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BOOK REVIEW

Scent and Alchemy: The Paperback

The Secret of Scent: Adventures in Perfume and the Science of Smell, by Luca Turin. Harper Perennial edition, New York, 2007. 207 pp, Paperback, $13.95. ISBN 978-0-06-113384-8.

Abstract

The *Secret of Scent* by Luca Turin is an ethereal excursion into the world of perfumes and the science of smell. The lyrical and tantalizing descriptions will leave the reader with an enhanced appreciation of the most enigmatic of our senses. If there is a secret revealed, it is that the recognizable odor features of complex perfumes are simple and may be caused by a single type of molecule. Turin claims that odor quality is determined by infrared vibrations despite overwhelming evidence that chemical functional groups and shape determine odor. The vibration theory of olfaction is a kind of alchemy where commonplace waves are transmuted into exotic odors. Despite its transcendent appeal, the vibration theory of olfaction has no scientific basis. Isotope substitution in odor stimuli has practically no effect on odor. If vibrations determined odor, isotope substitution would evoke odor differences as large as the differences between colors of the rainbow. The mechanism of frequency analysis proposed by Turin—inelastic electron tunneling spectroscopy—is erroneous because free electrons have no natural occurrence in biology. Turin can be appreciated for his art of perfumery, but his "science" of smell is contrary to facts and basic scientific principles.

Introduction

The paperback edition of *The secret of scent: adventures in perfume and the science of smell* by Luca Turin (2007) is a book about the art of perfumery and the selling of a science myth about smell. It is essentially a duplicate of the hardcover version (Turin 2006). A few typographical errors have been corrected in the paperback edition, but the corrections do not change the flawed central facts and concepts in the book. The book can be divided into 3 parts: 1) the sensory properties of perfumes, 2) odor chemistry, and 3) the vibration theory of odor. The book is a worthwhile reference for scientists interested in perfumes because it provides an overview of the sensory characteristics of perfume components and how perfumes are created. However, the chemistry and theoretical foundations are extremely weak. I would hesitate to recommend the book to nonspecialists because it contains numerous errors of fact, chemistry, and concepts that are not easy for the average reader to evaluate.

Perfumes

The first section deals with the sensory properties of perfumes. It is here that Turin is in his comfort zone, describing with elaborate visual and auditory allusions the rich world of scent. He explains the basic strategy of perfume formulation and how odor cocktails exude their different notes: high notes for small, volatile, fleeting molecules; "heart notes" that give perfumes their main character; and long-lasting low notes for bulky, tenacious molecules. He tells us about the great odor categories, how odors blend and merge, and why he thinks there are no true odor antagonists (p. 107). His answer for the last idea is that there are no receptor antagonists for molecular vibrations—the foundation of his new theory. However, Oka et al. (2004) have reported evidence for receptor-based antagonism in olfaction.

Natural odors are often complex mixtures of many chemicals whose contributions may be difficult to assess. Turin provides interesting examples of single chemicals that seem to embody natural smells: *trans*,*cis*-2,6-nonadienal (p. 55) is immediately perceived as cucumber; allyl amyl glycolate (p. 65) "smells like a pineapple the size of a carnival float"; alpha-methyl ionone smells "convincingly of violet flowers" (p. 62); and phenylethyl alcohol is a rose, rose oxide is a rose, and geraniol is a rose (p. 56), though none can exactly substitute for the real thing. We learn the intriguing relationships among musk, amber, and wood odors and that benzyl salicylate, though odorless to most people, inexplicably gives away its presence in mixtures.

Turin remarks (p. 59) that a new synthetic perfume with a sulfur-containing thiophene group "keeps its infernal thoughts to itself." However, thiophene, despite containing sulfur, really is not vile. Through the magic of chemistry, thiophene is an electronic and steric analog of benzene (Pauling 1946) and has an odor reminiscent of benzene (The Merck Index 2001).

Throughout the book we get glimpses of Turin's flamboyant character. In the parlance of the topic of the book, his writing style is a mixture of vanilla, sandalwood, and musk, with a heavy dose of mercaptans. Without any substantiation, he claims that he "cracked the code" for smell (p. 7) and that his company's "success rate was one product in ten molecules synthesized, two orders of magnitude better than the industry standard of one in a thousand" (p. 189).

