Selective removal of contact sensitizers from oils and plant extracts

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Many plants, especially those of the Compositae family, are responsible for allergic contact dermatitis (ACD).[1] As a number of plant extracts used in the perfume and cosmetics industry contain significant amounts of allergenic components, it becomes very important to develop a mild procedure for the removal of these undesirable substances. We describe here one such method in which the allergens are removed by selective binding to insoluble polymer gels.

Previous studies with natural extracts

Laurel oil has been known for a long time as a contact sensitizer.[2,3] Early work on Strasbourg showed that its allergenic properties could be completely suppressed by treating the oil with *sodium borohydride*.[3] The *activity of laurel oil* (extracted from the leaves of *Laurus Nobilis* L., fam. Lauraceae) has been attributed to the α-methylene-γ-butyrolactones it contains.[4–6] Sodium borohydride reacts with these unsaturated lactones and completely suppresses their sensitizing activity as the α-methylene group is reduced with formation of innocuous[6] α-methyl-

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γ-lactones (fig. 1). In other cases, a loss of sensitizing activity was observed upon addition of an amino acid such as cystein to sesquiterpene lactones.[7]

Several attempts have been made to reduce the sensitizing power of oil of turpentine. Successful ones included distillation, which left the allergens (Δ^3-carene peroxide) in the flask,[8] and chemical reduction of the peroxides, which only lowered the allergenicity of the oil.[9] The main problem with the chemical approach to deactivation is that further treatment, such as solvent extraction or other forms of separation, is required to recover the oil. Such treatments can be time-consuming and therefore costly.

Use of polymers in selective chemical extraction processes

There are numerous processes in which functionalized polymers have been used to extract some types of substances from more or less complex mixtures. These include, for example, ion exchange, hydrometallurgy, and affinity chromatography. Fewer instances of systems which act by selective formation of a chemical bond between a polymer and one component of a mixture are found in the literature.[10] Interesting examples include the preparation of threaded macrocycles or of unsymmetrical porphyrins, and our earlier work in Ottawa on the selective extraction of cis-diols from cis-trans mixtures.[11–13] In the latter case, a mixture of cis- and trans-diols (1,2 or 1,3 cyclohexane diols) is passed through a column containing insoluble beads of poly (styrylboronic acid).[13,14] The cis-diol, which can form a 5-membered ring boronate, is retained by the polymer while the trans isomer passes through the column unretarded. Post treatment of the column with a moist or alcoholic solvent frees the cis-diol and also regenerates the polymer for further use (fig. 2).[13]

Design of the polymer and its use in the removal of allergens

In the mechanism of ACD, it is believed that the allergen (hapten, sensitizer) penetrates the skin and becomes covalently bound to a skin protein, giving the antigen.[15] The proteins react through their nucleophilic groups either by substitution or by nucleophilic addition (Michael addition) onto an electrophile. Inspired by this general phenomenon, we thought of using

