natively, the greater rate of urea synthesis in rats may reflect the greater metabolic rate and protein metabolism of small animals compared to larger ones (*6*).

In a similar experiment, four rhesus macaques and four stump-tailed macaques (*Macaca arctoides*) took isocaloric low casein (1.3 g/kg per day) and high casein (13 g/kg per day) diets for 14-day trials. Although caloric intake was less than 90 cal/kg per day and the animals lost an average of 5 percent of body weight, adaptation occurred in all eight monkeys. Enzyme activities did not differ by species, sex, or dietary sequence. The adaptive ratios, based on wet weight of liver, were: CPS, 2.7; OCT, 1.9; AS, 2.1; AL, 1.6; and arginase, 1.8. Differences of the means for each enzyme were significant at $P < .01$.

Stephen and Waterlow (*7*) reported that the liver argininosuccinase activities of 11 children with protein malnutrition averaged 1.06 units per milligram of liver protein and increased to 1.47 units with refeeding. In biopsies of normal livers from two men and six women, 30 to 70 years of age, undergoing abdominal surgery, we found activities matching those of the eight macaques on a comparable protein intake (Table 2). These two findings, along with the evidence that the five enzyme levels reflect protein nutrition in monkeys as in rats, imply that adaptation occurs in man. In testing for defects of urea synthesis, prudent interpretation of enzyme assays requires control data from normal subjects on the same protein and calorie intake.

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4. The New England Regional Primate Research Center, Southboro, Massachusetts, provided macaques, animal care, and surgical facilities. Biopsies were obtained under phencyclidine anesthesia.
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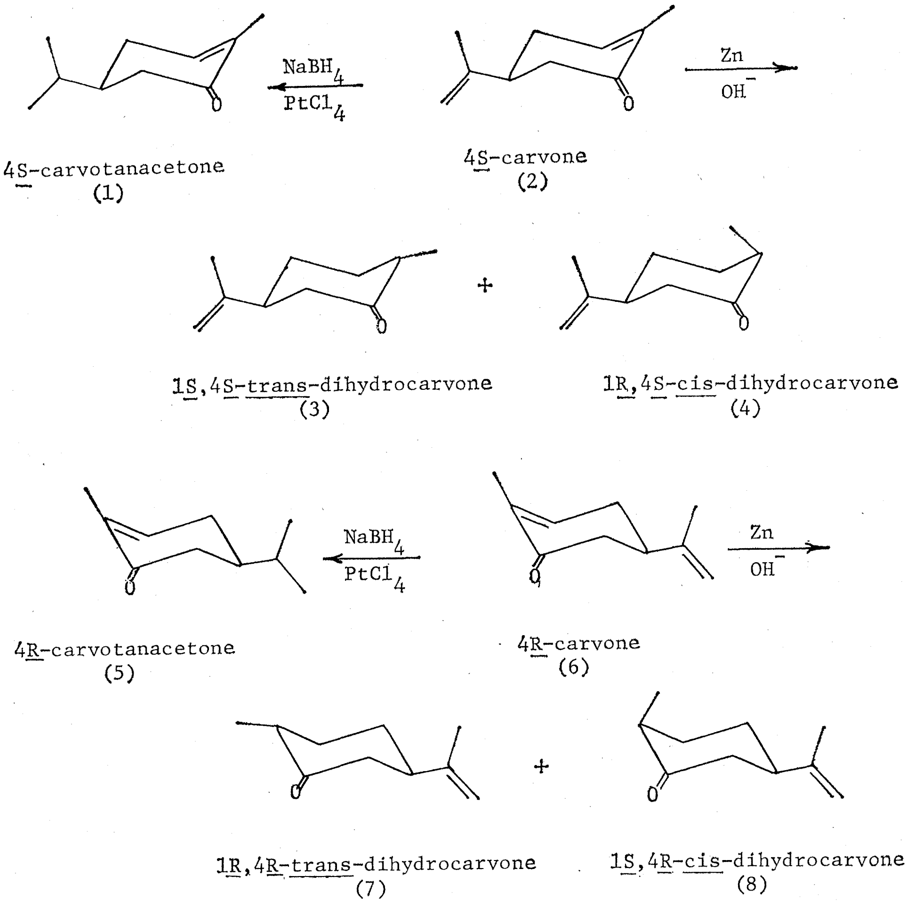
Odor Differences between Enantiomeric Isomers

Abstract. *The enantiomers of* R- *and* S-*carvone,* R- *and* S-*carvotanacetone,* R- *and* S-trans-*dihydrocarvone, and* R- *and* S-cis-*dihydrocarvone were synthesized from* R- *and* S-*carvone, and all were subjected to gas-liquid chromatographic purification. Sensory analysis of the highly purified compounds revealed odor differences between enantiomeric pairs.*

Considerable controversy has surrounded the theories of odor perception (*1*). Claims of odor differences between enantiomeric isomers (*2*) have been open to question because of doubts concerning impurities, chemical resolution, and questionable methods of sensory analysis. Many biological systems such as enzyme-substrate interactions are highly dependent on, and subject to, enantiomeric stereospecificity; however, the degree to which odor perception depends on structure has remained unsettled.