And what is this new odor code? According to Turin, the mechanism for detection and recognition of odors is to be found in infrared vibrations of the odorants, not particularly in their chemical structures. He claims that olfaction is not a chemical sense but a spectral sense like vision and hearing. The main reason for believing this is that some chemicals (he claims) have similar odors and similar infrared absorption bands despite having different shapes and functional groups. The theory really is not all that new since it goes back at least to 1938. He provides a thorough and reasonably accurate history of the vibration theory of olfaction, including its early development by Malcolm Dyson and Robert H. Wright. It is just that they were unable (according to Turin) to make the key connection between the odors of boranes and thiols that Turin was able to do.

Turin does a disservice to Linus Pauling, John Amoore, and R.W. Moncrieff by implying that they believed odor was determined solely by molecular shape. As chemists who established some of the basic physical and chemical rules governing structure–quality relationships in olfaction, they were aware that molecular shape alone did not determine odor quality but that functional groups, polarity, and overall chemical constitution were equally important. Turin's simplistic argument that ethanol and ethanethiol would have similar smells if shape determined odor disregards the enormous differences in physical and chemical properties of the 2 compounds due largely to differences in polarity and H-bonding capability of alcohols and thiols—features that no chemist would ever ignore.

Turin takes too literally Pauling's concept of shape in biological interactions. In his 1946 paper, Pauling (1946) was making an important distinction between chemical reactions and biological recognition. For example, in biochemical reactions such as occur in glycolysis, covalent bonds are made and broken according to functional group chemistry; but in immunology or receptor-based signaling, with few exceptions, no chemical transformation of the ligand occurs, and a degree of substitution across chemical groups, such as replacement of a methyl group by a chlorine atom, is allowed. Indeed, Pauling even used this distinction to decide whether a particular biochemical process was based on a specific chemical reaction or broader feature recognition. A good example of the complex interaction of chemistry, shape, and functionality in biological recognition is the use of sucralose as a noncaloric sweetener. The substitution of 3 of the 8 hydroxyl groups of sucrose by chlorine atoms retains most of the biochemical features of the molecule, enhances its sweetness, but renders it metabolically inert.

Chemistry

The second part of the book is an excursion into basic chemistry. The expression "the science of smell" in the title is rather presumptuous considering the admission of the author (p. 7) that he has "no formal training in chemistry." One would think that knowledge of chemistry would be a prerequisite to teaching chemistry in a book dealing with the chemical senses. Turin's statement (p. 167) that "reading all that matters in structure-odour relations takes a few months" is a gross underestimate in view of the many errors in chemistry evident in the book.

On page 83, Turin refers to a compound with the formula $C_{44}H_{69}O_{12}N$ that he says is an enzyme called isomerase. That cannot be the case because it contains just a single N atom, whereas most enzymes contain more than 100 amino acid residues and 100 N atoms. The formula indicates that the compound is probably an antibiotic named tacrolimus that is completely unrelated to enzymes. This egregious error has not been corrected in the paperback edition. On page 82, the structures for *trans*- and *cis*-2-hydroxycinnamic acid are both incorrect. Other errors in chemistry occur on pages 51 and 52 where mandelonitrile and benzonitrile are shown with angled –CN group attachments that are incorrect for sp (linear) orbital hybridization; on page 52, nitrobenzene should have an N=O double bond and the structural formula for azidobenzene is incorrectly shown as benzyl azide; on page 111, the structure called "nitrite" is in fact a nitrile; and on page 174, Turin incorrectly considered propanone to be a "heavier analogue" of acetone when they are actually 2 names for the same chemical. None of these errors were noted in reviews of the hardcover edition or apparently by editors of the book.

There is an indirect reference to another "glaring error" (p. 153) in one of Turin's papers. Though Turin does not explicitly say what this error was, it is likely that it refers to a comment (Turin 1996) that "glycine contains only exchangeable protons," which was made in the context of whether fish could distinguish normal and deuterated glycine by smell. The alpha hydrogens of glycine in fact do not exchange their protons with water. If they did, so would the alpha hydrogens of all natural L-amino acids. Because the mechanism of exchange involves the inversion of configuration to D-amino acids, a nontrivial consequence would be that life as we know it would be impossible.

