Quantum Origins of Molecular Recognition and Olfaction in Drosophila

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The standard model for molecular recognition of an odorant is that receptor sites discriminate by molecular geometry as evidenced that two chiral molecules may smell very differently. However, recent studies of isotopically labeled olfactants indicate that there may be a molecular vibration-sensing component to olfactory reception, specifically in the spectral region around 2300 cm\(^{-1}\). Here we present a donor-bridge-acceptor model for olfaction which attempts to explain this effect. Our model, based upon accurate quantum chemical calculations of the olfactant (bridge) in its neutral and ionized states, posits that internal modes of the olfactant are excited impulsively during hole transfer from a donor to acceptor site on the receptor, specifically those modes that are resonant with the tunneling gap. By projecting the impulsive force onto the internal modes, we can determine which modes are excited at a given value of the donor-acceptor tunneling gap. Only those modes resonant with the tunneling gap and are impulsively excited will give a significant contribution to the inelastic transfer rate. Using acetophenone as a test case, our model and experiments on D. melanogaster suggest that isotopomers of a given olfactant give rise to different odorant qualities. These results support the notion that inelastic scattering effects may play a role in discriminating between isotopomers but that this is not a general spectroscopic effect.

I. INTRODUCTION

The general model for detection is that the response is triggered by the transfer of an electron from a donor (D) to an acceptor (A) within the receptor site by the presence of an olfactant molecule that provides a bridge between the two. In the absence of the odorant, the distance between D and A is too great and electron transfer is inefficient. Placing an olfactant (B) between the two allows the electron transfer to occur either as a single coherent scattering event from D to A, or as a sequence of two incoherent hops, first from D to B then from B to A. This simple model is consistent with the standard "swipe-card" model for odor detection since implicit in this is that B must fit into some sort of pocket and be in a correct alignment between D and A in order for the charge transfer process to occur.

An interesting extension to this paradigm is that molecular shape may not be the sole deciding factor in scent recognition. Indeed, it has been observed recently that fruit flies (D. melanogaster) can naively discriminate between several isopentanol isomers substituted for hydrogen\(^1\). These flies can also be trained to associate a specific odor with an electric shock resulting in the specific avoidance of the conditioned odorant\(^2\). Flies trained in this manner can discriminate deuterated from hydrogenated isopentanols, indicating an ability to perceive differences in these odorants. The ability to discriminate between the h-ACP and the d8-ACP has been shown to require the Orco (Or83b) olfactory co-receptor\(^1,3\). Mutant flies that lack the gene are broadly anosmic and fail to discriminate between isopentanol isomers, indicating the behavioral discrimination of isopentanol relies on olfactory perception. In addition, there is a curious observation that fruit flies trained to discriminate deuterated olefins also discriminate non-deuterated olfactants with strong IR peaks in the 2300 cm\(^{-1}\) range.\(^1,4–6\) Lastly, using the negatively-reinforced learning paradigm, Drosophila has been shown capable of generalizing a trained odorant to another that shares a similar vibrational spectrum. For example, when deuterated d5-benzaldehyde is paired with electric shocks, the flies will subsequently avoid fully-deuterated d17-octanol (vs. undeuterated h-octanol), suggesting that the C-D vibrational mode is a salient feature of odorant perception in this species.

A controversial and speculative explanation of these observations is that there is an spectroscopic component to olfaction.\(^5,6\) This model supposes that the bridge facilitates inelastic electron scattering and as such the olfactory response can be predicted by comparing infra-red (IR) spectra of various olfactants. Isotopic substitution of H for D shifts the CH stretching frequency from the 2850 - 3100 cm\(^{-1}\) range into the 2300 cm\(^{-1}\) range. Few molecules absorb in this IR region and there is little or no biological need or evolutionary pressure that we know for detecting deuterated compounds. Needless to say, this theory has been met with considerable skepticism since it runs contrary to more commonly held model in which the geometric shape and chemical nature of the olfactant are the primary components of olfactory reception.\(^7\) Moreover, many of the claims in Ref. 5 and Ref. 6 were show to be inconsistent with psychophysical tests performed on human subjects by Keller and Vosshall.\(^8\) For example, in this study human subjects could not discriminate by smell between deuterated and non-deuterated forms of acetophenone. On the other hand, the molecular mechanism for olfaction in humans might be different since humans have far fewer active odor receptor genes than other mammals and insects.
II. THEORETICAL MODEL