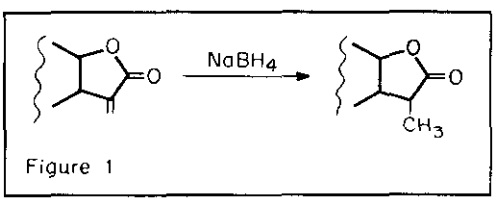


Figure 1

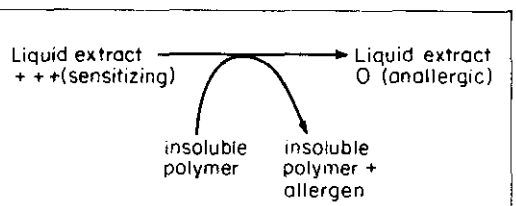


Figure 2

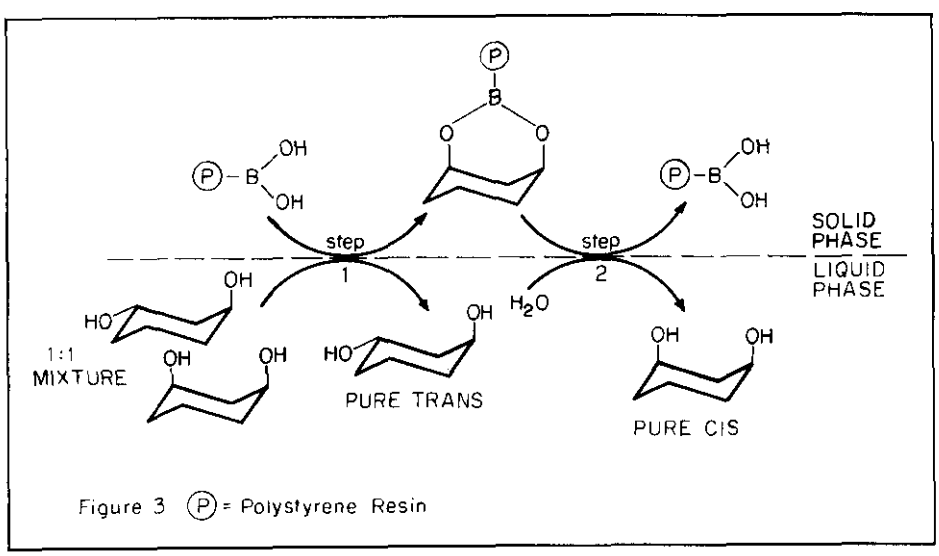


Figure 3 (P) = Polystyrene Resin

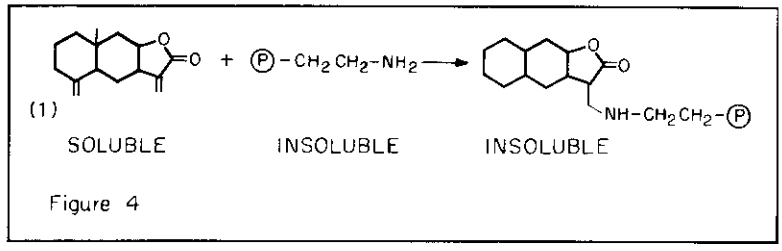
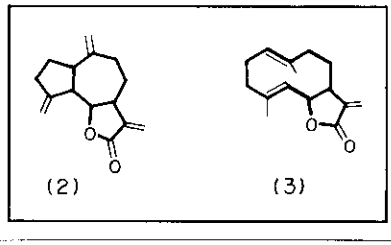


Figure 4

polymeric nucleophiles to remove the sensitizers which, in most cases, are electrophiles.[16] Thus, the principle of our method is the following: A liquid plant extract is stirred with an insoluble functionalized polymer which can bind the contact sensitizer through a chemical reaction. A simple filtration affords the allergen-free oil in the soluble phase while the allergenic substances are retained in the solid phase (fig. 3).

We prepared a number of polymers containing nucleophilic amino groups.[17,18] After testing several polymers, we chose to carry out most of our study using a crosslinked poly(aminoethyl styrene) which is prepared in two steps from poly(chloromethyl styrene). To check the efficiency of the method, we used a model allergen, isoalantolactone (*1*), a sesquiterpene lactone isolated from *Inula helenium* L. (fam. Compositae). After testing a number of reaction conditions we found that ethanol gave best results, with more than 99% binding in a few hours of stirring at room temperature (fig. 4).

An attractive test substance for our method seemed to be Costus oil from *Saussurea lappa* C. (fam. Compositae) which is used in perfumery, but is known to cause ACD.[5,19] Costus oil contains several sesquiterpene lactones among which dehydrocostuslactone (2) and costunolide (3), both are known as contact sensitizers. We used the aminoethylpolystyrene for removing lactones from costus oil and costus essential oil.[20] In the first case, up to 40% of the total oil remained bound to the polymer, while in the latter one, up to 13% of the total essential oil was bound.



To check the efficiency of the method to make the oils nonallergenic, we sensitized a group of guinea pigs to the untreated essential oil and another group to the polymer-treated oil. Only the first group was sensitive to dehydrocostuslactone (2) as shown by open epicutaneous testing. *The second group could not be sensitized.* Examination of the oil before and after treatment with the polymer showed that more than 99% of the dehydrocostuslactone was removed by the polymer.

Finally, it is also possible to recover the bound lactones by permethylating the amino group, and treating it with sodium bicarbonate.[20] This provides, therefore, a method for isolating lactones from complex mixtures. However, some

artifacts can result from such a treatment.[20] We are currently investigating several other promising approaches and polymer systems as well as the application of the method to other natural oils.

Conclusion

In conclusion, the method described here provides a way of making sensitizing oils non-allergic. Of course, an important question remains: what about the fragrance properties? Hopefully, this question will soon be answered.

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