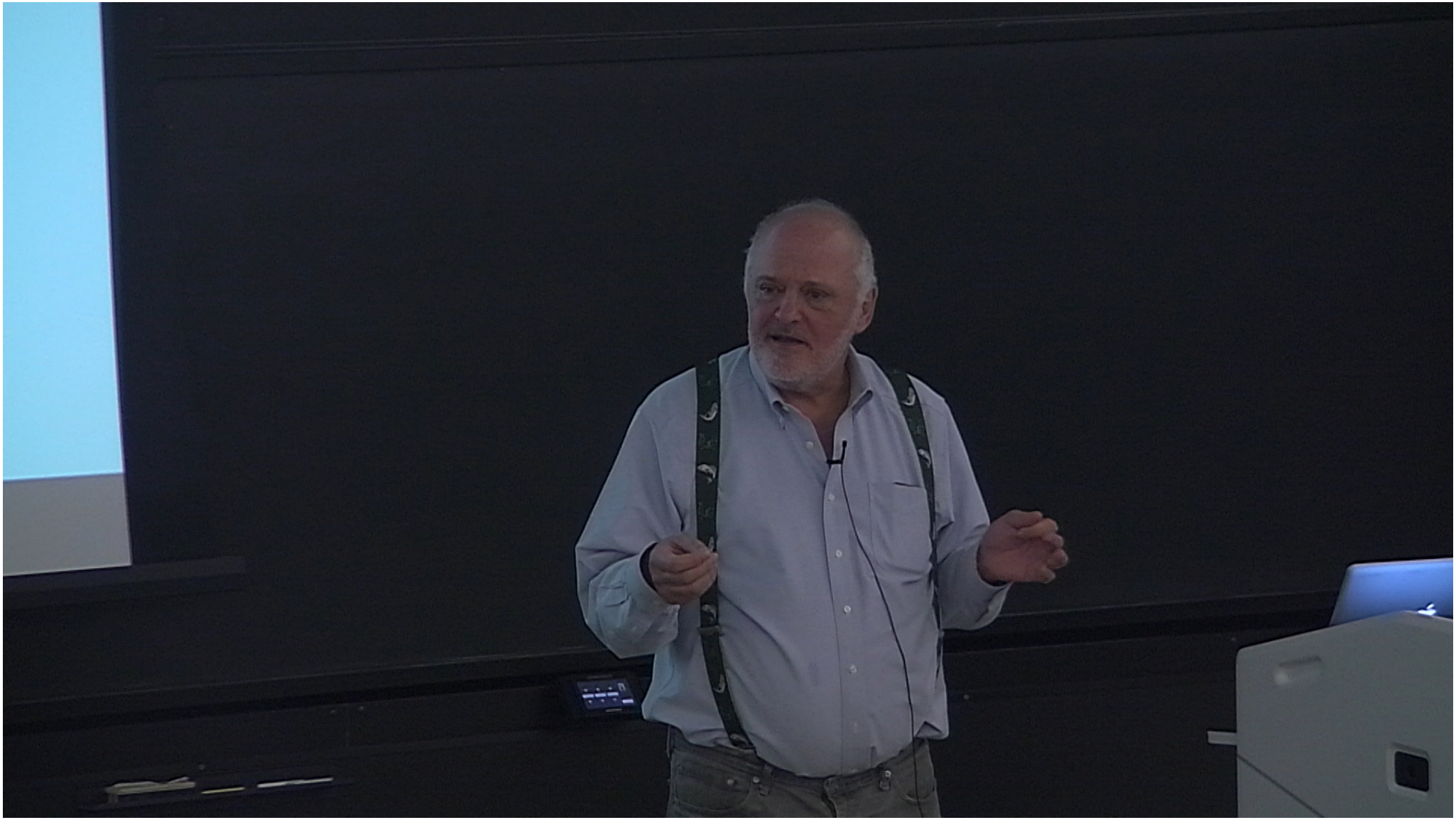
Abstract

A novel theory of primary olfactory reception is described. It proposes that olfactory receptors respond not to the shape of the molecules but to their vibrations. It differs from previous vibrational theories (Dyson, Wright) in providing a detailed and plausible mechanism for biological transduction of molecular vibrations: inelastic electron tunnelling. Elements of the tunnelling spectroscope are identified in putative olfactory receptors and their associated G-protein. Means of calculating electron tunnelling spectra of odorant molecules are described. Several examples are given of correlations between tunnelling spectrum and odour in structurally unrelated molecules. As predicted, molecules of very similar shape but differing in vibrations smell different. The most striking instance is that of pure acetophenone and its fully deuterated analogue acetophenone-d_8, which smell different despite being identical in structure. This fact cannot, it seems, be explained by structure-based theories of odour. The evidence presented here suggests instead that olfaction, like colour vision and hearing, is a spectral sense. **Chem. Senses 21: 773–791, 1996.**

Introduction

Putative olfactory receptors have been identified previously (Buck and Axel, 1991; Buck, 1993; Ngai *et al.*, 1993; Raming *et al.*, 1993). Signal transduction is known to involve a G-protein-coupled adenylate cyclase mechanism (for review see Shepherd, 1994). However, the mechanism by which receptors detect odorants, and thus the molecular basis of odour, remain unclear. As has been repeatedly pointed out, structure–odour relations provide conflicting evidence (Beets, 1971, 1978; Klopping, 1971; Ohloff, 1986; Weyerstahl, 1994). On the one hand, molecules of widely different structures can have similar odours, e.g. the bitter almond character, shared by as many as 75 molecules, including the triatomic molecule HCN. On the other hand, minor changes to the structure of a molecule can alter its smell character completely. For example, isomers such as vanillin (3-methoxy-4-hydroxy-benzaldehyde) and isovanillin (3-hydroxy-4-methoxybenz-aldehyde), and enantiomers such as R- and S-carvone smell very different (Arctander,


electron tunneling receptor
donor level
acceptor level

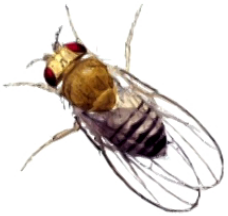


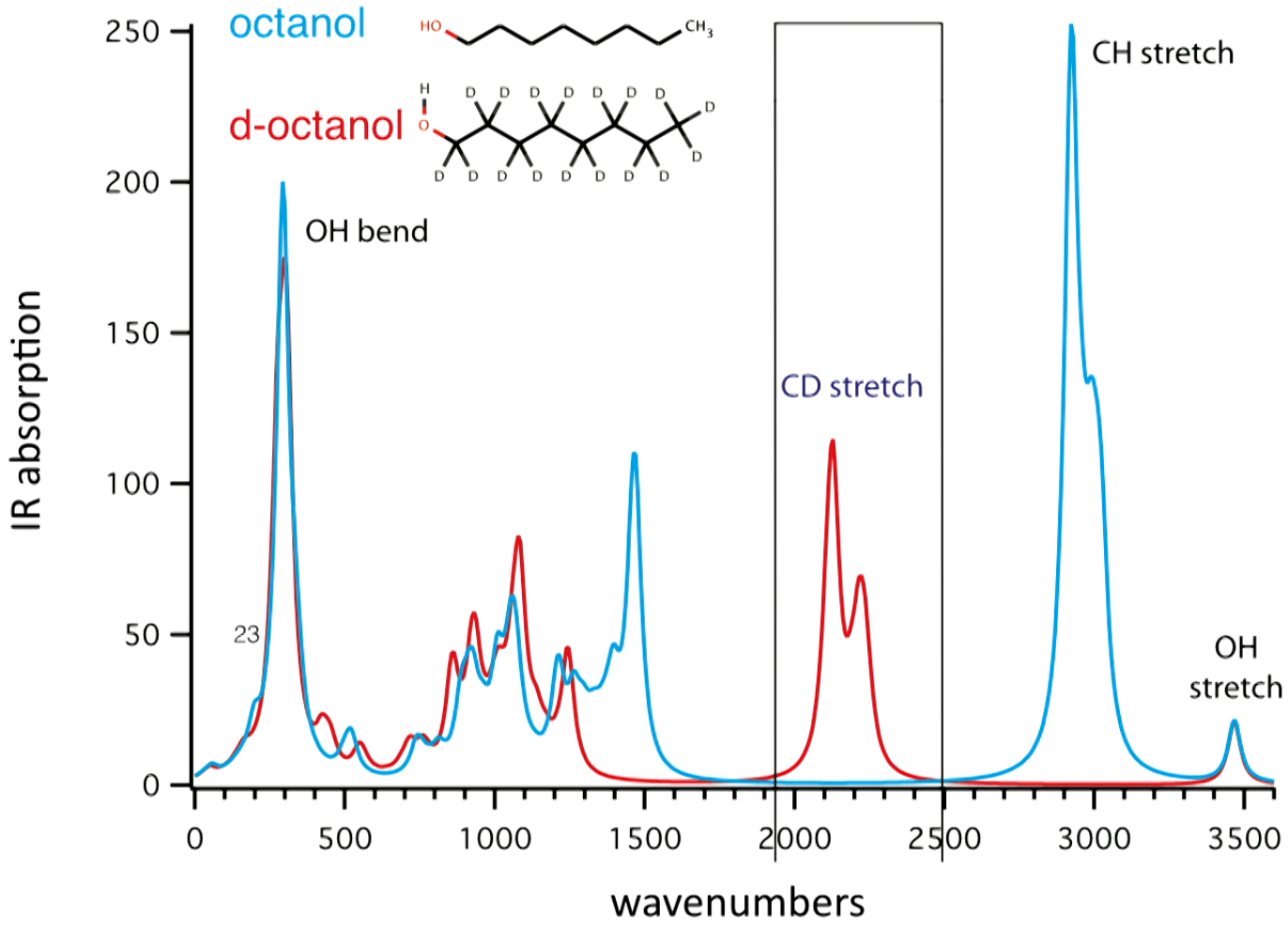
ALEXANDER FLEMING
Biomedical Sciences Research Center

E M C “Makis” Skoulakis

Why Drosophila is insanely great

- genome known: 14,000 genes
- most genes available as RNAi
- 7-day life cycle
- 75% match with human disease genes
- 100% sharing of mutants and constructs

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d-octanol
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CD stretch
CH stretch
OH
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1500
2000
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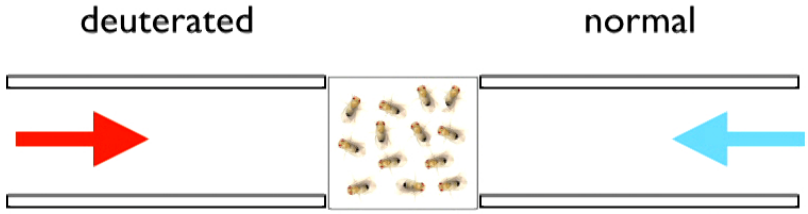
3000
3500