Commercial *R*- and *S*-carvone have been described as having the odors of spearmint and caraway, respectively (*3*). Samples of each isomer, obtained commercially (*4*), were highly purified by gas-liquid chromatography (GLC). Each isomer was successively passed through at least two dissimilar GLC columns. The purified isomers were trapped in forms which were chemically "pure" to the limits of detectability (*5*). The enantiomeric carvotanacetones were synthesized (Fig. 1) from the respective carvones via hydrogen reduction (*6*). Enantiomeric *cis*- and *trans*-dihydrocarvones were synthesized by Wallach reduction of the respective carvones, and the diastereoisomers were



4S-carvotanacetone (1)

4S-carvone (2)

1S,4S-trans-dihydrocarvone (3)

1R,4S-cis-dihydrocarvone (4)

4R-carvotanacetone (5)

4R-carvone (6)

1R,4R-trans-dihydrocarvone (7)

1S,4R-cis-dihydrocarvone (8)

Fig. 1. Structures of carvones and related compounds.

separated by GLC. Each of these derived compounds was subjected to the purification procedure described above.

The enantiomeric pairs were trapped from the final GLC purification step in specially designed glass-packed tubes. These were then mounted in a three-channel micro-olfactometer designed to accommodate small samples collected from gas chromatographs (*7*). The olfactometer was linked through a heated stainless steel line to a gas chromatograph by which the stimuli concentrations were monitored. The odorant stimuli, at a concentration of 180 ng per milliliter of nitrogen carrier gas, were evaluated by a panel of trained judges. The sample presentation followed the general format for Duo-Trio difference testing (*8*). The judges were presented via the olfactometer, as described (*7*), a labeled standard of one enantiomer along with two coded samples—the same compound as the reference, and the other enantiomer—in all possible combinations. They were then asked to pick the coded sample which more closely resembled the reference standard. The judges were also asked to describe the odors of the compounds tested. In addition to the eight odorant stimuli (four enantiomeric pairs) isolated as described above, the two enantiomers of carvone obtained by inversion synthesis (*1, 9*) were also purified in an identical manner and presented to the panel. The results are summarized in Table 1.

Table 1. Odor comparisons between enantiomeric stereoisomers. Numbers in parentheses are percentages.

Comparison	Evaluations (No.)	Correct (No.)	Adj. χ^2
2 versus 6	75	68 (89)	24.0*
1 versus 5	56	34 (82)	13.6*
3 versus 7†	60	55 (92)	20.0*
4 versus 8†	42	36 (86)	11.9*
2 versus 6‡	65	58 (89)	20.8*

* Highly significant ($P < .001$). † See (*11*). ‡ Samples supplied as per (*9*).

The enantiomers subjected to sensory analysis, whether they were isolated from natural products or synthesized chemically, had significantly different odors. After preliminary sessions, round table discussions were held to evaluate odor qualities of sample standards such as caraway oil and spearmint oil. The judges' descriptions of the odors for compounds reported in our study were consistently indicative of different odor qualities. Compounds **1**, **2**, and **3** (Fig. 1) were described as having the odor of caraway; compounds **5**, **6**, and **7** were described as having the odor of spearmint. The judges had difficulty describing the odors of **4** and **8** (akin to musty and woody), but had no difficulty distinguishing between the enantiomeric pairs. Compounds **1**, **2**, and **3**, which all have a caraway odor, have similar geometry, as do compounds **5**, **6**, and **7**, which have a spearmint odor. Compounds **4** and **8** differ from the other compounds both in geometry and odor quality. These observations lend definite support to stereochemical considerations of odor perception. The experimental data (on the compounds investigated) indicate different physiological responses to isomers differing only in their steric enantiomorphism. These data do not support a vibrational theory of odor (*10*), as differences in vibrational and rotational internal energies would be identical for the isomeric pairs.

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9. The samples of carvone were obtained after the other components described in the text had been analyzed. The same panel of judges was convened, and identical experimental conditions were used for the enantiomers sent by Prof. Friedman.
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11. A trace of the corresponding tautomeric stereoisomer for each of the *cis*- and *trans*-dihydrocarvones was generated by the GLC conditions, but in trace amounts that did not affect the sensory judgments as these were below threshold levels of detection.

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Odor Incongruity and Chirality

Abstract. *The enantiomers* R-(−)- *and* S-(+)-*carvone are the organoleptic constituents in oil of spearmint and caraway, respectively. Their odor distinctiveness has been unambiguously demonstrated by chemical interconversion, independent synthesis, and resolution. Odor differences between other chiral isomers were also firmly established.*

Theories attempting to explain the basis for the human perception of odor have revolved about vibrational energy levels, intermolecular interaction, and molecular size and shape (*1–7*). None of these specifically examines the possible effect of chirality in odor. This is not unexpected since, for over 50 years, this has been an area of controversy (*5*, p. 134; *3*, p. 144; *6*, p. 30; *8–11*). Unfortunately, claims that enantiomers have different odors have been discredited by invective or because the enantiomers may have been contaminated with impurities (*9*; *10*; *7*, p. 30).

Inasmuch as most life processes are chiral-dependent, a priori, odor perception could indeed be responsive to chiral differences. The absence of a definitive investigation to clarify this point, utilizing appropriate model compounds together with modern synthetic and analytical techniques, is inexplicable since results would be of utmost importance in formulating more accurate concepts of odor perception.

"Optically pure" *R*-(−)- and *S*-(+)-carvone are commercially available (*12*), naturally occurring α,β-unsaturated terpenoid ketones. The *R*-(−) isomer is the organoleptic principle in oil of spearmint and has a strong, clear, sharp spearmint odor (*13*). The *S*-(+) isomer is found in oil of caraway and has the odor associated with caraway (*13*). These odor incongruences are discernible by most people [apparently 8 to 10 percent of the population (this study) suffer from carvone anosmia; that is, carvone odor blindness. This is an unambiguous example of specific chiral anosmia (*14*)]. In spite of this, these odor differences were ignored or claimed (*5, 3, 6, 8–11*) to be a result of minute amounts of all-powerful (low threshold), albeit unknown, impurities. Fortunately, carvone is unusual in that it lends itself to simple chemical manipulations. By