An error in the structure of acetic anhydride (p. 42) has been corrected in the paperback edition, though the structure of coumarin on the same page is now incorrectly shown as dihydrocoumarin. The paperback edition also corrects (p. 189) a misquote ("critical journalists" in the hardcover edition) of a comment published in Nature Neuroscience: "the extraordinary—and inappropriate—degree of publicity

that the theory has received from uncritical journalists'' (Anonymous 2004). The misquote was repeated (and corrected) in a review in the New York Times (Lanchester 2006).

Vibrations

The third part of the book is a complete meltdown into a world of imagined facts and imagined myth masquerading as theory (the vibration theory of olfaction). Turin does not seem to trust anything but his own stated perceptions, and he invents an outrageous mechanism (inelastic electron tunneling spectroscopy) to explain them. The vibration theory of olfaction is an alchemist's dream—a universal method to convert waves into odors—but it is not supported by facts or basic scientific principles.

The starting point for Turin is his persistent argument that decaborane ($B_{10}H_{14}$) has an odor similar to thiols because both have similar infrared absorption bands near 2550 cm^{-1}. As most people will not have had the chance to smell decaborane because it is rather toxic, we have to take his observation on faith. In truth, descriptions of the odor of decaborane and other boranes, although they suggest a foul odor, do not necessarily equate to a particular sulfurous compound. Indeed, Turin is inconsistent in how he describes the odor of decaborane, at times saying it smells like sulfur, rotten eggs, thiols, leeks, or boiled onions. Turin's imprecision here is disturbing. It is important to know exactly what chemicals are being compared in order to determine whether their spectral bands are correlated with particular odors.

The region of the infrared spectrum near 2550 cm^{-1} for most compounds is generally deficient in absorption bands, but the S–H stretch of thiols rather uniquely occurs here. However, the intensity of the band is weak and barely noticeable in some thiols. From a teleological perspective, it would seem inefficient for a molecular recognition system in biology to depend on this particularly weak absorption band. Decaborane has an intense B–H stretch band in this region; so the overall comparison between decaborane and thiols is actually rather poor. In *The secret of scent*, Turin provides an infrared spectrum of diborane (p. 125) but no spectrum of a thiol for comparison. The weakness of the S–H stretch band in thiols would show the fatal weakness of his argument. Presumably, the position (frequency or wavelength) of the absorption bands would determine odor quality, and the strength of the bands would determine odor intensity. If particular bands are weak, they would be expected to contribute little to odor quality.

Turin and Yoshii (2003) reported that the *ortho*, *meta*, and *para* isomers of carborane ($C_2B_{10}H_{12}$) have a camphoraceous rather than a sulfurous odor and therefore assumed that they had weak absorption bands around 2550 cm^{-1}. Bands in this region were calculated (Brookes et al. 2007) to be weak. However, these presumptions are not borne out by the facts that show prominent infrared absorption bands near 2550 cm^{-1} for all 3 carborane isomers (Grafstein and Dvorak 1963; Schroeder et al. 1963; Papetti and Heying 1964). In fact, as for decaborane, the bands appear stronger in the carboranes than in thiols. This indicates that 1) Turin is selective in the data he chooses to consider and 2) the infrared bands do not define the odor.

The most direct test of the vibration theory of olfaction is achieved by isotope substitution. Turin claimed that acetophenone and its fully deuterated derivative have different odors even though they have practically the same shape. Turin described this odor difference as either ''striking'' (Turin 1996) or ''subtle'' (Turin 2007, p. 188). Keller and Vosshall (2004), in a controlled study with 36 subjects, found that normal and deuterated acetophenone could not be distinguished by smell. But Turin did not accept the conclusions, claiming the subjects were ''naive'' (Turin 2007). It is here that we reach an impasse. Unlike most scientists, Turin appears to think that he alone is the judge of what is true, that he does not need other researchers to test his findings, and that he does not need statistics because he can rely on anecdotal observations.

Normal and deuterated odorants have essentially the same odor. Yet Turin (1996) reported that the C–H stretch band of acetophenone near 3080 cm^{-1} was shifted to about 2290 cm^{-1} for the C–D stretch band in the deuterated compound, a difference of about 34%. This is not very different from the 40% difference between the stretch frequencies of the O–H and S–H groups in ethanol (3665 cm^{-1}) and ethanethiol (2615 cm^{-1}) (National Institute of Standards and Technology Standard Reference Database 2005), whose odors are as different as roses and skunks. If the infrared bands determined odor, the odor difference between normal and deuterated acetophenone should not be ''subtle'' but should be enormous. In the visual system, a truly spectral sense, red/green or yellow/blue opponent colors each differ in wavelength by only about 22%. If absorption frequency determined odor, distinguishing normal and deuterated compounds would require no more sophistication than recognizing the colors of the rainbow.