While vertebrate olfactory receptors are G-protein coupled, insect ORs appear to have a deferent structure and act as ligand-gated cation channels. The Or83b odorant receptor gene is a broadly expressed receptor in drosophila and is remarkably conserved amongst the insect species. Information concerning the molecular structure at the olfactant binding site remains illusive, may involve odorants binding to Cu(II) and Zn(II) ions bound to the protein loop, activating the G protein through a structural a “shuttle-cock” mechanism that leads to cascade of events that eventually leads to some neural activity.9

Since very little is known about the molecular level details of the binding of the olfactant to a receptor site, our goal here is to piece apart the possible contributions to the transfer rate, determine whether or not a given bridge molecule can have an inelastic component to the rate, and give at best an indication of the relative strengths of the inelastic components. However, for a given chemical olfactant, it is unlikely that discrimination between isotopomers can be a purely electronic effect since isotopomers have identical electronic structures within the Born-Oppenheimer approximation. It is unlikely that the discrimination could be differences in mass since this would account for at most a few percent in terms of the diffusivity. For example, in comparing the diffusion constant of acetophenone to its fully deuterated isotopomer, one has at best a 3% difference. Also, at ordinary physiological temperatures, there is no significant vibrational contribution to the heat capacity coming from the relevant C-H or C-D stretching or bending modes at 3100 cm$^{-1}$ and 2300 cm$^{-1}$, respectively.

We assume that at the heart of the process, a charge is transferred from a donor to an acceptor within the receptor site itself. In the absence of an odorant, the distance between the donor and acceptor is too great to allow efficient electron transfer. When the odorant is present, it acts like a bridge between the donor and acceptor allowing for more efficient electron tunneling between the two.10 Aromatic compounds are typically better electron donors (i.e. hole receptors) due to their electron-rich π-system. With this in mind, we shall assume that the bridge/olfactant acts as an intermediate for hole transfer between a donor site and an acceptor site. Energy conservation requires that the energy transferred to vibrational motion is equal to the tunneling gap.

For a donor-bridge-acceptor (DBA) system in the nonadiabatic limit of electron transfer theory, the golden rule rate is given by

$$k_{da} = \frac{2\pi}{\hbar} |V_{da}|^2 F(E_{da}).$$

There are two contributing factors to the transfer rate. First, $V_{da}$ is the effective coupling between donor and acceptor which depends upon the electronic coupling between the donor and acceptor and $F(E_{da})$ is the thermally averaged Franck-Condon weighted density of nuclear vibrational states between the donor and acceptor and $E_{da}$ is the energy gap between donor and acceptor.

A. Inelastic scattering model

Before describing our approach, let us briefly review the model by Lambe and Jakelvic for molecular vibrational spectroscopy via inelastic electron tunneling in a tunnel junction system.11 In a tunneling device, where there is a
barrier potential $U(z)$ separating two metallic leads, the WKB approximation give the electronic part of the tunneling matrix element as

$$|V_{da}| \propto \exp \left[ -\int_0^L \left( \frac{2m}{\hbar^2} \right) (U(z) + U_{int}(z) - (E - E_\perp))^{1/2} dz \right]$$

(1)

where $L$ is the spacing between leads (i.e. the spatial thickness of the barrier), $E$ is the total electronic energy, $E_\perp$ is the kinetic energy associated with motion perpendicular to the barrier, and $U_{int}(z)$ is small perturbing potential due to the presence of an impurity molecule in the tunneling region.

In a classic paper by Scalapino and Marcus$^{12}$, they considered the case where a molecule with a permanent dipole moment $\mu_o$ is located close to one of the electrodes so that its image dipole must be included. This leads to an interaction potential between the passing electron and dipole of the form

$$U_{int}(z) = 2e\mu_oz/(z^2 + r_\perp^2)^{3/2}$$

(2)

where $r_\perp$ is the distance from the molecule and the electrode and $\mu_o$ is the molecular dipole operator. For the case of a single molecule in the tunneling region the current couples to the dipole oscillations of the molecule leading to an inelastic contribution that contains the vibrational transition moment. Lambe and Jakelvic also show that even in when the molecules in the tunneling gap lack permanent dipole moments, the current can couple to the polarizability of the molecules leading to Raman contributions to the inelastic current. Here, again one considers the interaction between the impurity molecule, the passing electron, and the nearest image dipole to show that