Drosophila behavior setup

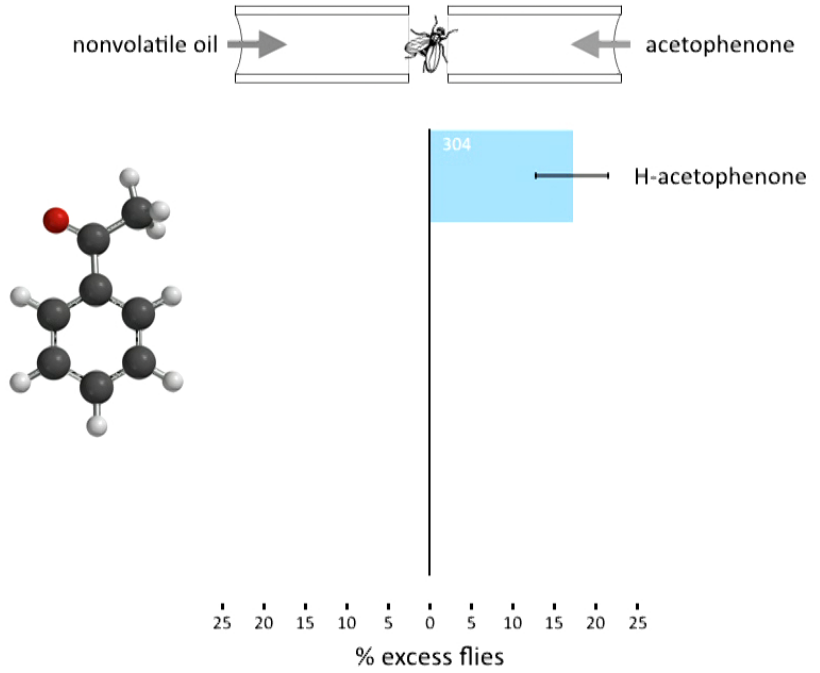


Drosophila behavior setup

spontaneous isotope preference

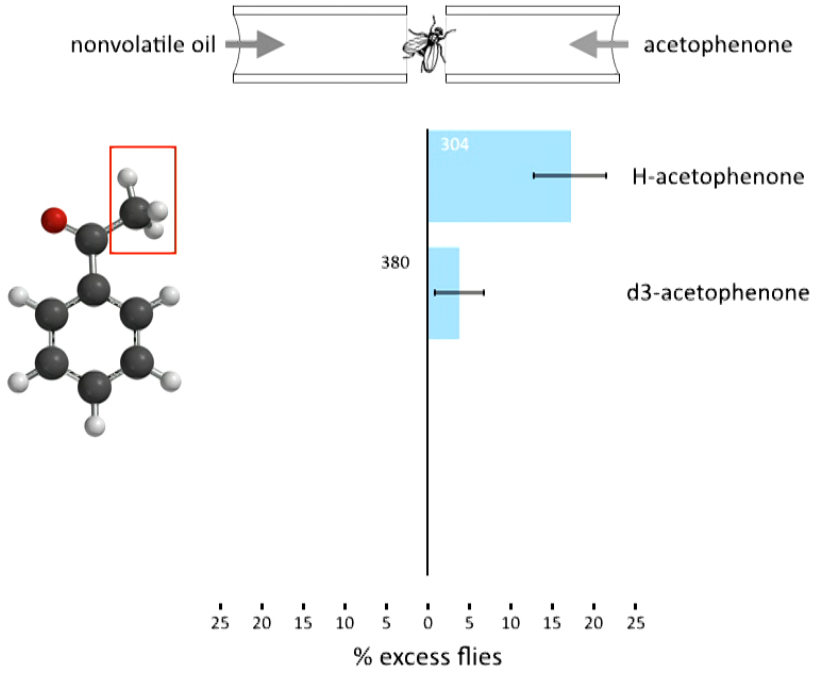
Drosophila behavior setup

spontaneous isotope preference



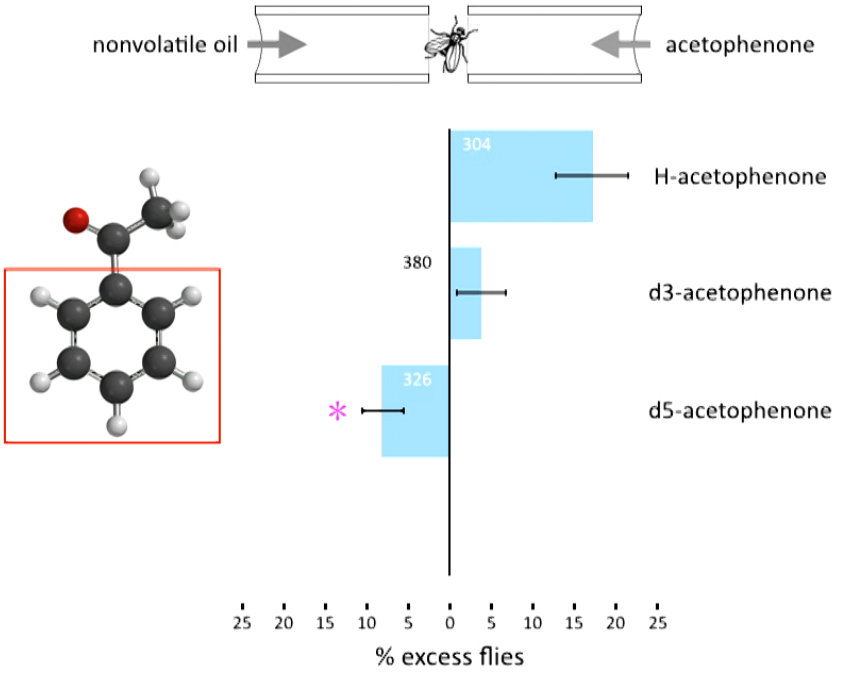
Drosophila behavior setup

spontaneous isotope preference



Drosophila behavior setup

spontaneous isotope preference



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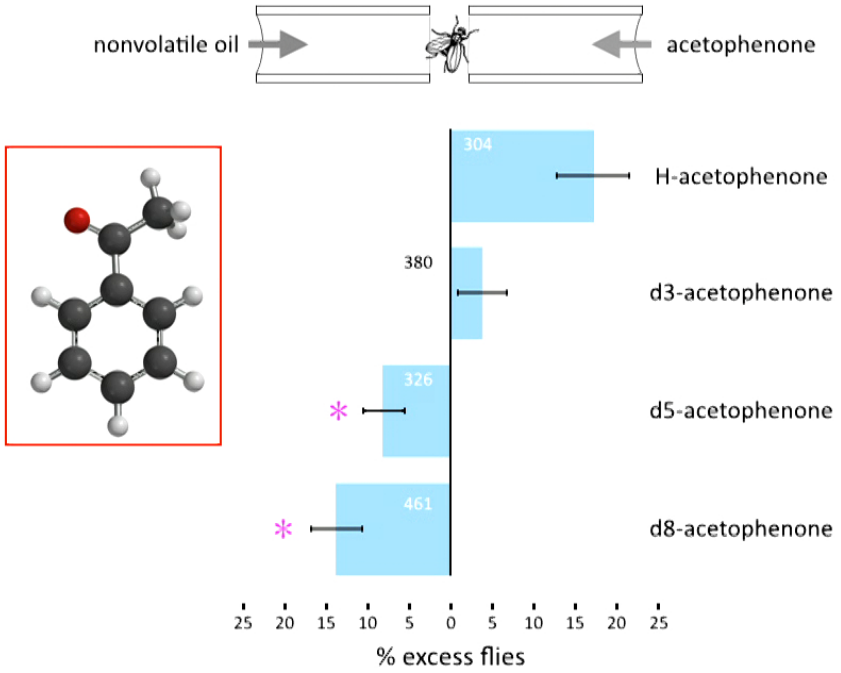
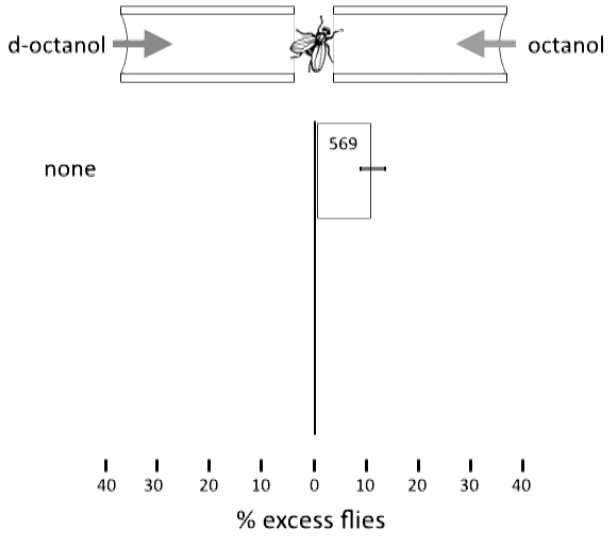
spontaneous isotope preference



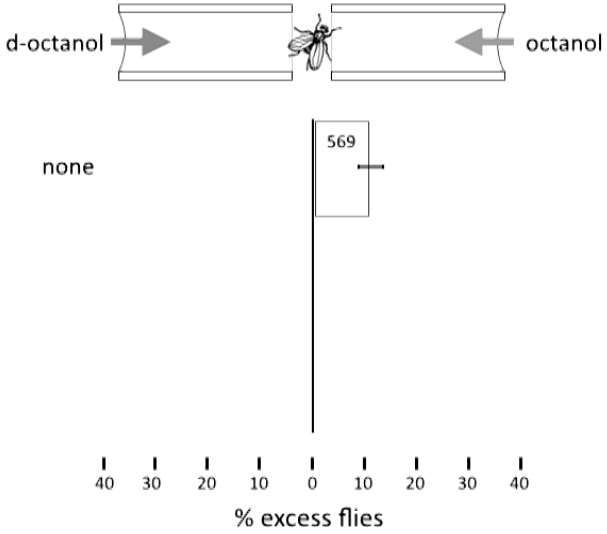
training

conditioned learning



training

conditioned learning



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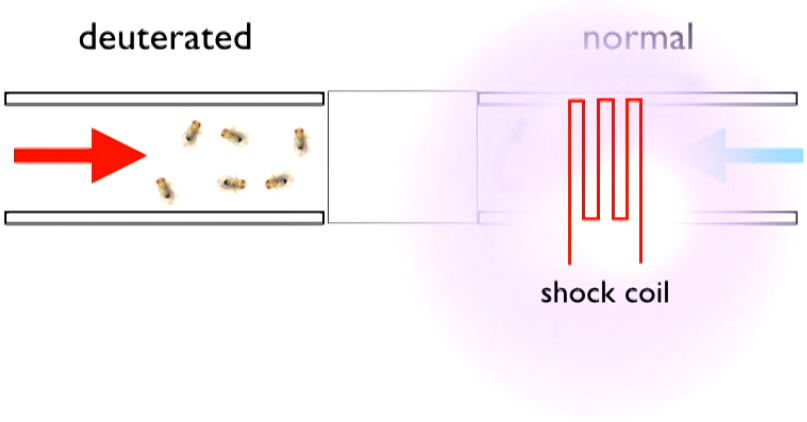
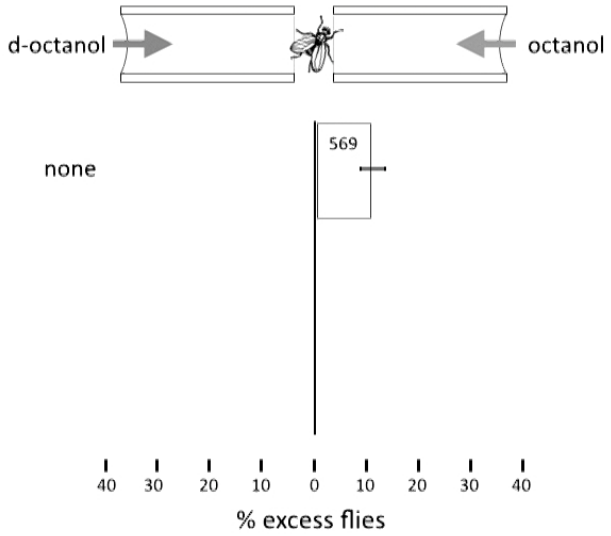
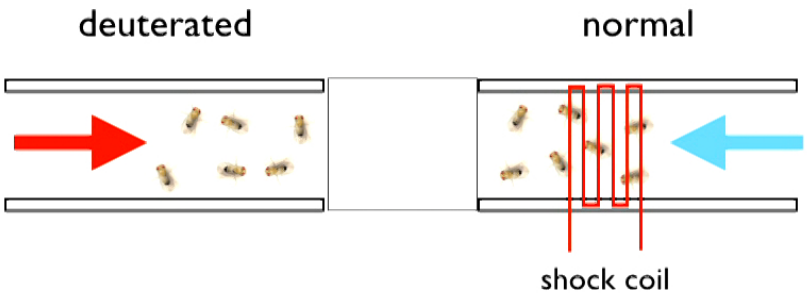