Isotope substitution plays an important role in testing the vibration theory because the infrared bands depend on the mass of the atoms much more than on their chemistry. Substitution of hydrogen by deuterium often has little effect on chemistry but is expected to change a vibration frequency by a large factor—theoretically by approximately $\sqrt{2}$ or a difference of 41%. Measured differences for the C–H and C–D stretch frequencies of acetophenone (34%) and naphthalene (35%) are close to the theoretical value.

The only systematic study reporting a difference in human perception due to isotope substitution is a study of normal and deuterated benzaldehyde (Haffenden et al. 2001). That study reported that 23 of 30 trained subjects could properly match the samples when presented with normal or deuterated benzaldehyde. The result was shown to be statistically significant, with the likelihood of chance occurrence of less than 1%. Further analysis of the data suggested that 47% of the subjects actually perceived a difference and that the performance of the other subjects was due to guessing. The

study did not report whether subjects thought deuterated benzaldehyde differed in quality from the bitter almond odor of normal benzaldehyde. Overall, the study suggests that the quality difference was marginal.

Wright (1982) reported that 4 of 6 subjects could distinguish normal naphthalene (mothballs) from deuterated naphthalene. The small sample does not allow an assessment of statistical significance, though the proportion is similar to that observed for benzaldehyde. The sharp difference in the infrared spectra between naphthalene and its deuterated counterpart (Figure 1) would almost certainly have resulted in a large odor difference if the absorption bands determined odor. The C–H stretching band is shifted from 3070 to 2280 cm^{-1} in the deuterated compound, a difference of 35%. Wright's failure to provide a convincing demonstration of an odor difference suggests that the difference is minimal or nonexistent.

The specific mechanism that Turin used to support the vibration theory—inelastic electron tunneling—is incorrect because his mechanism uses free electrons generated from dihydropyridine nucleotides (Turin 1996). Redox mechanisms involving NADH and NADPH have been proven to use reversible and stereospecific transfer of hydrogen to redox partners. (Fisher et al. 1953; Clark 1960). The ''electron gun'' model of Turin would neither be reversible nor allow specific hydrogen transfer. Free electrons in biological systems are mostly used for bookkeeping purposes and not to be taken literally except where radioactive or high-voltage sources are used. Even in neurons that are considered to be the hallmark of bioelectricity, it is the ions (anions and cations) and not electrons that are the carriers of current. Electron transfer in biological redox reactions is a formalism in much the same way as Lavoisier's concept that respiration is equivalent to combustion. In an aqueous biological environment, there are no free electrons and no flames.

There has been a long debate over fundamental concepts such as oxidation and reduction. Originally, oxidation was considered to be a gain in oxygen and reduction was the opposite, the loss of oxygen. With organic carbon compounds, reduction can be viewed as a gain in hydrogen (hydrogenation), whereas oxidation can be considered to be a loss of hydrogen (dehydrogenation). More generally, oxidation is equivalent to a loss of electrons and reduction is equivalent to a gain of electrons.

In order to clarify the nature of the oxidation–reduction (redox) reaction, it is often split into 2 parts, or half-reactions: the oxidation part and the reduction part. Each half-reaction shows, for convenience, the fate of the electrons as well as the charges of all species including the negative charges of the electrons. To balance each half-reaction, the numbers of each atom type must be the same on each side of the equation and the net charge must also be equal. In the case of alcohol dehydrogenase (written as the reduction of acetaldehyde by NADH), the half-reactions are:

