

POLYMERIC SEPARATION MEDIA: BINDING OF α, β -UNSATURATED
CARBONYL COMPOUNDS TO INSOLUBLE RESINS THROUGH MICHAEL
ADDITIONS OR CHELATION OF DERIVATIVES

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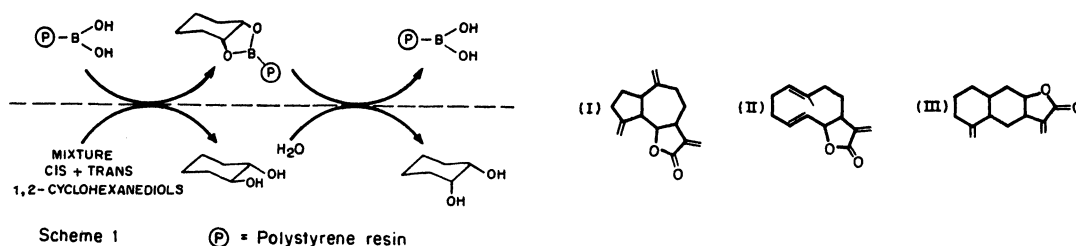
Abstract. Four different types of crosslinked polymers have been prepared for use in the binding of α, β -unsaturated compounds. The polymers have been tested in their reactions with unsaturated ketones, aldehydes, esters, acids, nitriles and/or lactones. The first three polymers were prepared by chemical modification of crosslinked polystyrene and contained amine, thiol, or sulfinate functional groups. They react with the unsaturated compounds through Michael additions. Simple procedures for the cleavage of the bound molecules from their solid support have been devised. All the nucleophilic polymers performed satisfactorily in the removal of allergenic α -methylene- γ -butyrolactones from a natural oil. The sulfinate resin is particularly attractive in view of its ability to be used repeatedly without requiring a regeneration step. The design of the fourth polymer which contained iminodiacetate copper groups allowed its use in ligand chromatography for the purification of amine-modified costus oil. The polymer is also very effective and recyclable.

INTRODUCTION

Functional polymer beads have been used extensively in a wide variety of tasks in which they performed as efficient separation media. For example, polymers have been used for the separation of ions in preparative systems (Ref. 1), the resolution of racemates by ligand-exchange chromatography (Ref. 2) or by chromatography through rigid resins containing chiral cavities (Ref. 3), and for numerous other chromatographic applications.

One property of functional polymers which has attracted the attention of organic chemists is their ability to be used in the selective removal of one or more components from a complex reaction mixture. This capability was illustrated in some very elegant syntheses such as that of a threaded macrocycle (Ref. 4) or of an unsymmetrical porphyrin (Ref. 5). Our first contribution to this field was the design of a polystyrylboronic acid resin which could be used to extract selectively cis diols from cis-trans mixtures (Ref. 6) [Scheme 1]. The diol binding ability of this resin was used in numerous other applications in organic syntheses (Ref. 7). In all of these applications at least one covalent bond is formed between the resin and the substance to be extracted, thus, the separation process is carried out in two distinct steps: attachment to, and detachment from the resin.

We have recently applied successfully this two-step separation technique to the removal and purification of allergenic substances from complex plant



extracts (Ref. 8). The allergens are α -methylene- γ -butyrolactones such as those shown in structures (I), (II) or (III), which are found in some plant extracts used in the perfume or cosmetics industry. For example, costus oil which is extracted from a plant of the widespread Compositae family, *Saussurea lappa* C., contains up to 51% of two allergenic unsaturated sesquiterpene lactones, dehydrocostuslactone (I), and costunolide (II).

Much of the early work (Ref. 9-11) toward the suppression of the allergenic properties of natural extracts was carried out in Strasbourg (Ref. 9-10) and focused on a study of Laurel oil. It was found that the oil could be made anallergic by treatment with sodium borohydride (Ref. 9) which suppresses the sensitizing activity of the α -methylene- γ -butyrolactones by reducing them to innocuous α -methyl- γ -lactones. Other studies (Ref. 11) along similar lines have shown that a loss of sensitizing activity was observed upon treatment of the sesquiterpene lactones with an amino-acid such as cysteine.