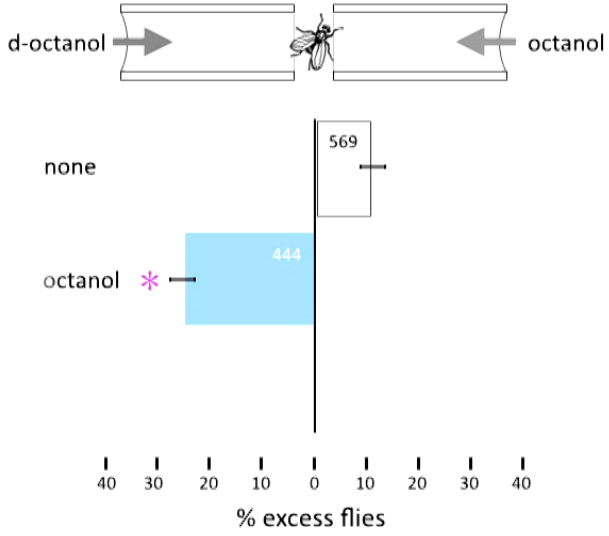
conditioned learning



training

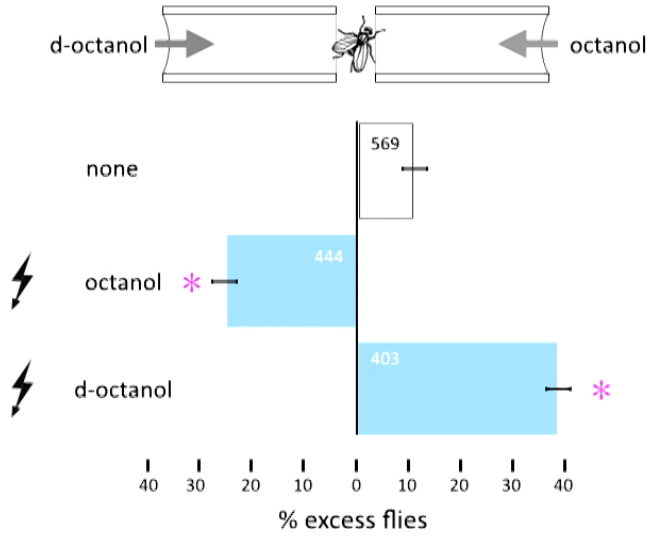


conditioned learning

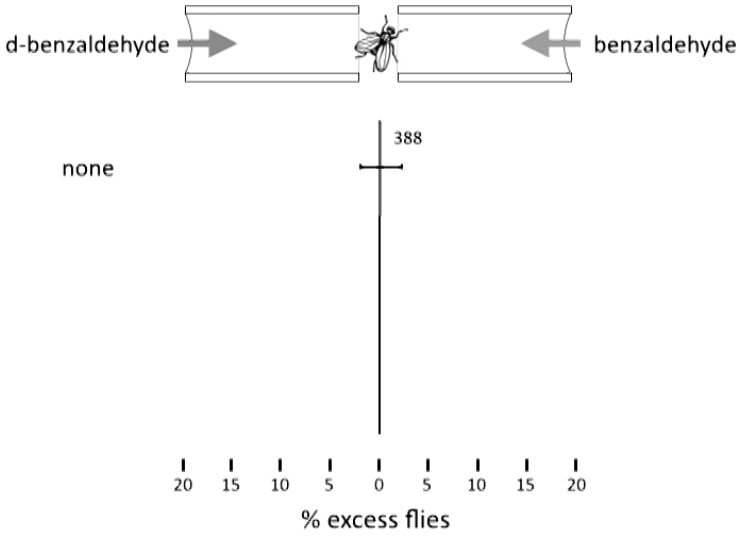


training

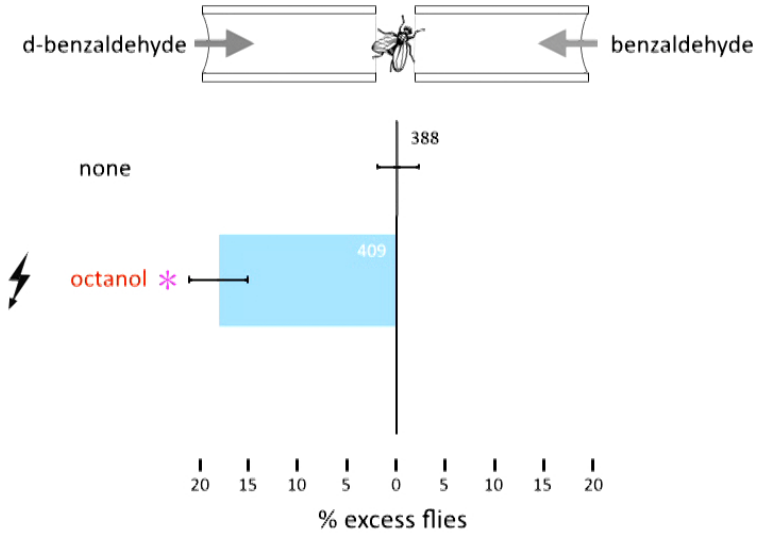
conditioned learning



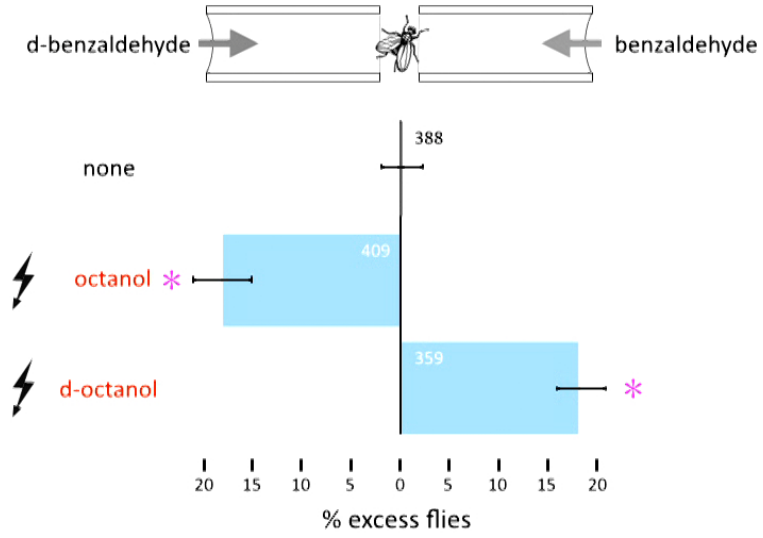
cross learning from deuterium to deuterium

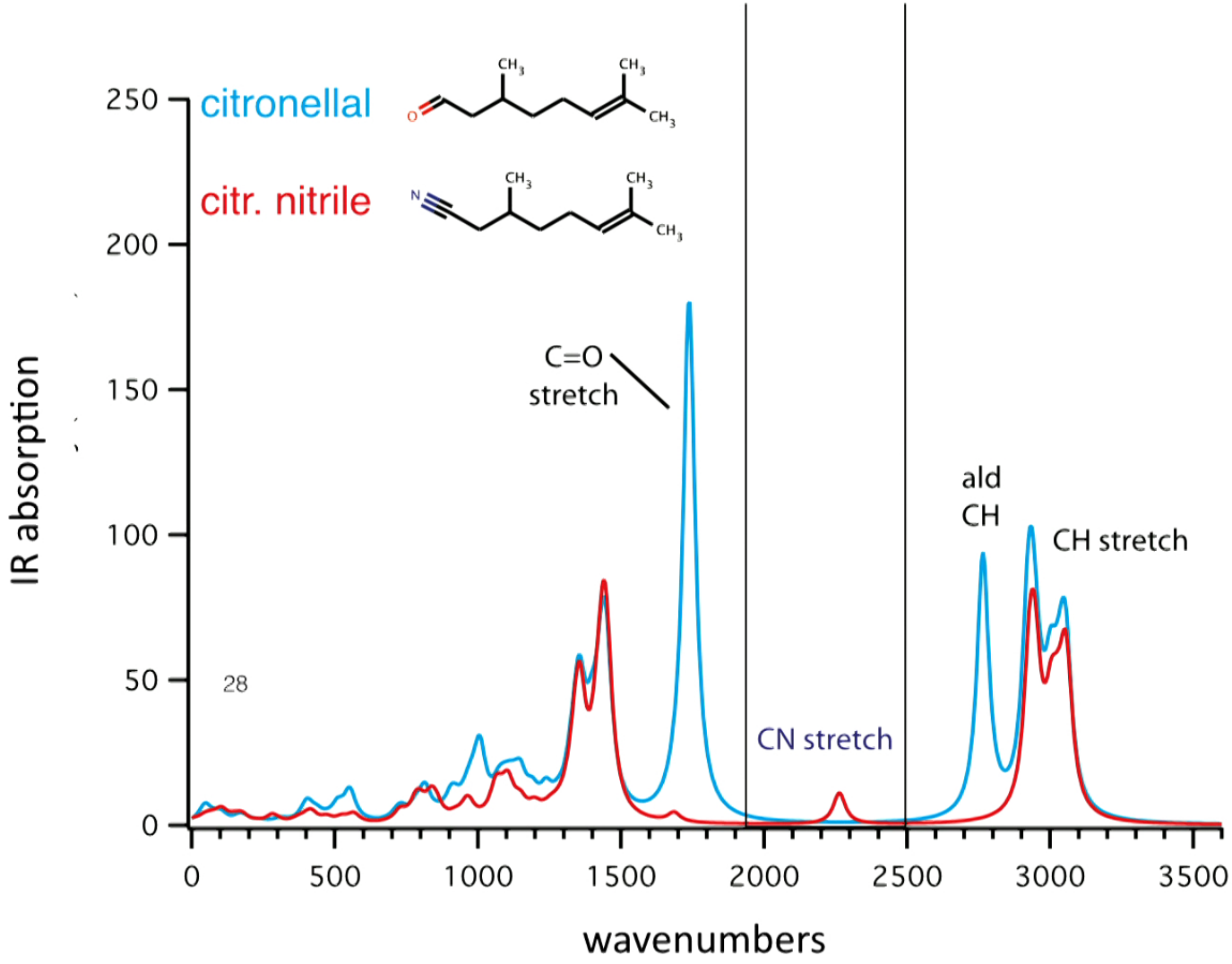


cross learning from deuterium to deuterium



cross learning from deuterium to deuterium




citronellal
citr. nitrile
C=O
stretch
ald
CH
CH stretch
CN stretch
28
IR absorption
wavenumbers
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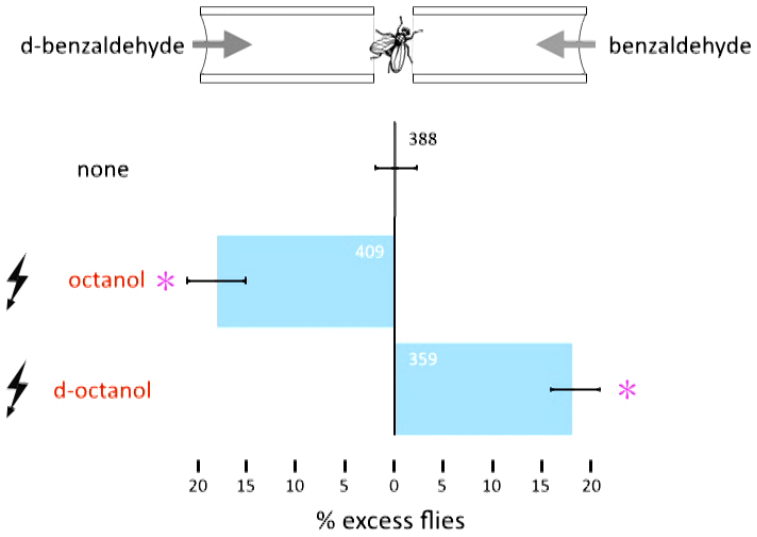
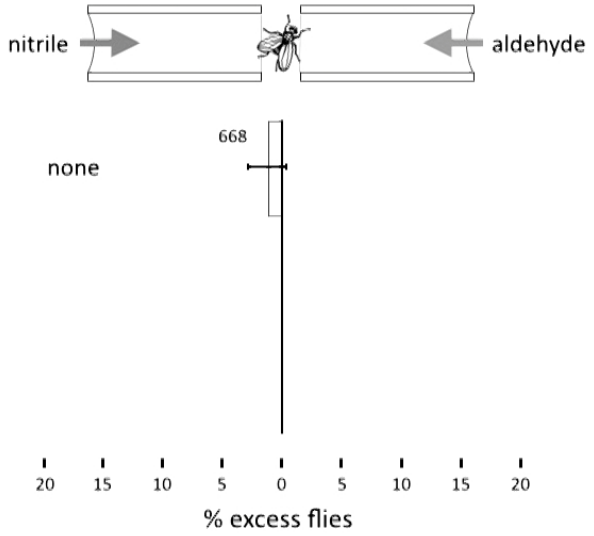
100
150
200
250
0
500
1000
1500
2000
2500
3000
3500