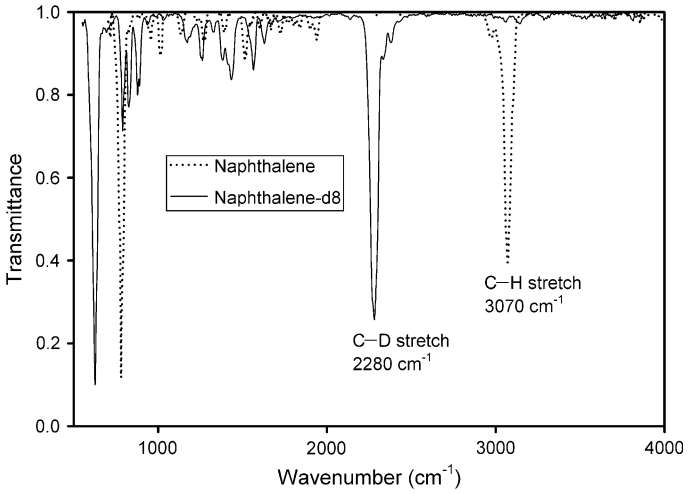

Figure 1 Infrared spectra of naphthalene and naphthalene-d8. The C–H stretching band of naphthalene occurs at a higher frequency than the C–D band in the deuterated compound. Vapor phase data from National Institute of Standards and Technology Standard Reference Database.

$$NADH \rightleftharpoons NAD^+ + H^+ + 2e^- \text{ (oxidation)}$$

$$CH_3CHO + 2H^+ + 2e^- \rightleftharpoons CH_3CH_2OH \text{ (reduction)}$$

Net reaction:

$$NADH + H^+ + CH_3CHO \rightleftharpoons NAD^+ + CH_3CH_2OH.$$

In the first half-reaction, the NADH is oxidized to NAD^+ and loses 2 electrons. In the second half-reaction, the acetaldehyde is reduced to ethanol and gains 2 electrons. The overall redox reaction is obtained by adding the 2 half-reactions. The electrons cancel in the net reaction.

Notwithstanding the formal participation of 2 electrons in each of the half-reactions, it is important to note that their existence is only virtual. Looking at the half-reactions, we might consider that NADH can be a source of free electrons. But a little knowledge can be dangerous. The half-reactions say nothing about the redox potentials of the chemical species involved. In aqueous solution, most chemical reactions take place within a narrow range of about 2 volts. Outside of this range, water will be oxidized and oxygen will be released or water will be reduced and hydrogen will be released. Allowing the existence of free electrons is tantamount to allowing the existence of the most extreme reducing agent that will reduce water and many solutes. An approximation to the existence of free electrons in water would be ionization of metallic sodium because of its exceptional propensity to lose electrons and form Na^+ ions. However, this exercise shows the absurdity of the idea because sodium reacts violently with water. The nascent electrons would combine instantly with water to liberate hydrogen gas.

The logic of NADH and NADPH reactions in biology cannot be fully appreciated by the equations given above. The

reaction of NADH with acetaldehyde does not occur in the absence of the enzyme alcohol dehydrogenase. Furthermore, as noted above, the enzyme-catalyzed reaction occurs in a reversible and stereospecific way such that a hydride ion (H^-) equivalent—a proton with 2 electrons ($H^+ + 2e^-$)—is shuttled directly from NADH to acetaldehyde. This has been proven by studying the transfer of labeled hydrogen between NADH and ethanol. The detailed mechanism is not described in all biochemistry texts, presumably because the historical treatment has given way to an emphasis on more recent discoveries. One of the best and most informative descriptions can be found in a recent text (Lehninger et al. 2005).

We now know that the olfactory receptors belong to a family of membrane proteins known as G-protein–coupled receptors (GPCRs) that function in many different signaling systems. GPCRs work by chemical binding of ligands to specific receptor sites to induce conformational changes in the receptor to activate an intracellular transduction cascade. No GPCRs are known that use electron tunneling. Though the basic functional concept of sensory signaling via GPCRs is well established, it will be a challenge to match the thousands of potential odor ligands with the hundreds of odor receptors. Molecular modeling of ligand binding to olfactory receptors (Katada et al. 2005) has demonstrated significant structural parallels with retinal binding to opsin in rhodopsin, the visual GPCR prototype. The reviews by Moncrieff (1967) and Rossiter (1996) provide overwhelming evidence that there exists a close relationship between the types of odors and the steric and electronic chemical features of odor molecules.

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Thomas P. Hettinger, PhD

Department of Oral Health and Diagnostic Sciences
University of Connecticut Health Center
263 Farmington Avenue
Farmington, CT 06030-1718, USA
e-mail: thetting@neuron.uchc.edu