$$U_{int}(z) = -4e^2\alpha z^2/(z^2 + r_\perp^2)^3$$

(3)

where $\alpha$ is the polarizability of the molecule. In this case, the scattering of the electron induces Raman-like transitions within the impurity molecule. Both cases lead to golden rule expressions for the inelastic contributions to the current-voltage curves in the presence of molecular impurities in the system. Brookes et al.$^{18}$ follow a similar lines and arrive at estimates for whether or not an inelastic tunneling component would be possible to observe in a model parameterized by physiological considerations.

However we argue that such inelastic barrier tunneling models are not suitable for the case at hand where we have electron transfer between localized states on the donor, bridge, and acceptor. While connection between the electron transfer rate and the zero-bias molecular conduction was discussed by Nitzan$^{14}$ in comparing the Landauer formula to the Marcus rate, the relation is established when the orbitals of the bridging molecule are in contact with orbitals of the donor and acceptor leads. This is not the case in the model described above.

B. Donor-Bridge-Acceptor model

Since the electron transfer rates are likely far slower than the structural responses they trigger, the central goal in this paper is to determine those internal vibrational modes of the bridge species that are important in accommodating the inelastic scattering rather than providing actual transition rates. Bridge mediated charge transfer is a broadly studied topic$^{15-21}$, and we start by assuming that we have three relevant sets of diabatic states denoted by $|\psi_d\rangle = |D^+BA\rangle$, $|\psi_b\rangle = |DB^+A\rangle$, and $|\psi_a\rangle = |DBA^+\rangle$ corresponding to the initial, intermediate, and final quantum states of the system. In $|\psi_d\rangle$, the charge is localized in a donor orbital and the bridge is in its neutral electronic state. In $|\psi_b\rangle$, the bridge is in a singly oxidized state, lastly in $|\psi_a\rangle$, the bridge is again in a neutral state and the charge is localized in an orbital on the acceptor. Within a diabatic picture, we have the following Hamiltonian:

$$H = \begin{bmatrix} \hat{H}_d & \hat{j}_{db} & 0 \\ \hat{j}_{bd} & \hat{H}_b & \hat{j}_{ba} \\ 0 & \hat{j}_{ab} & \hat{H}_a \end{bmatrix}$$

(4)

where each term on the diagonal represents the electronic + nuclear Hamiltonians for each state. $\hat{J}_{bd}$ and $\hat{J}_{ba}$ are the electronic interactions between bridge and donor or acceptor states respectively. We assume that the through-space coupling between the donor and acceptor are negligible compared to the other couplings in the system.$^{22}$

Let us re-cast this as a reduced two state problem using the Feshbach method so that the transition from the donor to acceptor states is via resonant scattering involving the bridge (olfactant) molecule.$^{23-26}$ The results in an effective Schrödinger equation

$$H_{eff} = \hat{H}_d + \hat{H}_a + V_{eff}(E)$$

(5)

where $\hat{H}_d + \hat{H}_a$ is the unperturbed system lacking the bridge and

$$V_{eff}(E) = \hat{j}_{ab} \frac{1}{(E - \hat{H}_b)} \hat{j}_{bd}$$

(6)

is an effective coupling matrix element between the donor and acceptor due to the presence of the bridging molecule which depends upon the scattering energy, $E$.$^{22,25,26}$ This operator has a series of poles located at the eigen-energies of $H_B$ and contains both resonant and non-resonant components.

At the heart of Eq. 6 is the Green’s function for the evolution of a nuclei on the potential energy surface of
the ionized species. We can imagine this in the dynamical sense: Upon ionization, the nuclei in $B$ experience a sudden change in their electronic environment corresponding to the charge transfer from the donor to the bridge. This creates a vibrational wave function on the potential energy surface of the ionized species centered about the ground-state nuclear geometry. We can write this as

$$V_{\text{eff}}(E) = \langle \psi_a | \hat{J}_{ab} G_b(E) \hat{J}_{bd} | \psi_d \rangle$$

$$= \frac{J_{ab} J_{bd}}{i \hbar} \int_0^\infty e^{-i E t / \hbar} C_{da}(t) dt \quad (7)$$