While these and other similar approaches were satisfactory in some cases, they usually involved the addition of external substances to the natural oils to suppress their allergenic properties. As these additives or their derivatives could not be removed from the oils in simple fashion, they also had an influence on other characteristics (e.g. fragrance properties) of the oils and did not allow the isolation of the pure allergenic substances for dermatological or pharmacological studies. In contrast, the approach we have designed can effect the complete removal of the allergens in a simple process which allows for their recovery, does not affect the other components of the oil, and leaves no additives which might adversely affect the characteristics of the natural oils.

DESIGN OF THE FUNCTIONAL POLYMERS

As the mechanism (Ref. 12) of allergic contact dermatitis to conjugated sesquiterpene lactones is thought to involve the covalent binding of the lactones with nucleophilic skin proteins through a simple Michael type addition, a similar reaction can be used to bind the lactones to a polymer bearing nucleophilic functionalities. In the treatment of a natural oil, all the unsaturated lactones would be insolubilized by attachment to the resin while the other components of the oil remain in the soluble phase and are unaffected. The design of the nucleophilic polymer should incorporate features which will allow the cleavage of the bound lactones from their solid support once the separation has been completed, and, whenever possible, means to regenerate and recycle the polymer in as simple a fashion as possible. It should be noted here that such nucleophilic polymers could be useful in a number of other applications (Ref. 13), for example as protecting groups for conjugated carbonyls or other Michael acceptors in synthetic applications.

A second possible approach would be to graft the lactone to a molecule which can bind reversibly to an insoluble polymer. Once the modified lactone has been detached from the polymer a simple chemical reaction could be used to regenerate it.

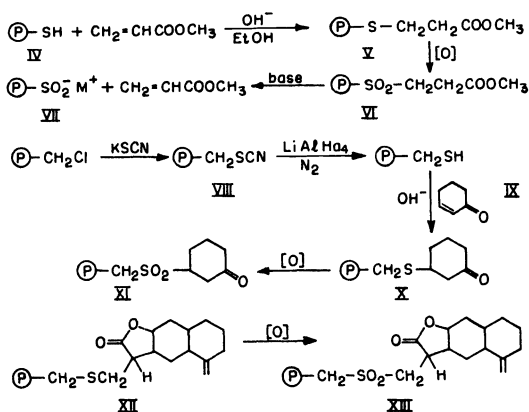
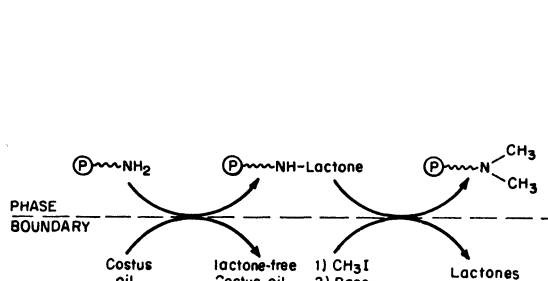
We have explored both of these approaches and have tested four different types of polymers which can be used in the selective removal of unsaturated lactones from mixtures. The first three of these polymers incorporate nucleophilic amino, thiol, or sulfinate functionalities for binding through Michael additions; some of these polymers were also tested in the binding of other α - β -unsaturated compounds such as acrylic acid, methyl acrylate, 2-cyclohexen-1-one, etc. The fourth polymer was designed for separations involving ligand chromatography on amine modified lactones.

MICHAEL ADDITIONS WITH AMINATED RESINS

Several polymers containing nucleophilic amino groups were prepared by chemical modification of crosslinked polystyrene beads or by terpolymerization of acrylonitrile, styrene, and divinylbenzene followed by reduction of the nitrile functional groups (Ref. 8, 14). Both macroporous and microporous gel resins were tested, best results being obtained with the microporous resins which had better mechanical stabilities and higher reactivities. The aminated resins were highly effective in the binding of unsaturated lactones as shown in Scheme 2. This scheme outlines the purification of costus oil by treatment with an aminated resin such as poly-(p-aminopropyl styrene). Simple treatment of the oil with the polymer results in complete binding of all allergenic lactones leaving the other desirable components of the oil untouched. After separation of the phases, and recovery of the anallergic purified costus oil, the polymer can be treated by permethylation - base treatment to cleave and recover the lactones (Ref. 8). A study (Ref. 15, 16) of the allergenic properties of the polymer-purified costus oil and of the lactones released from the polymer in the second step of the separation shows that:

- the purified oil is non-allergic,
- the released lactones are powerful allergens.