cross learning from deuterium to deuterium

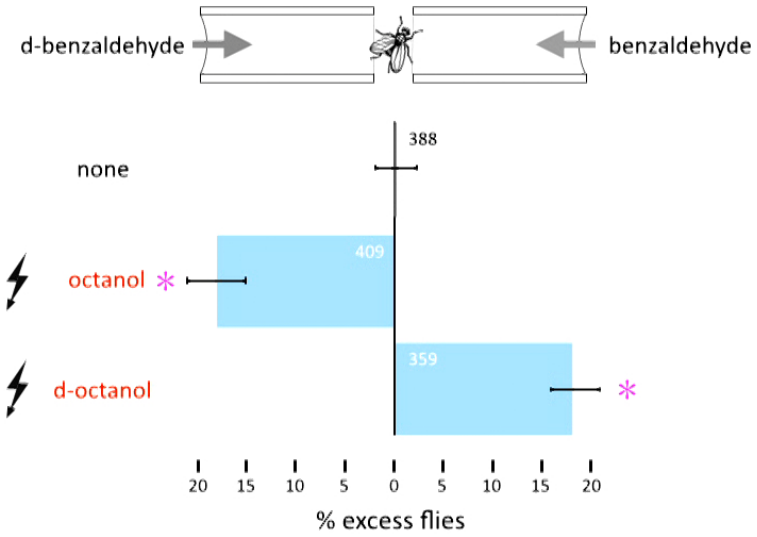


cross learning from deuterium to nitrile

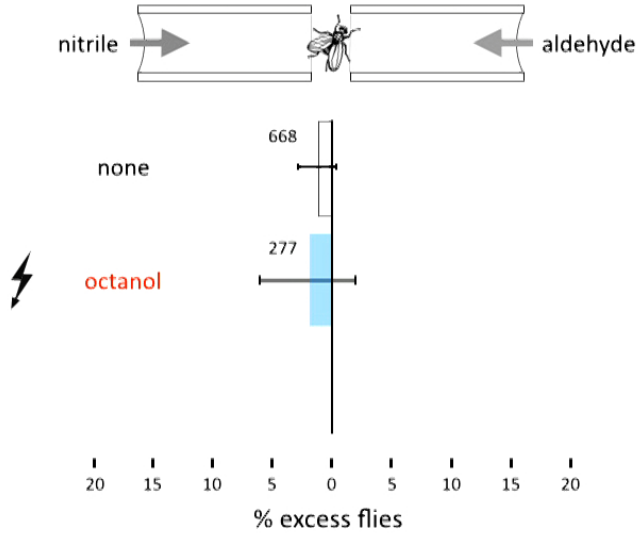


29

cross learning from deuterium to deuterium



cross learning from deuterium to nitrile



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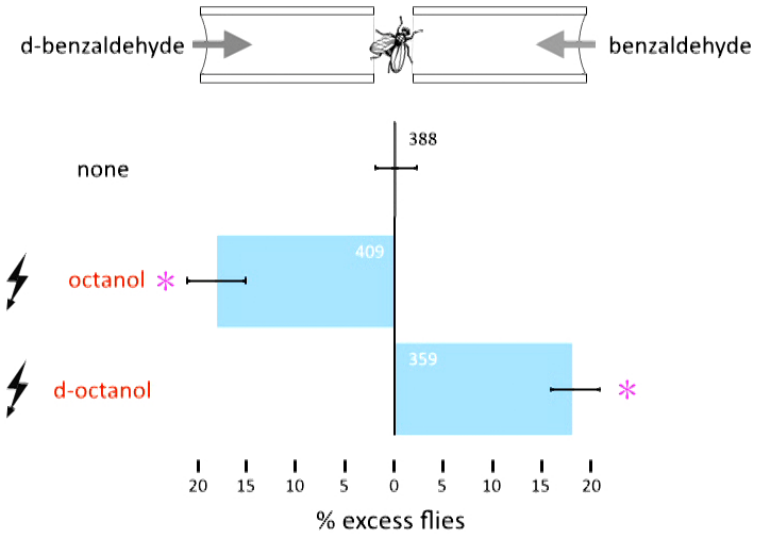
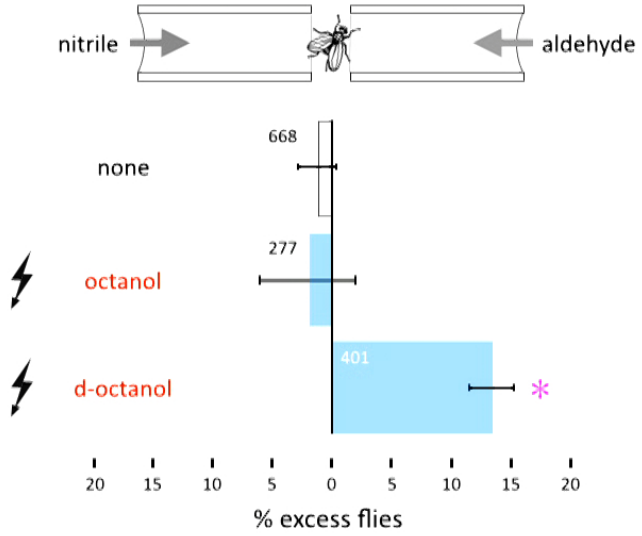


cross learning from deuterium to nitrile



29

C–H Activation

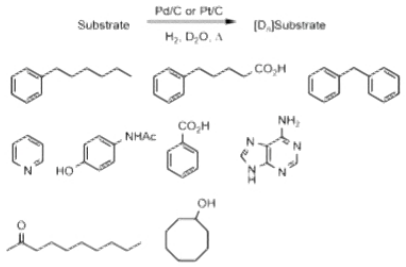
DOI: 10.1002/anie.200800941

Mild and Efficient H/D Exchange of Alkanes Based on C–H Activation Catalyzed by Rhodium on Charcoal**

*Tomohiro Maegawa, Yuta Fujiwara, Yuya Inagaki, Hiroyoshi Esaki, Yasunari Monguchi, and Hironao Sajiki**

The C–H bond activation of organic compounds is one of the most useful synthetic methods for the fuctionalization of simple molecules.[1] The activation of unsaturated compounds can be achieved using transition-metal catalysts, and the coordination of a metal center to the π bond plays an important role in the reaction process.[1b] On the other hand, alkanes (saturated organic compounds) are known to be much less reactive towards C–H bond activation than unsaturated compounds because alkanes possess no coordination sites for metals. Therefore only a few processes, such as oxidation, H/D exchange, dehydrogenation, and radical reactions, have been reported as being C–H activation-induced, even though extensive efforts to activate alkanes have been made.[1] The H/D exchange reaction[2] is a basic transformation of alkanes. Deuterated products have received attention not only as useful tools for the investigation of human metabolism[3] or reaction mechanisms,[4] but also as functional materials[5] like deuterated polymers as components of optical fibers for high-speed telecommunications systems.[5a] Deuterated pesticides and pharmaceuticals are also effective for quantitative analyses and bioanalytical investigations as internal standards,[5b–d] while deuterated alkanes are expected to be applied as marker molecules to prevent the distribution of illegally mixed light diesel oil.[5e] Owing to this increasing interest, it is important to develop an efficient and facile H/D exchange method for alkanes. Since the first H/D exchange of alkanes was reported by Shilov and co-workers,[6] other H/D exchange reactions of alkanes have been developed.[1] Recently, Bergman and co-workers reported an efficient H/D exchange method for various substrates, including alkanes, by using a homogeneous cationic Ir hydride complex under mild conditions.[7] The H/D exchange reaction with deuterium oxide catalyzed by Pd/C under hydrothermal conditions has also been reported.[8]

We have recently established a method for deuterium incorporation into organic molecules by using a combination of Pd/C (or Pt/C) in D_2O under H_2, which has led to efficient H/D exchange for a variety of organic molecules such as aromatic compounds,[9,10] ketones, and alcohols[11] (Scheme 1). As part of an ongoing program for the development of H/D exchange reactions induced by heterogeneous catalysts, we have discovered a unique protocol for the C–H activation based deuteration of the C–H bond of alkanes, which do not possess functional groups. Herein we report deuteration of the C–H bond by the heterogeneous Rh/C-catalyzed multi-H/D exchange of simple alkanes. The reaction is carried out with D_2O as a solvent and as a deuterium source under nearly atmospheric pressure,[12] and the addition of cyclohexane as a co-solvent improves the efficiency of deuterium incorporation.



Scheme 1. Deuterium incorporation into alcohols, ketones, and aromatic compounds by using Pd/C (or Pt/C) in D_2O under H_2.

As an extension of our study, we examined the H/D exchange reaction of *n*-dodecane, which possesses no functional groups and thus cannot coordinate to metal catalysts. Unexpectedly, deuterium incorporation was observed on all the carbon atoms of *n*-dodecane with a 57–61% deuterium incorporation in the presence of Pd/C in D_2O under H_2 at 160°C. Encouraged by this result, we screened the effect of other Group VIII metal catalysts under the same reaction conditions. Rh/C was found to be the most effective catalyst for the deuteration of alkanes, where the deuterium incorpo-