where $C_{da}(t)$ is correlation function for the propagation a vibrational wave packet on the Born-Oppenheimer potential, $V^{(\pm)}$, corresponding to this new electronic configuration, then projected onto the manifold of vibrational states of the final electronic configuration, where as above we partition the electronic contribution from the nuclear dynamics, except that our time evolution occurs on the $V^{(\pm)}$ potential corresponding to the bridging state. This gives the correlation function as

$$C_{da}(t) = \sum_a \langle n_a | e^{-i H_\text{tot} t / \hbar} | 0_d \rangle = \sum_a \langle n_a | \psi(t) \rangle$$

where we have assumed the initial wave packet to be the ground-state vibrational wave function and the sum is over final vibrational states $| n_a \rangle$. Upon promotion to the ionized state, the nuclei receive an impulsive force along the direction of the gradient of $V^{(\pm)}$. This is certainly the case for a classical oscillator displaced from its equilibrium position $q_o$ to $q'$ where the force acting on the particle is $-k(q' - q_o)$. The oscillator then follows an elliptical trajectory in phase-space. Secondly, since the wave function is simply the displaced harmonic oscillator ground-state wave function and the well is harmonic, the shifted state evolves as a Glauber coherent state in phase space without spreading or contracting. Thus, we approximate the time correlation function as

$$C_{da}(t) = \sum_j e^{i \omega_j t} \langle n_j | e^{i p_j x} | 0_d \rangle$$

$$\approx \sum_j e^{i \omega_j t} i p_j \mu_j / c \quad (8)$$

where $p_j$ is the momentum imparted along normal coordinate $j$, $\omega_j$ is the normal mode frequency, and $\mu_j = c \langle 1_j | x | 0_d \rangle$ is the transition dipole moment for the $j$th vibrational transition.

We can now evaluate Eq. 7 by taking the Fourier transform of the correlation function. This gives the effective potential as a series of $\delta$-functions

$$V_{\text{eff}}(E) \approx J_{ab} J_{bd} \sum_a p_b(\omega_a) \langle 1_a | x | 0_d \rangle \delta(E_{da} - \hbar \omega_a) \quad (9)$$

and we recall that the delta-function carries units of inverse-energy. Energy conservation requires that total momentum transferred to all the oscillators be such that $E_{da} = \sum_a p_a^2 / 2$ in mass-scaled units. From above, we assumed that the momentum transferred to the mode is proportional to the energy gradient of the ionized species along that direction evaluated at the equilibrium position of the neutral. This implies that to a first approximation the inelastic scattering of an electron via the bridge species excites the vibrational modes of the bridge that are also infra-red (IR) active. This is a central component of Turin’s spectroscopic theory of olfaction.\textsuperscript{1,5,6} However, here we see that only those modes that are directed along $\nabla V^{(\pm)}$ will be excited by the impulsive scattering process.

Eq. (9) gives us a direct way to rapidly screen whether or not a given odorant is expected to exhibit an isotope effect using quantum chemical means. Starting from the equilibrium position of the neutral, one first determines the vibrational normal modes and frequencies of a given olfactant. This gives the IR response of the molecule. We then determine the energy gradient of the ionized species at this geometry and project this onto the normal mode coordinates, which are normalized linear combinations of the cartesian displacement coordinates for each atom in the molecule. Since $E_{da}$ remains an unknown in our model, we require that this energy be distributed amongst the normal coordinates in proportion to their projection onto the energy gradient. Thus, even if a mode has a strong IR response and satisfies energy conservation, unless that mode is directly excited by the impulsive scattering process, then it will not contribute to the overall transition rate. Moreover, in order for CD stretches to play any role in the transfer rate, we have to make the assumption that $E_{da} \approx 2300 \text{cm}^{-1}$.