These observations confirm the value of our approach and its applicability to the binding of substances which can undergo Michael additions



MICHAEL ADDITIONS WITH THIOL RESINS

Under base catalysis thiols react as nucleophiles with Michael acceptors (Ref. 17) to yield the expected additions products. We have recently described the preparation of a resin containing p-vinyl-thiophenol functional groups by chemical modification of crosslinked polystyrene (Ref. 18, 19). This thiophenol resin (IV) was tested in Michael additions with methyl or ethyl acrylate. The reactions carried out in ethanol containing an equivalent amount of sodium hydroxide was essentially quantitative. This reaction could be used with other Michael acceptors such as unsaturated ketones or lactones. However, cleavage of the bound-moiety from the resin is not feasible in simple fashion and requires an additional step to oxidize the sulfide adduct (V) to the corresponding sulfone (VI). Cleavage of the acrylate from the polymer is then possible through a base-promoted β -elimination as shown in Scheme 3. A similar reaction scheme can be used with a resin containing p-vinyl-benzyl-thiol units (IX) which is prepared as described earlier (Ref. 16) or by chemical modification of chloromethylated polystyrene as shown in Scheme 3. Displacement of chloride with thiocyanate affords a resin with thiocyanate pendant groups (VIII) which can be reduced under inert atmosphere to the free thiol by reaction with lithium aluminium hydride. Resin (IX) should be handled under inert atmosphere when used in the presence of base to avoid the rapid formation of disulfides. The Michael addition of (IX) with 2-cyclohexen-1-one proceeds readily and essentially quantitatively in the presence of base. Oxidation of (X) to the sulfone (XI) can be achieved with m-chloroperbenzoic acid or hydrogen peroxide in the presence of a catalytic amount of sodium tungstate.

The same thiol resin (IX) was also tested in additions with isoalantolactone (III), a sesquiterpene lactone isolated from *Inula helenium* L. (fam. compositae). Once again the reaction proceeded satisfactorily but some

problems arose in the oxidation of the sulfide polymer (XII) to the sulfone (XIII) due to some partial epoxidation of the free vinyl group of the polymer-bound lactone (XII).

This troublesome side-reaction which affects recovery of the starting unsaturated lactone after cleavage could be eliminated completely through the use of a more chemoselective oxidizing agent such as potassium hydrogen persulfate (Ref. 20) which oxidizes only the sulfide functionality but does not affect the pendant vinyl groups. Using this reagent we were able to recover the unsaturated lactone in high yield after oxidation of (XII) and cleavage by β -elimination.

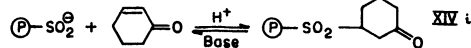
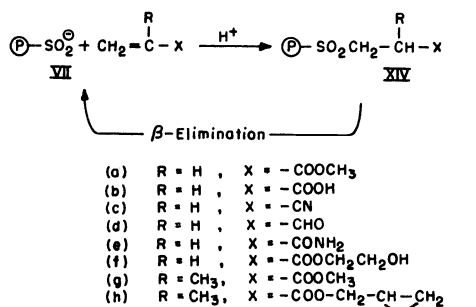
These reactions confirm that the thiol resins are also very useful in the binding of Michael acceptors. The thiol resins themselves cannot be regenerated in simple fashion, however, the final polymeric product obtained using the reactions shown in Scheme 3 is a sulfinate resin (VII) which, itself, is a fully recyclable separation medium as will be seen below.