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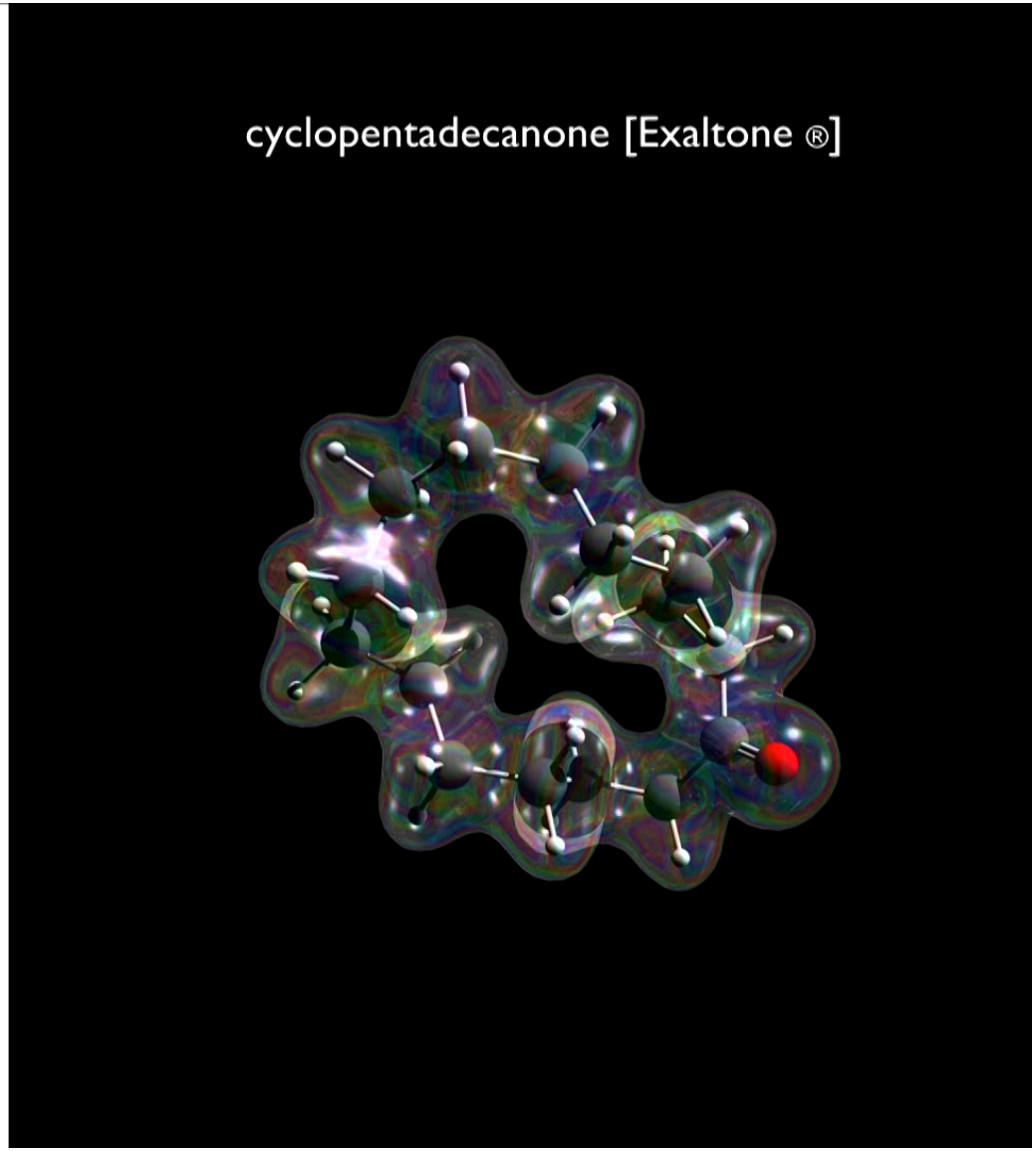
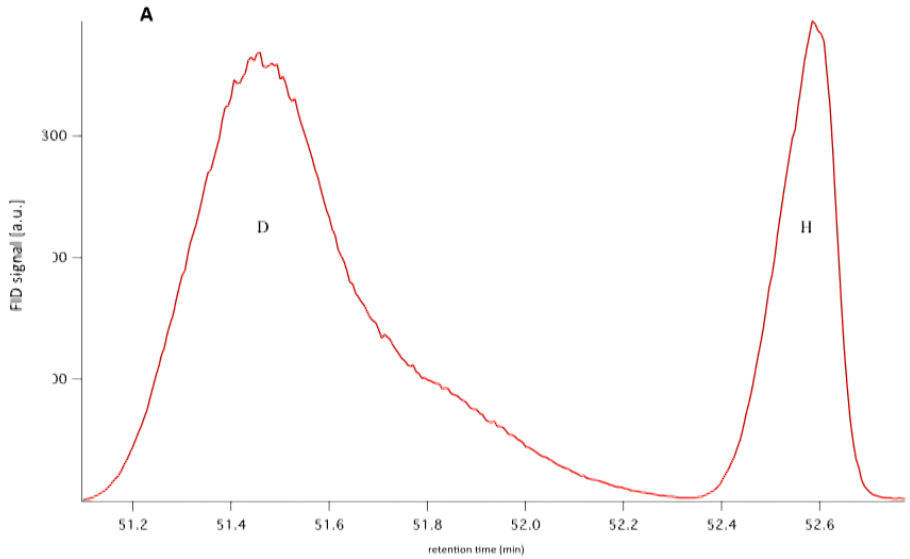
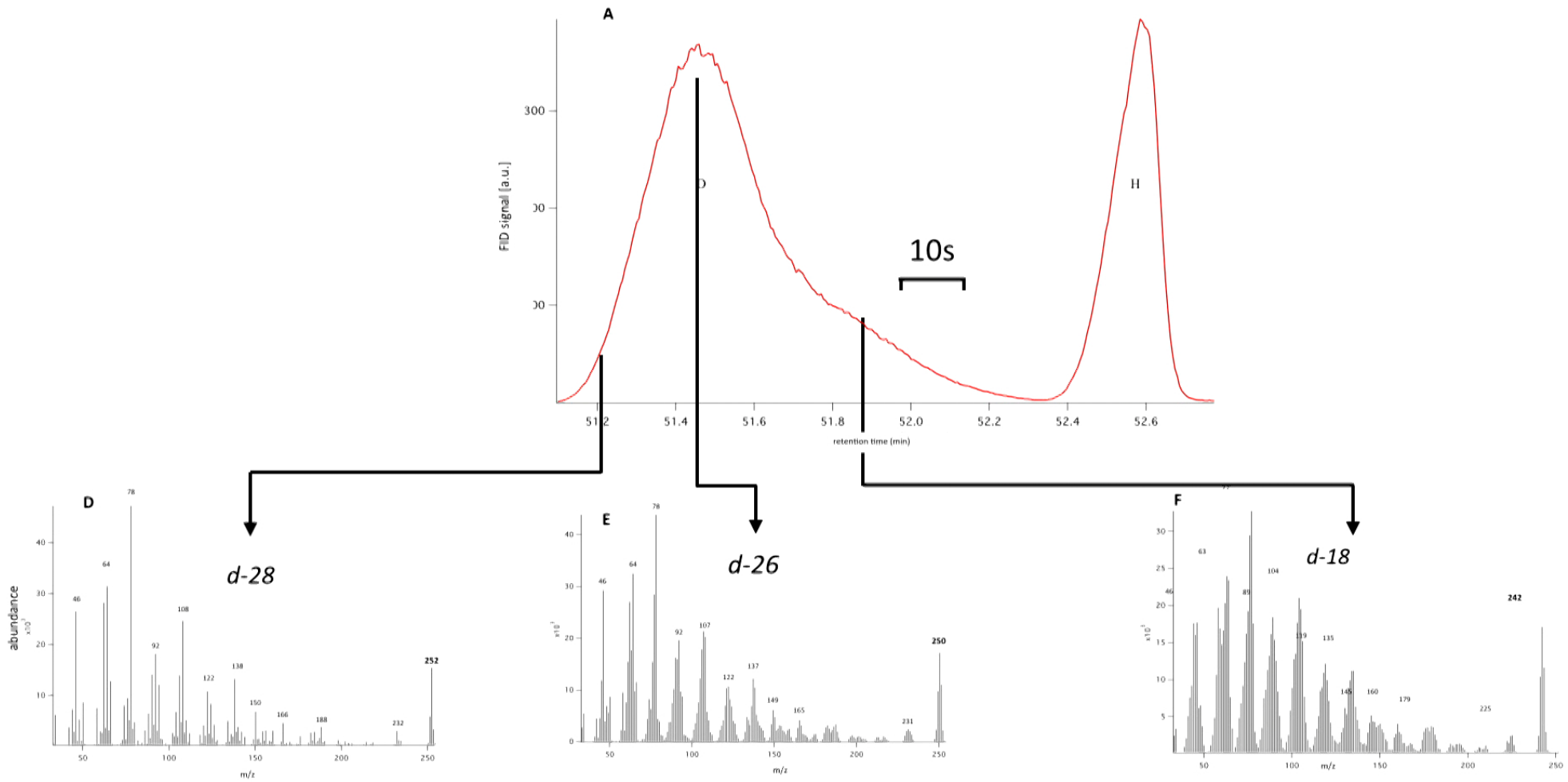
Laboratory of Medicinal Chemistry
Gifu Pharmaceutical University
5-6-1 Mitahora-higashi Gifu 502-8585 (Japan)
Fax: (+81) 58-237-5979



GC/MS of deuterated cyclopentadecanone



GC/MS of deuterated cyclopentadecanone



discrimination between h and d cyclopentadecanone

Subject	MG	LT	KF	KM	KF	KM	KF	KM	KF	KM	KF
number correct	9	12	6	17	12	9	12	11	12	9	10
number of trials	10	12	8	17	12	12	13	12	12	12	12
binomial p	0.0215	0.0005	0.2891	1.52 10^{-5}	0.0005	0.146	0.0034	0.0063	0.0005	0.146	0.0386

total number of successes: 119/132

$p < 2.2\ 10^{-16}$

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Molecular Vibration-Sensing Component in Human Olfaction

Simon Gane[1☯], Dimitris Georganakis[2☯], Klio Maniati[3☯], Manolis Vamvakias[2], Nikitas Ragoussis[2], Efthimios M. C. Skoulakis[3], Luca Turin[3]*

1 Royal National Throat, Nose and Ear Hospital, University College London, London, United Kingdom, **2** Vioryl S.A., Aflidnes, Greece, **3** Neurobiology Division, Biomedical Sciences Research Centre "Alexander Fleming", Vari, Greece

Abstract

Whether olfaction recognizes odorants by their shape, their molecular vibrations, or both remains an open and controversial question. A convenient way to address it is to test for odor character differences between deuterated and undeuterated odorant isotopomers, since these have identical ground-state conformations but different vibrational modes. In a previous paper (Franco et al. (2011) Proc Natl Acad Sci USA 108:9, 3797-802) we showed that fruit flies can recognize the presence of deuterium in odorants by a vibrational mechanism. Here we address the question of whether humans too can distinguish deuterated and undeuterated odorants. A previous report (Keller and Vosshall (2004) Nat Neurosci 7:4, 337-8) indicated that naive subjects are incapable of distinguishing acetophenone and d-8 acetophenone. Here we confirm and extend those results to trained subjects and gas-chromatography [GC]-pure odorants. However, we also show that subjects easily distinguish deuterated and undeuterated musk odorants purified to GC-pure standard. These results are consistent with a vibrational component in human olfaction.

Citation: Gane S, Georganakis D, Maniati K, Vamvakias M, Ragoussis N, et al. (2013) Molecular Vibration-Sensing Component in Human Olfaction. PLoS ONE 8(1): e55780. doi:10.1371/journal.pone.0055780

Editor: Wulfila Gronenberg, University of Arizona, United States of America

Received October 4, 2012; **Accepted** January 4, 2013; **Published** January 25, 2013

Funding: Funded by the Greek Ministry of Education and Research. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors declare that authors DG, MV and NR are affiliated with Vioryl, a commercial company. The authors attest that no foreseeable commercial applications of the findings described in the paper exist at the present time, no intellectual property arises from it and no funding was provided by Vioryl to the other authors. This does not alter the authors' adherence to all the PLOS ONE policies on sharing data and materials.

* E-mail: turin@fleming.gr

☯ These authors contributed equally to this work.

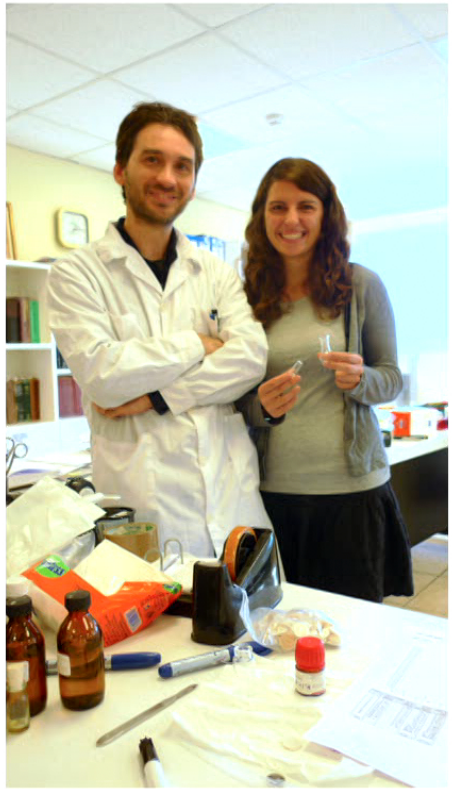
Introduction

The human sense of smell uses the input from several hundred receptors to discriminate between tens of thousands of odorants. Although human olfactory receptors are members of the G-protein coupled receptor superfamily, the exact mechanism by which an odorant activates a receptor is still unclear. Specifically, we do not know whether olfactory receptors detect the shape of odorant molecules by a classical lock-and-key mechanism [1–4], their vibrations [5,6] by a quantum mechanism [7–10], or a combination of both.

In principle, odorant isotopomers provide a possible test of shape vs. vibration mechanisms: replacing, for example, hydrogen with deuterium in an odorant leaves the ground-state conformation of the molecule unaltered while doubling atomic mass and so altering the frequency of all its vibrational modes to a greater or lesser extent [11]. To first order, deuteration should therefore have little or no effect on the smell character of an odorant recognized

However, human trials using commercially available deuterated odorants [benzaldehyde and acetophenone] have yielded conflicting results, both positive [15] and negative [16]. Here, using GC-pure samples and a different experimental technique, we fully confirm Keller and Vosshall's finding that humans, both naive and trained subjects, are unable to discriminate between acetophenone isotopomers.