C. Numerical results

As a test case, we consider acetophenone (ACP) and its deuterated isotopomers. In d3-ACP, the hydrogens on the methyl group are replaced, in d5-ACP the hydrogens on the phenyl ring are replaced, and in d8-ACP all hydrogens are replaced with deuteriums. In all cases, we first perform geometry optimizations of the neutral species followed by calculations of vibrational frequencies using the B3LYP density functional with 6-31G(d) basis set in vacuum using the NWChem quantum chemistry package.\textsuperscript{27} The same functional and basis set were then used to calculate the nuclear gradients and frequencies of the radical cation at the equilibrium geometry of the neutral. The gradients are then projected on to the normal mode eigenvectors giving the projection of the force onto a given normal mode with frequency giving us $p(\omega)$. The normal mode calculations also give us the infra-red response, $\mu(\omega)$. Since we know little about the actual binding site, we can only assume that the transfer integrals $J_{ab}$ and $J_{bd}$ are independent of the vibrational modes and are the same for each isotopomer. Figure 1(b) shows the results of our calculations for the deuterated and non-deuterated forms of ACP along with the predicted infra-red responses. This approach is numerically
reliable and produces accurate potentials and gradients for this system without undue effort. Moreover, this general procedure can be applied to a broad set of olfactants.

Briefly, the peaks around 3100 cm\(^{-1}\) correspond to the C-H stretching modes of the molecule. In the fully deuterated d8-ACP, this peak is shifted to 2300 cm\(^{-1}\), consistent with the typical isotope shift of a C-D stretching mode. Furthermore, the IR spectra for all but the d8-ACP is void of peaks between 1800 - 3000 cm\(^{-1}\). Only the fully deuterated d8-ACP has any appreciable spectral density in this region. While there is little to note in comparing the intensities for the modes below 1800 cm\(^{-1}\), the contribution to the gradient coming from the C-H and C-D stretching modes is remarkably strong. Most notable, the peak at 2300 cm\(^{-1}\) is more or less the sum of contributions from the ring and methyl C-D stretching modes.

Based upon the relative intensities of both the IR and energy gradients around 2300 cm\(^{-1}\), the electron transfer model suggests that D. melanogaster should readily discriminate h-ACP and d8-ACP. In comparing the predicted IR spectra, there is almost no IR oscillator strength in the C-D stretching modes for d3- and d5-ACP while d8-ACP exhibits a fairly strong signal. However, in comparing the gradients, the d5-ACP gradient has considerably smaller projection onto the C-D stretches modes and the d3-ACP projection is almost vanishingly small. Based upon gradients, one predicts that there should be an ability to differentiate between h-ACP and d8-ACP. Moreover, the flies may be able to discriminate between d3-ACP and d5-ACP even though both have very weak IR signals at 2300cm\(^{-1}\).

A crucial test of our model would be to identify an olfactant that can not be discriminated from its deuterated isotopomers. For example, in removing an electron from ethylene, the C=C bond-length in C\(_2\)H\(_4\) will be longer than in C\(_2\)H\(_4\) (due to reduction in bond-order) but the C-H bond-lengths will be more or less unchanged. This suggests that the energy gradient in our model will be directed primarily along the C=C bond. Quantum chemical calculations of the sorts described above on ethylene and two of its isotopomers, HDCCH\(_2\) and D\(_2\)CCH\(_2\), indicate the forces along the CD stretching coordinates these are far weaker in magnitude than along the CH stretching coordinates. More over they are about 40-fold weaker than the corresponding forces in d8ACP but are only half of those in d3ACP. However, the IR spectrum of ethylene does show an obvious isotope shift of the C-H stretching modes into the 2300cm\(^{-1}\) region. Consequently, our model would predict that while Drosophila can discriminate between hACP and d3ACP it is doubtful that they could discriminate between ethylene and its isotopomers within the limits of the error bars of the T-maze experiments.

### III. EXPERIMENTAL TESTS

Previously, d5-ACP and d8-ACP odorants were found to be significantly more aversive to Drosophila than h-ACP\(^1\). We verified this result, examining the naïve avoidance of Drosophila \(w^{1118}\) to 0.3% h, d3, d5, and d8-ACP using an olfactory T-Maze\(^2\) (Figure 3a). The avoidance response to h-ACP and d3-ACP were indistinguishable (\(F_{3,80} = 11.724\), Bonferroni-Dunn post hoc \(p = 0.276\)); the responses to d5 and d8 were also not significantly different from each other (\(p = 0.842\)). However, the avoidance response to d5-ACP was significantly greater than the response to d3-ACP (\(p = 0.0016\)), suggesting deuteriums on the benzene ring provided a different odorant quality than the methyl deuteriums, leading to an increased saliency for the d5-ACP and d8-ACP. To test this hypothesis, we used negatively-reinforced olfactory learning\(^28\).