MICHAEL ADDITIONS WITH SULFINATE RESINS

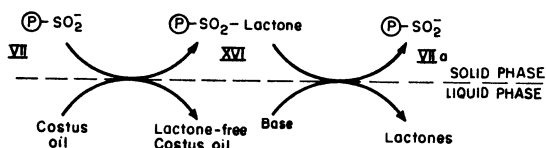
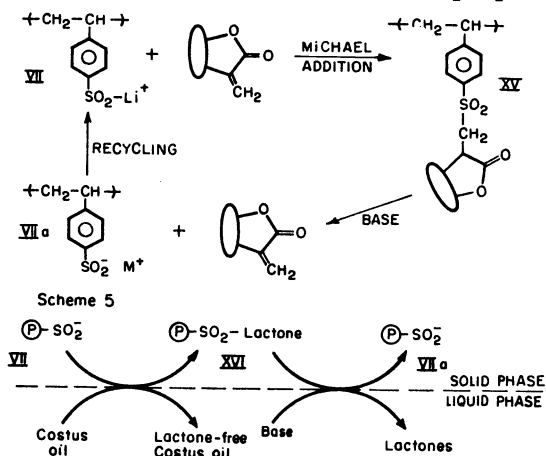
As was shown in Scheme 3, the thiol resins are useful in a reaction cycle which eventually transforms them into sulfinate resins (VII). The sulfinate resins themselves can be prepared directly by lithiation of polystyrene followed by quenching with sulfur dioxide (Ref. 13). Our previous work on sulfinate resins having shown that they were sufficiently nucleophilic to be used in halide displacement reactions (Ref. 13), we decided to test them in simple Michael additions as they seemed to be ideally suited for use as a fully recyclable separation medium.

Scheme 4 shows a number of Michael additions which were successfully carried out with (VII). In general, these reactions gave best results under phase-transfer conditions although excellent results were also obtained under more classical conditions. The reaction with neutral Michael acceptors such as methyl acrylate required the presence of an equivalent of acetic acid as proton donor. Some substrates such as acrylic acid did not require the addition of external protons to react with the sulfinate resin. The adduct (XIVa) obtained by reaction of resin (VII) with methyl acrylate and acetic acid showed the characteristic sulfone as well as ester bands in its infrared spectrum. Cleavage of methyl acrylate from the polymer through β -elimination proceeded satisfactorily; this reaction also regenerated the starting polymer which can be reused directly without any additional regeneration step. The recyclability of the resin was tested in five successive coupling-cleavage cycles with 2-cyclohexen-1-one which reacts in very high yield with (VII) to afford (XIVi). After treatment with base, the infrared spectrum of the resin showed no remaining ketone or sulfone bands and the reactivity of the polymer seemed to be unaffected.

The sulfinate resin could be used to extract lactones such as (I) or (III) from solutions (Scheme 5) and had good reactivity. Scheme 6 shows its application to the purification of costus oil by removal of unsaturated lactones (I) and (II). The infrared spectra shown on Figure 1 depict three reactions carried out in succession on a single batch of sulfinate resin (VII). The top spectrum (structure XVI from Scheme 6) is that of the polymer



Scheme 4



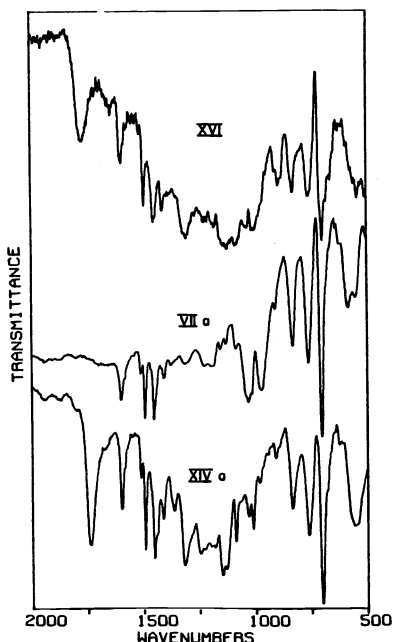


FIGURE 1

isolated after treatment of costus oil. The FT-IR spectrum shows clearly the presence of the unsaturated lactone on the polymer with a carbonyl absorption at 1770 cm^{-1} , a small C=C vinyl band at 1639 cm^{-1} , and two sulfone bands at 1310 and 1142 cm^{-1} over a polystyrene background. Difference infrared spectroscopy also shows very clearly the structural features of (I) when the polystyrene background is subtracted. The second spectrum is that of the polymer after cleavage of the lactones from (XVI) by β -elimination. This polymer has clearly lost its strong carbonyl and sulfone bands; its reactivity is comparable to that of the starting polymer (VII) as shown by its reaction with methyl acrylate in the presence of an equivalent amount of acetic acid which yields polymer (XIVa). The FT-IR spectrum of XIVa is shown on the lower part of Figure 1, it includes the expected carbonyl band at 1740 cm^{-1} and sulfone bands at 1318 and 1149 cm^{-1} . This series of reaction was extended on the same polymer sample with three further coupling-cleavage cycles using successively 2-cyclohexen-1-one, methyl acrylate, and isoalantolactone.