However, since deuteration exerts the largest effect on the parts of the vibrational spectrum involving C-H motions, it seemed interesting to ask whether the effect of deuterium–if any–on smell character might be detectable in odorants containing more carbons, and therefore more CH groups. Musks are among the largest odorants and typically contain 15–18 carbons and 28 or more hydrogens [17], as compared to 8 carbons and 8 hydrogens for acetophenone. We now report that deuterated musks of diverse structures smell strikingly different from the parent compounds and similar to each other, even to naive subjects. The difference in smell character caused by deuteration persists when the most stringent



Dimitris Georganakis &
Klio Maniati

Simon Gane & Ian Smith

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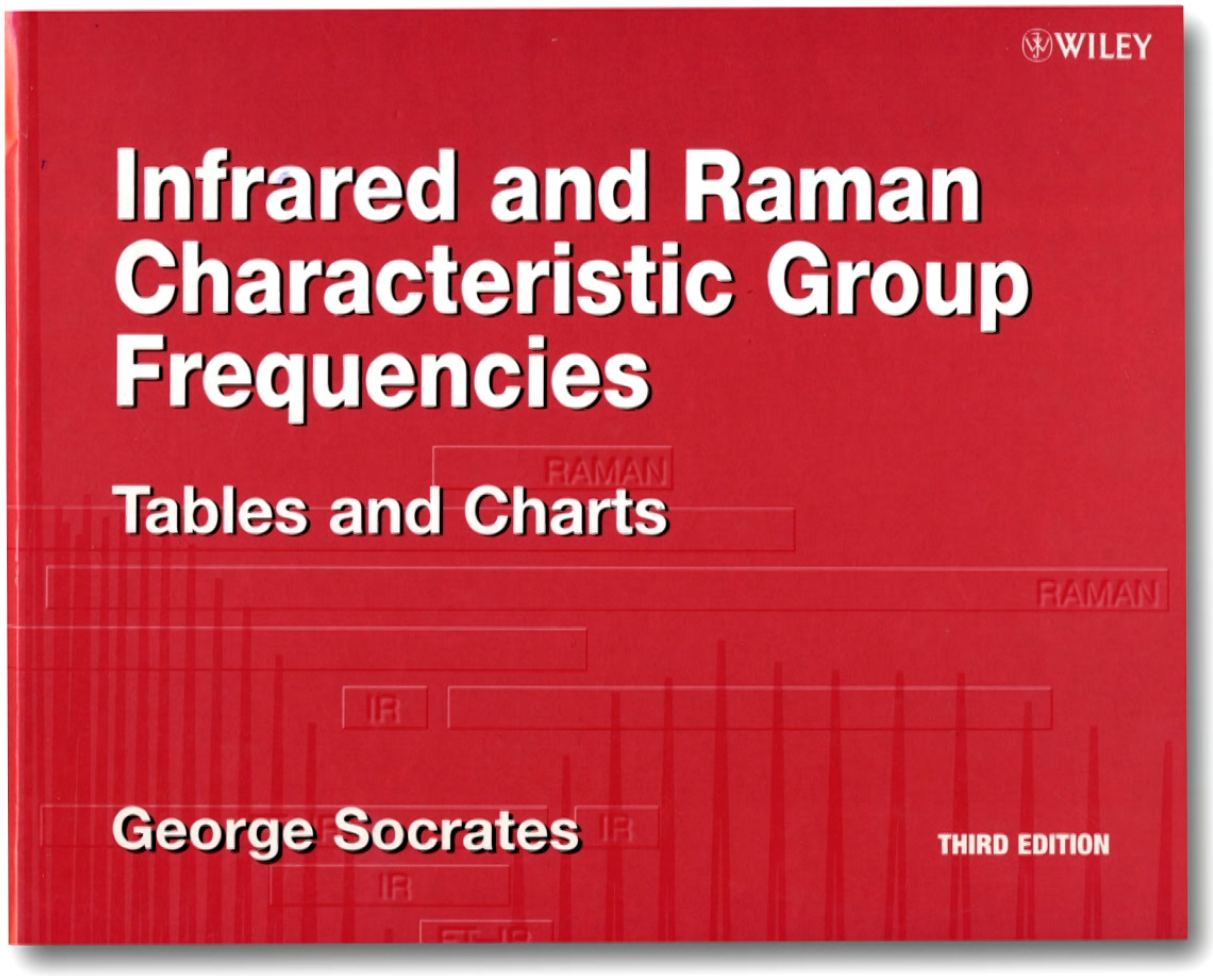
If olfaction is lock-and-key

If olfaction is lock-and-key
what happens when you change all the locks?

a classic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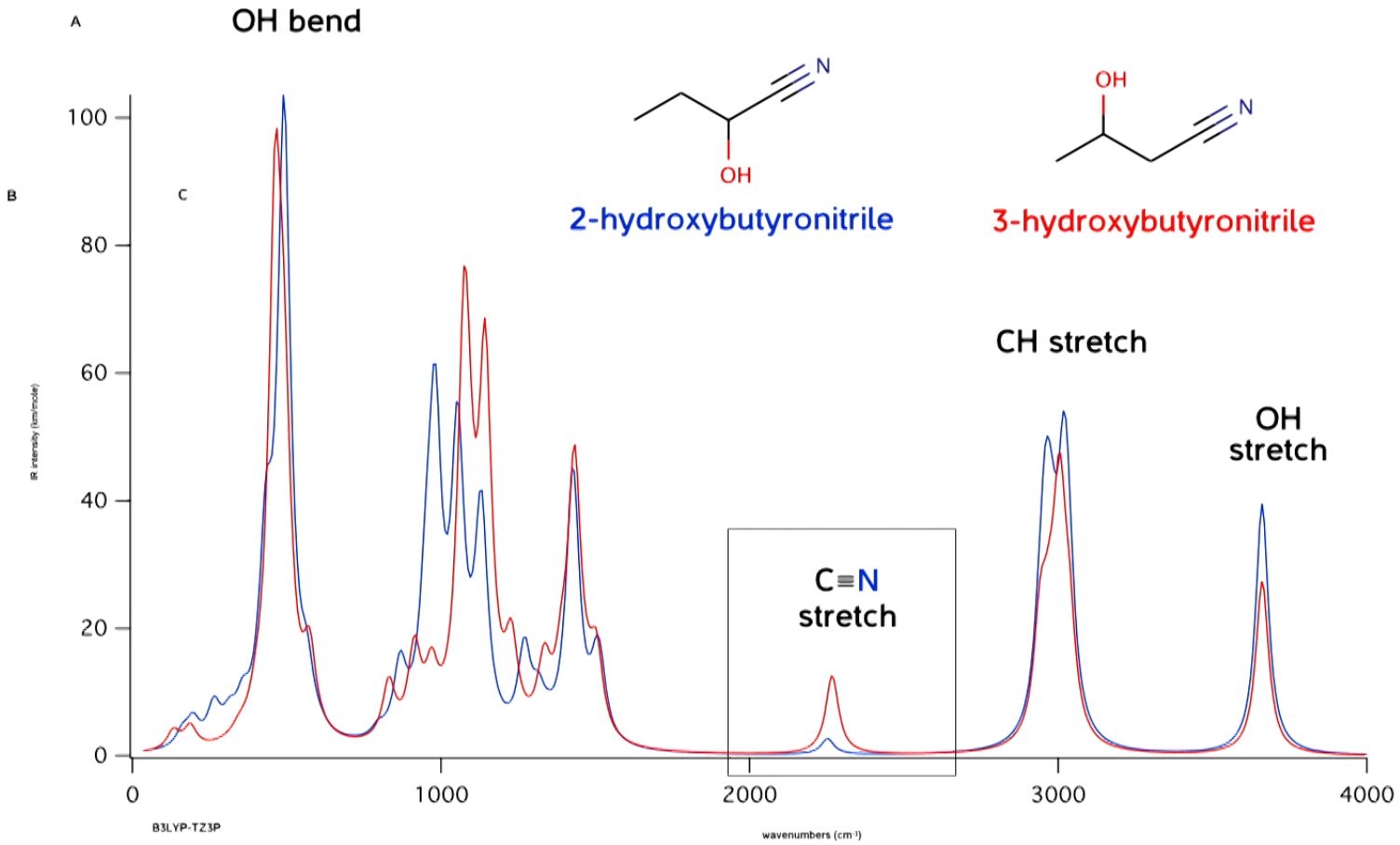
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B
C
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CH stretch
OH
stretch
C≡N
stretch
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2000
3000
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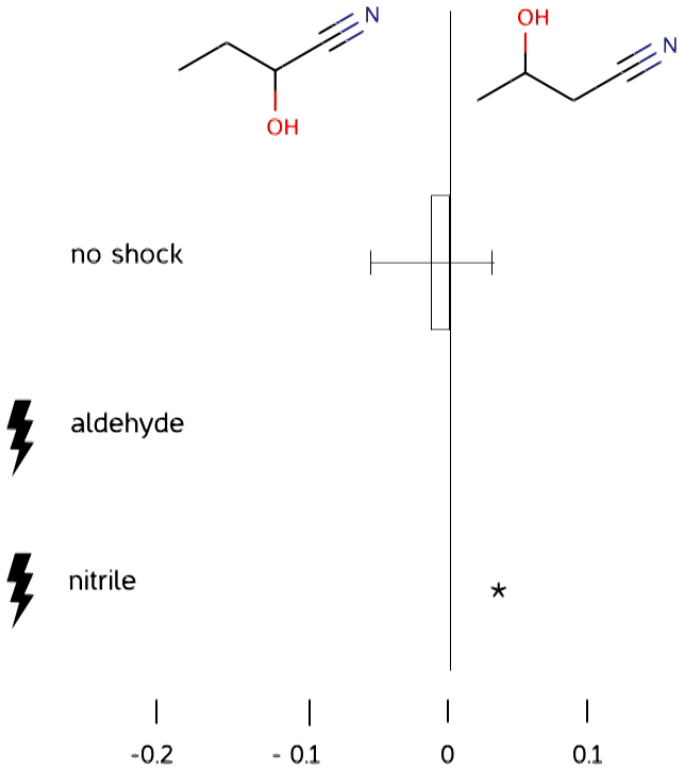
B3LYP-TZ3P
wavenumbers (cm⁻¹)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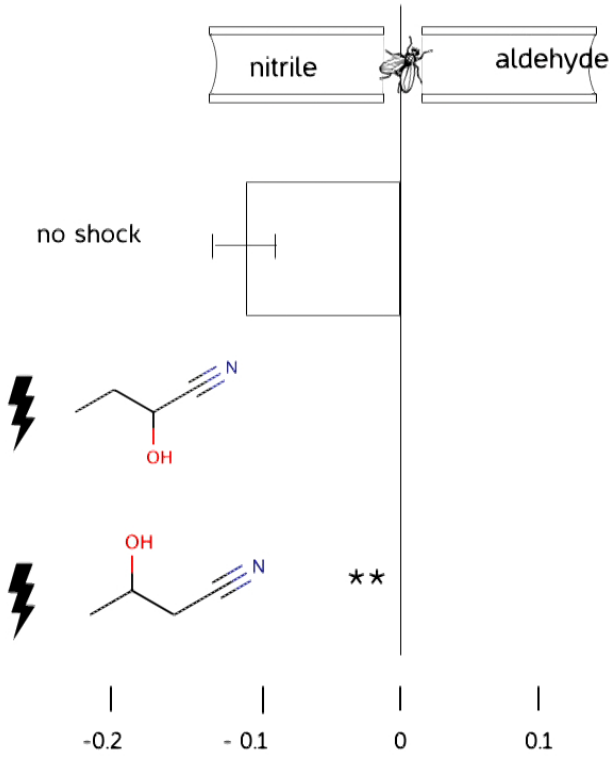
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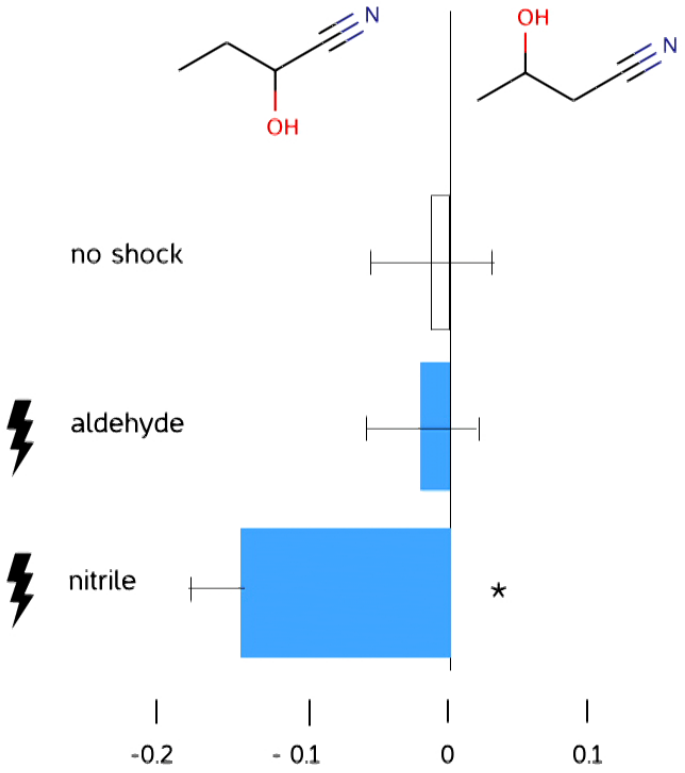
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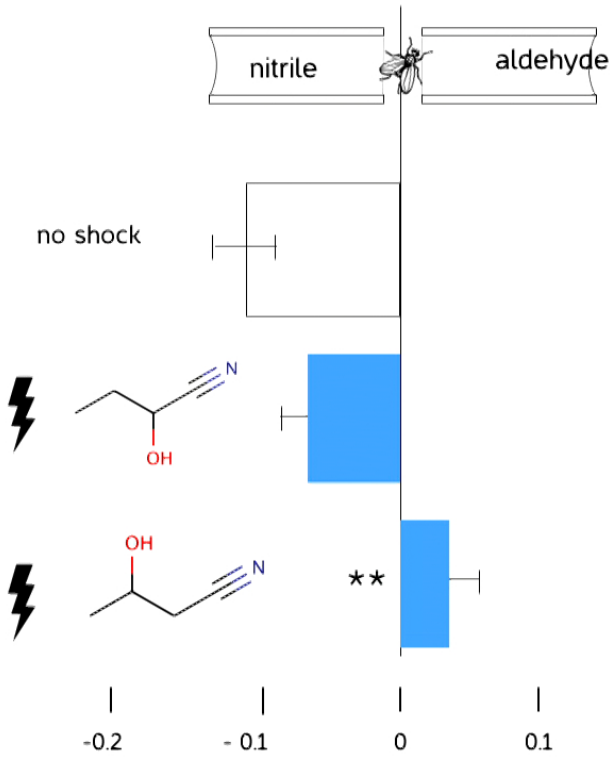
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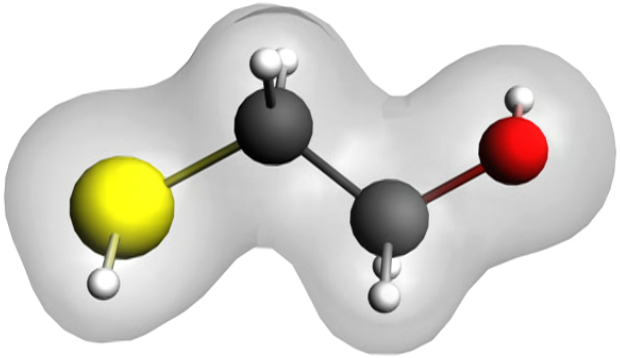