Surprisingly, the \(w^{1118}\) flies are capable of discriminating between d5-ACP and d3-ACP after training, indicating a significant difference in perceptual quality between these odorants (Figure 3b; \(t = 24.714\), \(p < 0.0001\)). The \(w^{1118}\) flies are also capable of discriminating between h-ACP and d3-ACP after training (Figure 3c; \(t = 10.596\); \(p < 0.001\)). The conditioned avoidance in this experiment was reduced in comparison to the conditioned avoidance of d5-ACP vs. d3-ACP, indicating that d3-ACP is more similar in odorant quality to h-ACP than to d5-ACP. The robust discrimination between these very closely related odorants is consistent with our model that predicts differences in the excitation of vibrational modes of the methyl and deuterium C-D bonds by the impulsive scatting.

### IV. SUMMARY

It is clearly evident that D. melanogaster can be trained to distinguish deuterated isotopomers of various olfactants. Whether or not this is the result of a spectroscopic detection mechanism is an another question. Our model predicted that Drosophila could be trained to discriminate between d8-ACP and d5-ACP, between d5-ACP and d3-ACP, and between d3-ACP and hACP based upon comparison of the gradients at 2300cm\(^{-1}\). This prediction was borne out in the training experiments. Moreover, discrimination between d8-ACP and d5-ACP would not have been predicted based upon just the IR spectrum. While deuteration does shift the C-H stretching mode into the otherwise empty 2300 cm\(^{-1}\) region, our model suggests that IR response alone does not determine whether or not the flies can discriminate isotopomers. Moreover, this effect appears to be limited to a single spectral region and does not involve the entire IR spectrum.\(^5,6\)

Lacking detailed molecular level knowledge of the receptor sites, we speculate the tunneling gap between donor and acceptor sites is around 2300 cm\(^{-1}\) and that
FIG. 2. Computed IR Spectrum of ethylene (a) and projection of the energy gradients of singly oxidized ethylene (b) and its deuterated isotopomers in the 2000-3500 cm\(^{-1}\) CD and CH stretching region. Color key: – \(C_2H_4\), – \(DHC_2 = C_2H_2\), – \(D_2C_2 = C_2H_2\).

FIG. 3. Olfactory Discrimination of Acetophenone isomers. a) Drosophila melanogaster (w\(^{1118}\)) naively avoid ACP in a T-maze. The behavioral responses to both d5-ACP and d8-ACP are significantly stronger than to both the d3-ACP and h-ACP. (\(n = 22\) groups each) (b) Drosophila can discriminate between d5-ACP and d3-ACP after training with electric shock. During the training session, populations of flies are exposed to one of the isotopomers paired with an electric shock. When subsequently tested in the T-maze, the flies significantly prefer the unpaired odorant over the paired odorant (\(p < 0.0001; n = 44\) groups each). (c) Drosophila can discriminate between h-ACP and d3-ACP after training with electric shock.

The narrow spectral region about \(E_{da}\) is giving rise to the observed ability for Drosophila to discriminate between deuterated isotopomers by scent. It is possible that the tunneling gap may be tuned to the nitrile (-C≡N) stretching mode which does lie in this spectral region and may serve a role in detecting a variety of naturally occurring nitrile containing odorants. A test of our model would be to identify an olfactant that has IR active C-H stretching modes but upon ionization distorts along modes that do not involve the C-H stretching modes. For example, it is known that upon ionization of ethylene, the C=C bond-length in \(C_2H_4^+\) is shorter than in \(C_2H_4\) and the C-H bond-lengths are unchanged. This suggests that the energy gradient in our model will be directed primarily along the C=C bond and have very little projection onto the C-H stretching modes. However, the IR spectrum does show an isotope shift of the CH stretching modes into the 2300 cm\(^{-1}\) region. This is evident in our computed spectra shown in Fig. 2. Our model then predicts that Drosophila should not be able to easily discriminate between ethylene and any of its isotopomers. The model also suggests that the isotope effect may not generalize between different classes of organic olfactants. For example, here we focused upon aromatic olfactants which are good hole acceptors since they have electron-rich \(\pi\)-systems. However, the electron transfer dynamics through aliphatic system would not likely involve transfer of a positive charge and may well involve different olfactory receptors all together.
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