Of the three types of resins described above, the sulfinato seems to be the most versatile as it possesses good reactivity and is the easiest to use as recovery of the bound products is simple and the cleavage step serves the additional purpose of regenerating the resin for further use. Applications of this polymer as protecting group in organic synthesis are under study.

USE OF LIGAND EXCHANGE TO EXTRACT UNSATURATED LACTONE DERIVATIVES FROM SOLUTION

Although the direct-binding approach used above with amino, thiol, and sulfinato resins is most attractive as it involves direct treatment of the crude mixture with the reactive polymer to insolubilize the target molecule, an indirect approach involving first a reaction in solution with an external additive, prior to separation on a polymer, is also attractive in some cases.

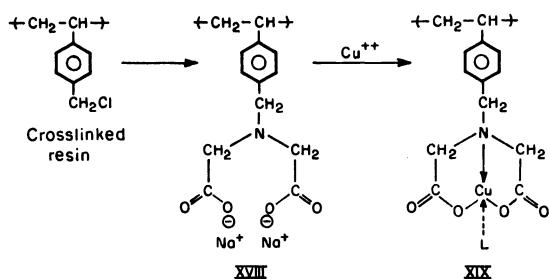
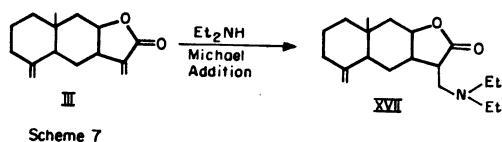
The strategy used (Ref. 21) for the separation of one component of a mixture using this approach is to couple the target molecule to a soluble substance which can be retained by an insoluble polymer in a ligand chromatography process. Once all the other soluble components of the mixture have been eluted, the polymer-retained moiety can be eluted by ligand exchange, thus completing the separation cycle. A final chemical reaction is then required to restore the target molecule to its original form.

We have tested this approach for the removal of allergenic lactones as follows.

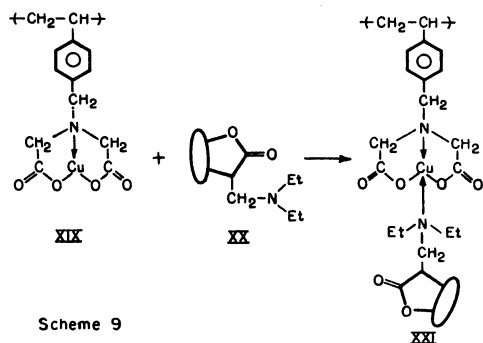
- The α -methylene- γ -butyrolactones are transformed into tertiary amines by treatment of the crude mixture with diethylamine (Michael addition).

- The amine-modified mixture is then passed through a column containing a resin with copper iminodiacetate functionalities. This resin which has affinity for aminated compounds (Ref. 22), retains the aminated lactones while other components of the mixture are eluted.
- The aminated lactones can then be eluted using a solution containing a stronger ligand.
- Finally, the aminated lactones are treated in an appropriate fashion to remove the amino groups and release the original unsaturated lactones.

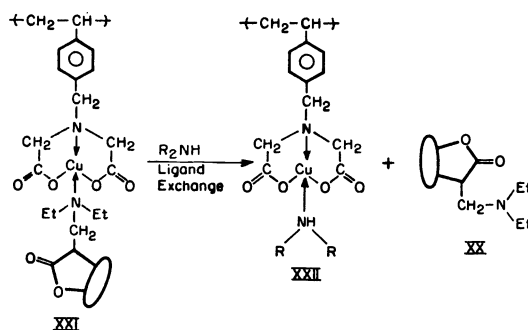
Preliminary testing of this system with isoalantolactone (III) demonstrated its feasibility. Isoalantolactone was first treated with excess diethylamine in a Michael addition (Scheme 7) to produce the aminated lactone (XVII).