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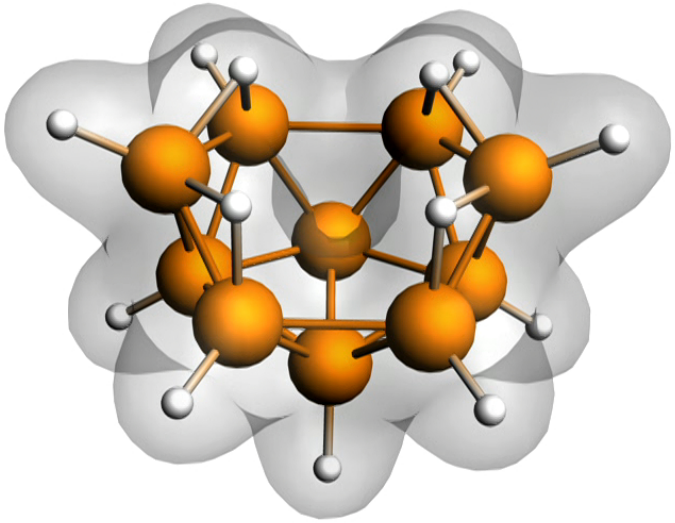

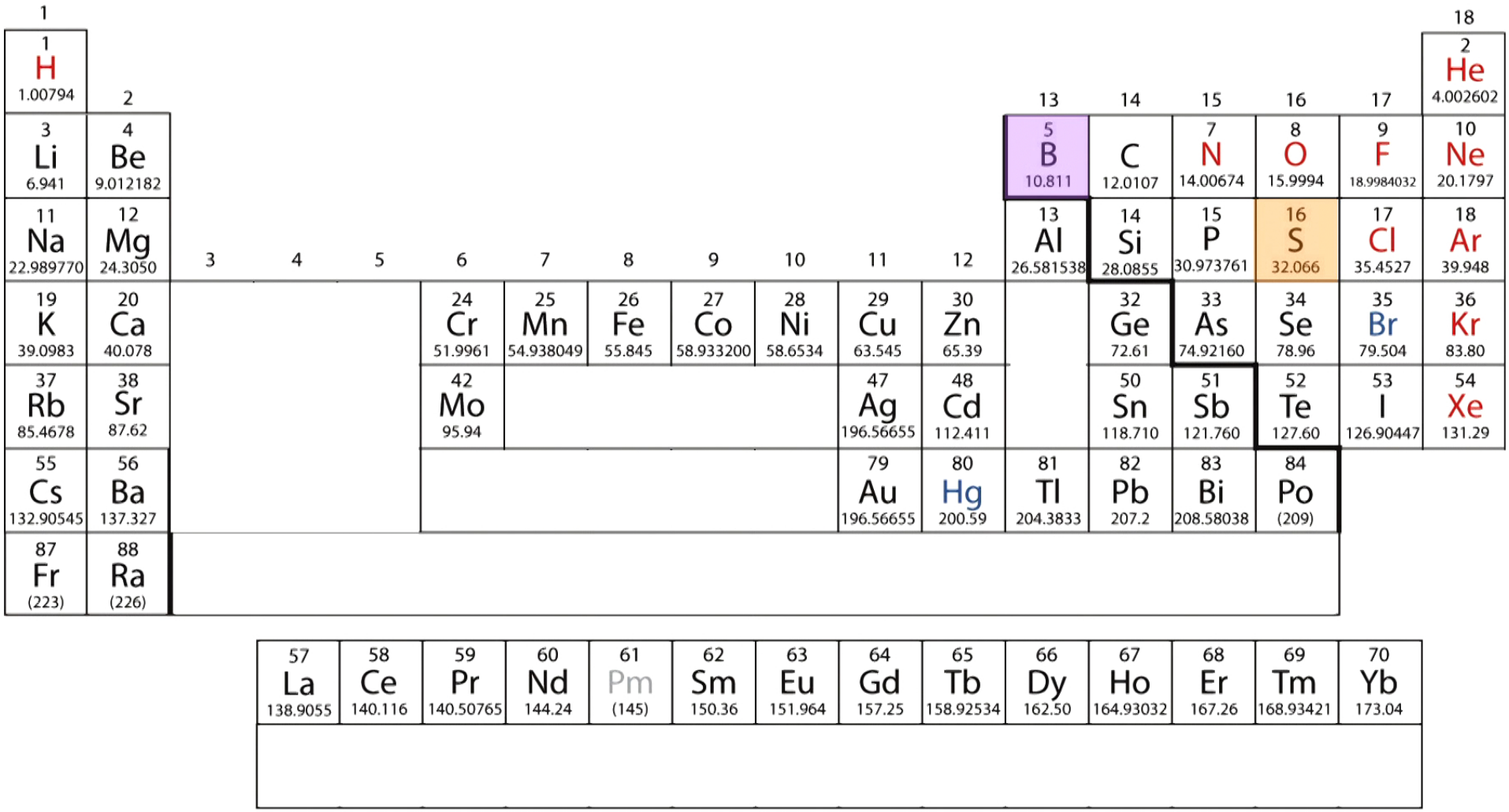
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48 Cd 112.411
55 Cs 132.90545
56 Ba 137.327
79 Au 196.56655
80 Hg 200.59
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88 Ra (226)
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7 N 14.00674
8 O 15.9994
9 F 18.9984032
10 Ne 20.1797
13 Al 26.581538
14 Si 28.0855
15 P 30.973761
16 S 32.066
17 Cl 35.4527
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32 Ge 72.61
33 As 74.92160
34 Se 78.96
35 Br 79.504
36 Kr 83.80
50 Sn 118.710
51 Sb 121.760
52 Te 127.60
53 I 126.90447
54 Xe 131.29
81 Tl 204.3833
82 Pb 207.2
83 Bi 208.58038
84 Po (209)
18
2 He 4.002602
57 La 138.9055
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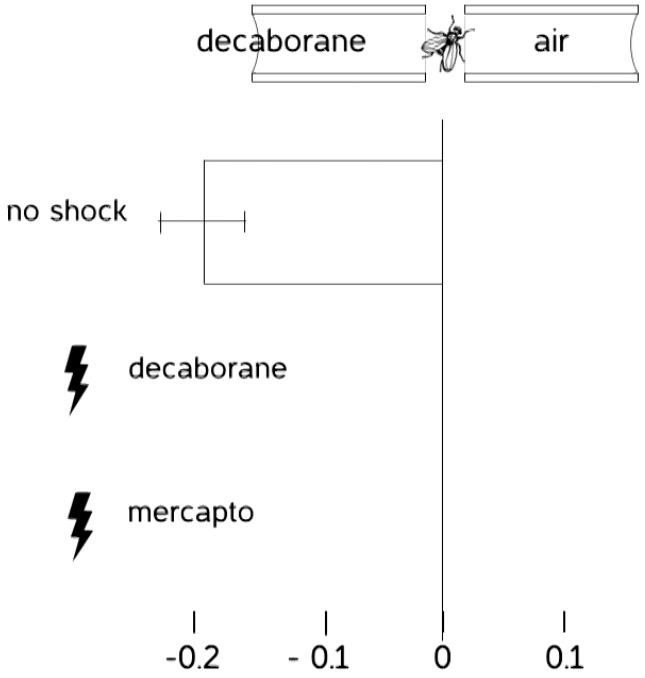
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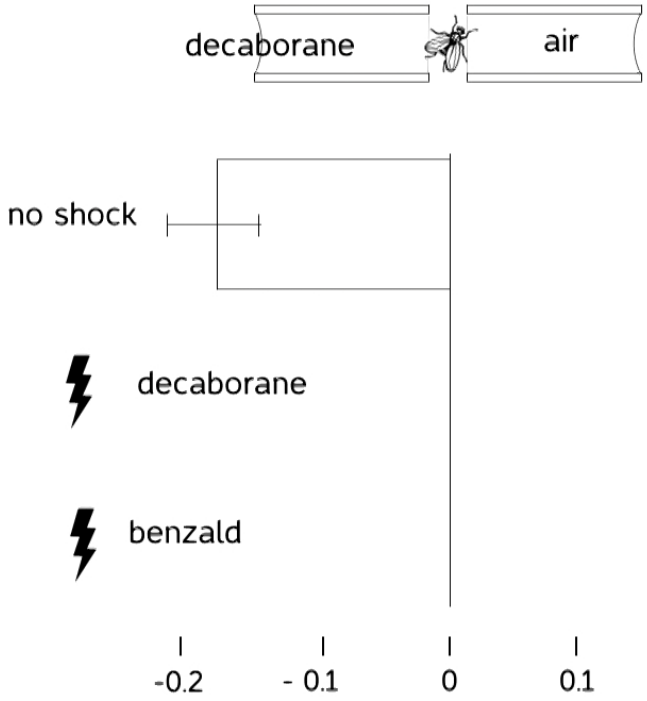
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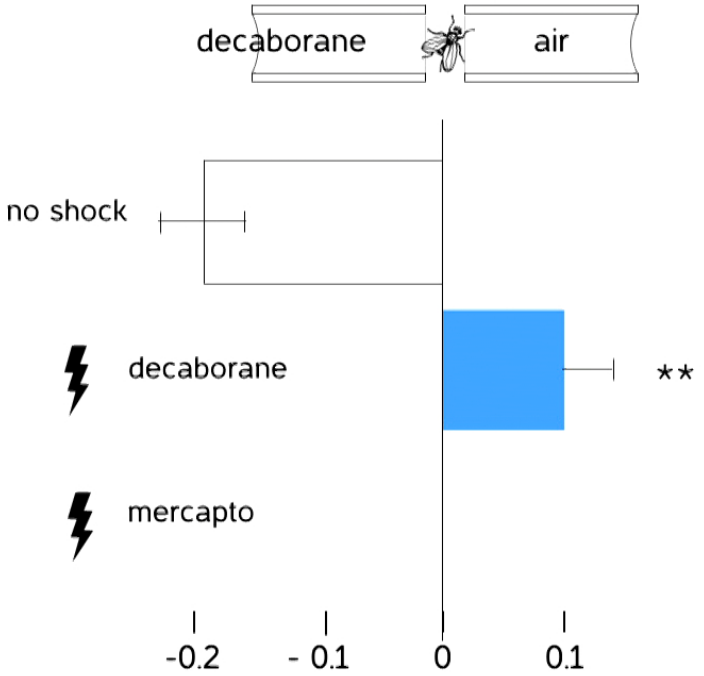
