

Mechanism of cinnamaldehyde sensitization*

VIMALA A. MAJETI AND RAYMOND R. SUSKIND

Department of Environmental Health, University of Cincinnati Medical Center,
University of Cincinnati, Cincinnati, Ohio, USA

The skin sensitization of cinnamaldehyde is probably initiated by the reaction of cinnamaldehyde with ϵ -amino groups on protein side chains. α -Substituted cinnamaldehydes, which are known not to be skin sensitizers, react very slowly or not at all with amines in comparison with cinnamaldehyde.

Key words: Cinnamaldehyde – mechanism – Schiff base – skin sensitization.

Received for publication September 20, 1976

The mechanism of sensitization by perfume chemicals is of much interest and little understood. There have been several reports recently concerning contact dermatitis due to cinnamaldehyde (Collins & Mitchell 1975, Schorr 1975, Magnusson & Wilkinson 1975, and Kirton & Wilkinson 1975).

We have been interested in the nature of the mechanism of sensitization by certain aroma chemicals, cinnamaldehyde, citral and phenylacetaldehyde, in particular, and of its inhibition by eugenol, d-limonene and phenyl ethylalcohol, respectively (Suskind & Majeti 1976). Fisher & Dooms-Goossens (1976) have suggested that the formation of a Schiff base by cinnamaldehyde in a perfume mixture during the process of aging may make cinnamaldehyde hypoallergenic, but they have failed to provide any experimental evidence to substantiate their claim. The present work describes our observations concerning the mechanism of cinnamaldehyde sensitization.

It is well known that aldehydes react with primary amines to give rise to condensation products known as Schiff bases. Cinnamaldehyde has been shown by us to react with amines and ϵ -amino groups on protein side chains giving rise to the corresponding Schiff base derivatives (Majeti & Suskind 1976) as shown in Fig. 1.

We have produced hypersensitivity in guinea pigs with cinnamaldehyde (Suskind & Majeti 1976). We believe that it is the Schiff base ligands of cinnamaldehyde on protein side chains which initiate the observed allergenic response. When this reaction of cinnamaldehyde with proteins is prevented by any number of means, the aldehyde becomes a weak or a nonsensitizer. In order to obtain further evidence in support of the proposed mechanism, we compared the reactivity of a series of α -alkyl substituted cinnamaldehydes shown in Fig. 2 towards primary amines.

* This work was supported by a grant from the Research Institute for Fragrance Materials (RIFM).

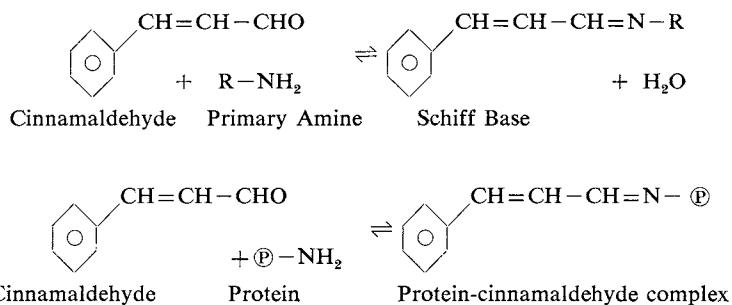


Fig. 1. Reaction of cinnamaldehyde with primary amines and proteins.

α -Methyl, α -amyl and α -hexyl cinnamaldehydes are shown to be nonsensitizers by human maximization studies (Opdyke 1973, 1974, 1975). No information is available at present about the sensitizing ability of α -butyl cinnamaldehyde. When reacted with cyclohexylamine under identical conditions (in toluene at room temperature), cinnamaldehyde reacted rapidly with generation of heat giving rise to the expected Schiff base (spectroscopic evidence), and none of the α -alkyl substituted cinnamaldehydes reacted. α -Methyl cinnamaldehyde was converted to the corresponding Schiff base after heating to about 60° . The other substituted aldehydes required prolonged heating at a higher temperature. Therefore, the chemical inactivity of α -alkyl substituted cinnamaldehyde relative to that of cinnamaldehyde may explain why they are not sensitizers.

Some of the possible explanations as to

why cinnamaldehyde is not a sensitizer when mixed with eugenol or in a perfume mixture after aging are:

1. Eugenol or the other perfume ingredients react or associate with cinnamaldehyde, thus preventing or slowing down the reaction of the latter with protein side chains to form Schiff base derivatives.

2. Eugenol or the perfume ingredients react or associate with the side chains of proteins preventing the reaction of cinnamaldehyde with proteins. Eugenol has been shown to form hydrogen-bonded complexes or salts with amines (Suskind & Majeti 1976).

3. Formation of a hemiacetal by cinnamaldehyde with eugenol or the hydroxy components in the perfume mixture. It is known that the acetal derivatives of cinnamaldehyde are not sensitizers (Opdyke, Fragrance Monographs).

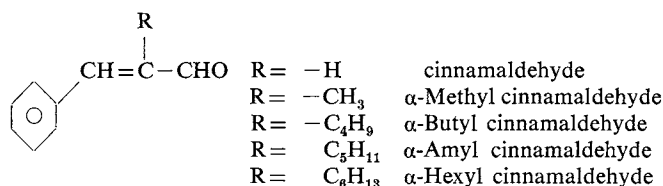


Fig. 2. α -Alkyl substituted cinnamaldehydes.

References

- Collins, F. W. & Mitchell, J. C. (1975) Aromatic chemicals. *Contact Dermatitis* 1, 43-47.
- Fisher, A. A. & Dooms-Goossens, A. (1976) The effect of perfume "ageing" on the allergenicity of individual perfume ingredients. *Contact Dermatitis* 2, 155-159.
- Kirton, V. & Wilkinson, D. S. (1975) Sensitivity to cinnamic aldehyde in a toothpaste. 2. Further studies. *Contact Dermatitis* 1, 77-80.
- Magnusson, B. & Wilkinson, D. S. (1975) Cinnamic aldehyde in toothpaste. 1. Clinical and patch tests. *Contact Dermatitis* 1, 70-76.
- Majeti, V. A. & Suskind, R. R. (1976) Reaction of cinnamaldehyde with ovalbumin. *International Journal of Protein and Peptide Research*. In press.
- Opdyke, D. L. J. (1973) Monographs on fragrance raw materials. Amyl cinnamic aldehyde. *Food and Cosmetics Toxicology* 11, 855-856.
- Opdyke, D. L. J. (1974) Monographs on fragrance raw materials. Hexyl cinnamic aldehyde. *Food and Cosmetics Toxicology* 12 (Special issue #1), 915.
- Opdyke, D. L. J. (1975) Monographs on fragrance raw materials. α -Methyl cinnamic aldehyde. *Food and Cosmetics Toxicology* 13 (Supplement), 853.
- Schorr, W. F. (1975) Cinnamic aldehyde allergy. *Contact Dermatitis* 1, 108-111.
- Suskind, R. R. & Majeti, V. A. (1976a) Occupational and environmental allergic problems of the skin. *The Journal of Dermatology* 3, 3-12.
- Suskind, R. R. & Majeti, V. A. (1976b) In preparation.

Address:

Vimala A. Majeti
Room 525I
College of Medicine
231 Bethesda Avenue
Cincinnati, Ohio 45267
U. S. A.