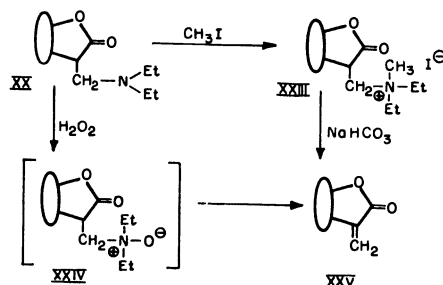
Scheme 8



Scheme 9



Scheme 10



Scheme 11

The iminodiacetate resin (XVIII) itself can be prepared by chemical modification of crosslinked chloromethylated polystyrene as shown in Scheme 8; similar resins are available commercially and the results described below were obtained using Chelex 100 from Bio-Rad Laboratories. Treatment of the iminodiacetate resin with excess copper sulfate (Ref. 23) affords the desired copper-resin (XIX). As can be seen in Scheme 8, this resin has a free ligand site which may be used to bind an appropriate molecule (shown as L in Scheme 8). Although the nominal capacity of the resin is approximately 1.4-1.5 meq Cu/g, a saturation study with (XVII) carried out according to Scheme 9 showed that only approximately 25% of the polymer's sites could become involved in the binding of the aminated lactone. The reason for this low capacity is that, although the polymer is normally best used in aqueous medium, its application with organic compounds such as (XVII) requires the use of organic solvents such as dichloromethane. Nevertheless, as an excess of the polymer is used, complete retention of the aminated lactone is possible, which affords adduct (XXI). Elution of the aminated lactone (XX) from the polymer is achieved through ligand exchange with excess diethylamine in dichloromethane (Scheme 10).

The final step of the overall reaction sequence is the regeneration of the free unsaturated lactone from (XX). This can be done using either of the two procedures shown on Scheme 11. The first procedure involves

permethylation of (XX) to (XXIII) followed by treatment with bicarbonate to effect the elimination; this procedure is somewhat similar to that (Ref. 8) we used to cleave the lactones from the aminated resins described earlier in this report. An alternate route involves the oxidation of (XX) to the N-oxide (XXIV) which decomposes spontaneously to the unsaturated lactone (XXV). Such spontaneous eliminations of N-oxides have been studied recently and were used to prepare carbonyl compounds or conjugated vinyl compounds from alkyl halides (Ref. 24). One drawback of the reaction sequence in this particular application is that amine oxide formation is accompanied by some oxidation side-reaction, perhaps involving the remaining vinyl group of (XVII).

This separation method was applied successfully to the removal of unsaturated lactones from costus oil. Although the composition of costus oil varies depending on its origin and the method used in its extraction from the plant, our study showed that the crude costus oil we used contained approximately 33% of dehydrocostuslactone (I) and 18% of costunolide (II). Some other constituents of the oil were also weakly retained by the polymer but these could be eluted with methanol and, under carefully controlled conditions, the separation of unsaturated lactones from the other components of the oil was found to be complete. The polymer itself can be regenerated by successive washings of (XXII) with aqueous acid, then base, and finally by treatment with copper sulfate prior to conditioning with organic solvents.

The main advantage of this procedure over the previous ones is that the actual separation step, involving only ligand exchange, is very mild and particularly well suited for an analytical study. Another advantage is the commercial availability of the resin. However, the overall process requires more steps than those involving direct Michael additions with reactive polymers, and great care must be exercised to ensure that only the desired lactones are retained by the copper resin. In addition, unlike the sulfinate resin which can be reused immediately after the cleavage step, the copper resin requires several steps, albeit relatively simple ones, prior to reuse.

CONCLUSION

The four types of resins described in this report are all suitable for use in the separation of unsaturated lactones and similar Michael acceptors from complex mixtures. However their use is limited to processes involving the separation of Michael acceptors or other molecules which can react with nucleophilic polymers from other substances which are inert to nucleophiles. The particular type of polymer which should be used in a given application will depend on the constraints imposed by the particular system involved as all four resins have different characteristics which are often complementary.

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