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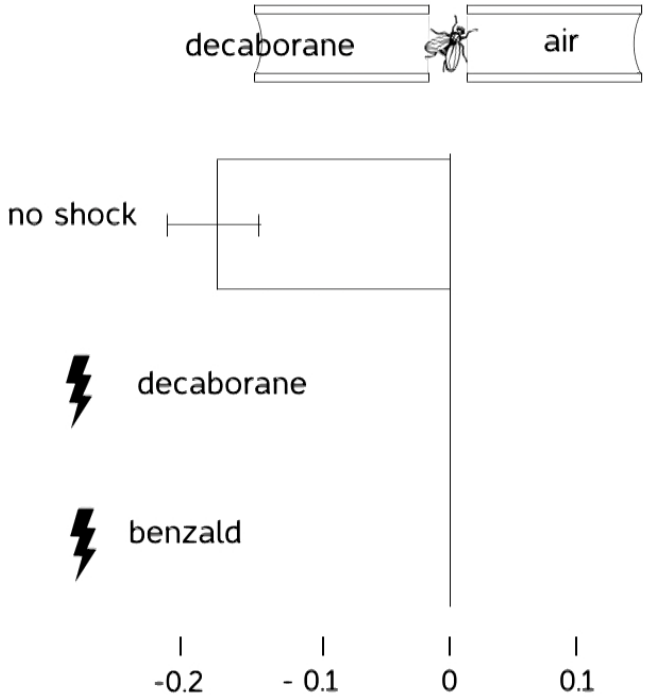
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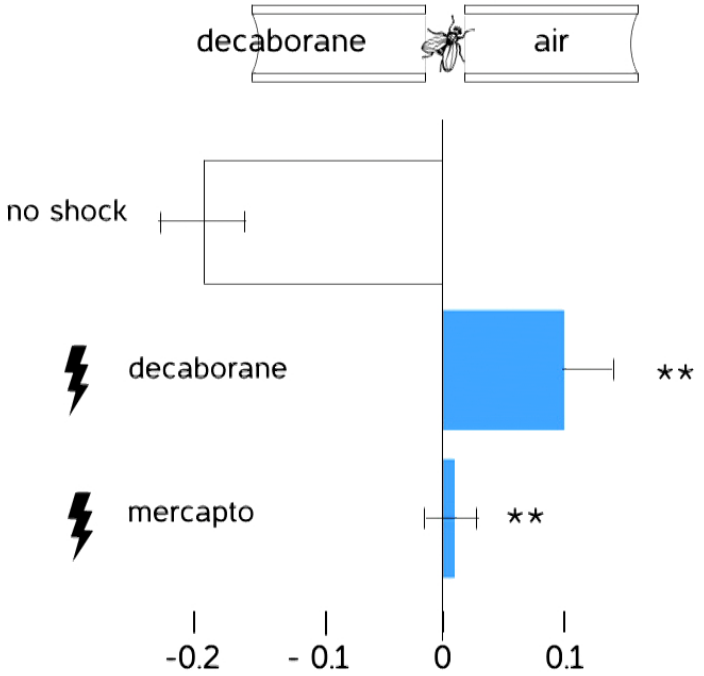
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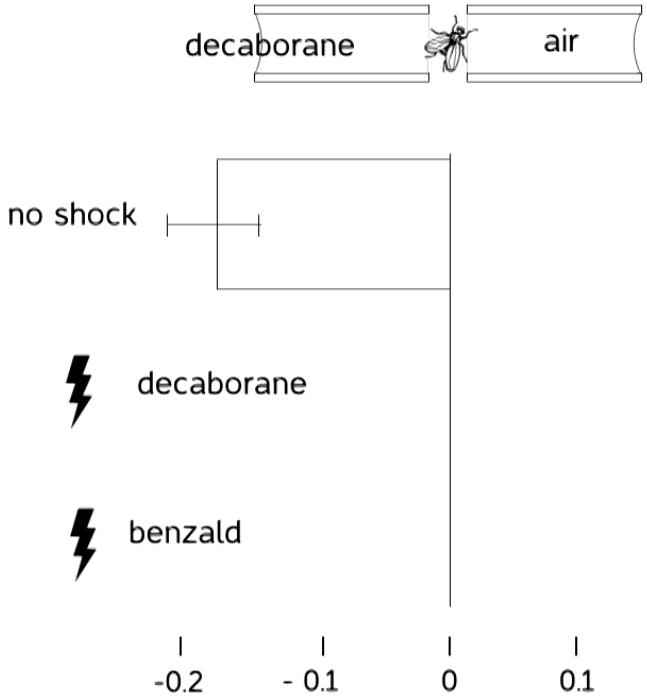
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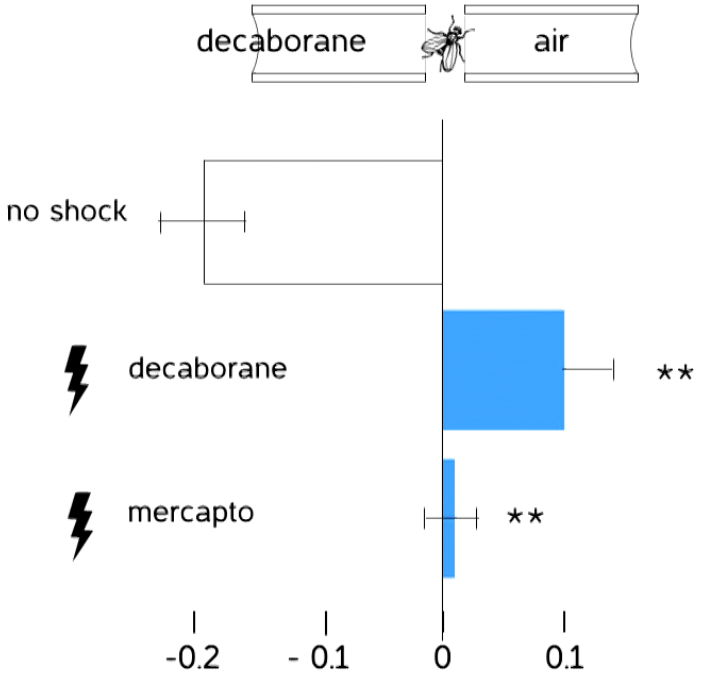
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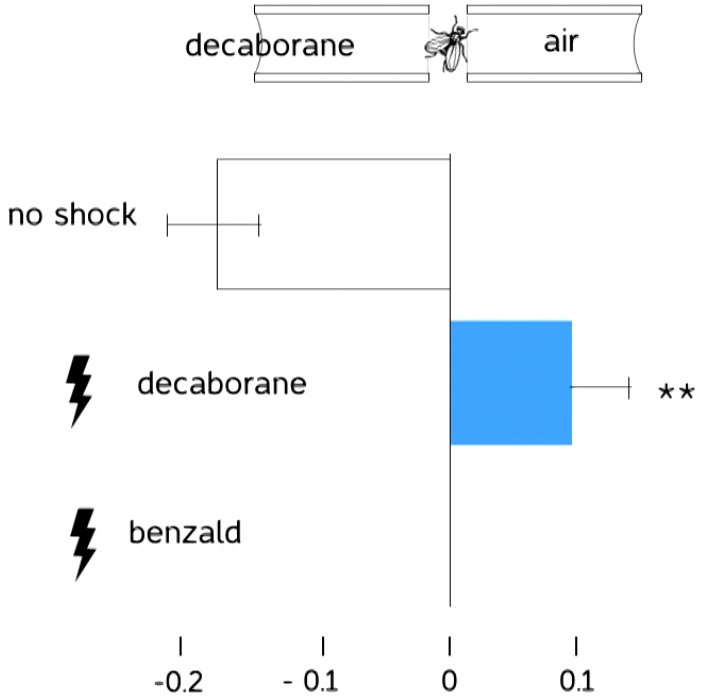
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air
no shock
decaborane
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benzald
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- 0.1
0
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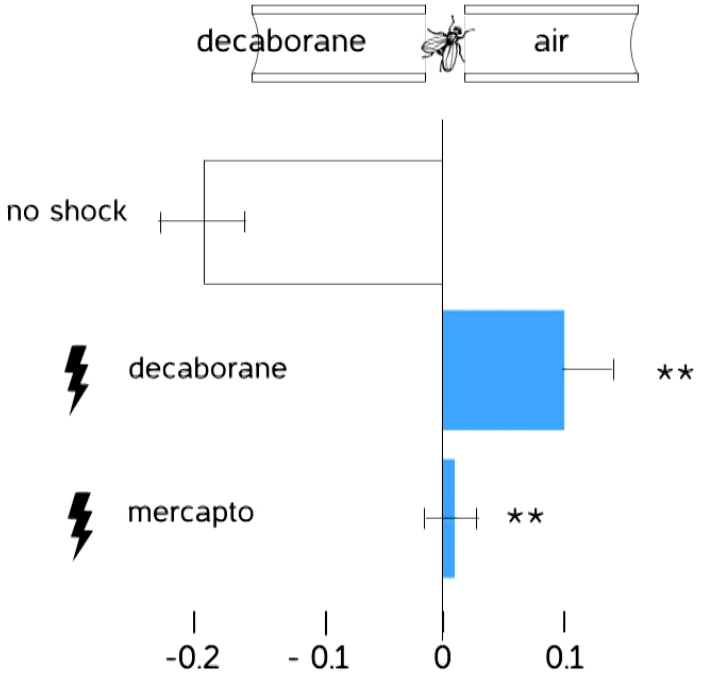
decaborane
air
no shock
decaborane
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mercapto
**
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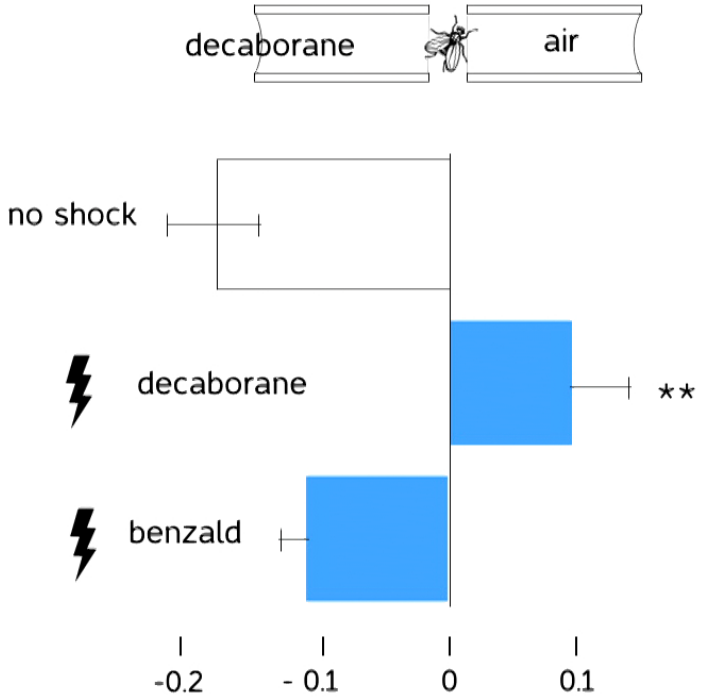
decaborane
air
no shock
decaborane
**
benzald
-0.2
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0
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