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Convenient Preparation of Functionalised Polymer-Based Resins via an Economical Preparation of Chloromethylated Polystyrene Resins (Merrifield Type)

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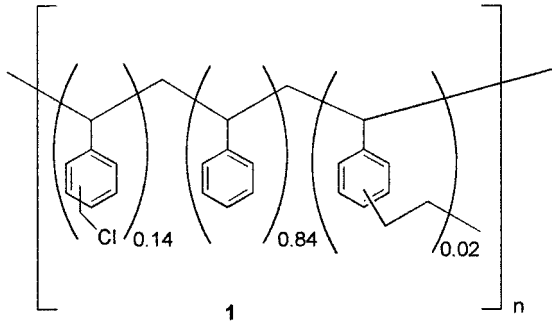
Abstract:

Initial studies on the preparation of cheap polymers suitable for the preparation of solid-supported metal catalysts and as solid supports for amino acids are described. The starting chloromethylated polystyrene resins (Merrifield type) were prepared using a reported procedure via the chlorination of a cheap polymer, poly(*m*-/*p*-methylstyrene). Convenient techniques are described for the analysis of the resins prepared. The preparations of novel polymer-based titanium catalysts from the resins are described.

Introduction

Functionalised, insoluble, cross-linked polymers are of considerable interest to the synthetic chemist. Such polymers can be used as starting materials for the preparation of solid-supported catalysts and ligands,[1] as a support for solid-phase peptide synthesis or combinatorial chemistry,[2] as active pharmaceutical agents (e.g., cholestyramine and related bile acid sequesterants),[3] and for the preparation of solid-supported reagents, an elegant use of which has recently been reported.[4]

A frequently used polymer is Merrifield resin (**1**),[5] a cross-linked chloromethylated polystyrene. This resin is commonly prepared by copolymerisation of a mixture *m*-/*p*-chloromethyl styrene, styrene, and divinyl benzene. The high cost of Merrifield resin is mainly due to the cost of *m*-/*p*-chloromethyl styrene (~£ 400 per kg), and large-scale preparation and use of this useful resin is therefore unattractive. Cross-linked polystyrene is a cheap and readily available polymer, and this can be directly chloromethylated using bis-chloromethyl ether (BCME) in the presence of a Lewis acid.[6] This approach to Merrifield resins suffers from two major drawbacks: the use of carcinogenic reagent BCME and additional cross-linking under the chloromethylation reaction conditions leading to a less reactive polymer. Prompted by recent reports of functionalisation of the aromatic methyl groups in poly(*p*-methylstyrene),[7] we considered that the most economical way to access chloromethylated polystyrene resins was via functionalisation of a cross-linked resin prepared from a mixture of *m*- and *p*-methylstyrene (cost of monomer ~£30 per kg). We report in this contribution our initial results into the preparation of solid-phase catalysts from cross-linked poly(*m*-/*p*-methylstyrene) (**2**) as a convenient and cheap starting material.



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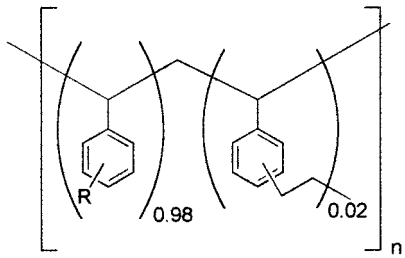

2: R = Me (60%m:40%p)
3: R = CH_2Cl (60%m:40%p)

Results and Discussion

The starting polymer (**2**) was prepared[8] by suspension polymerisation of the commercially available mixture of *m*-/*p*-methylstyrene (60:40) with 2% w/w divinyl benzene. The

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Table 1. **Chlorination of cross-linked poly(methylstyrene)**

batch	A	B	C
chlorinating agent	bleach/ PTC	bleach/ PTC	sulfuryl chloride/ AIBN
microanal.[a]			
%C	79.0	66.0	64.0
%H	6.9	5.5	5.0
%Cl	11.4	20.4	31.0 (34%)[b]
FTIR	1265 cm^{-1}	1265 cm^{-1}	1265 cm^{-1}
ss^{13}C NMR	47 ppm	47 ppm	47 ppm

[a] Average of two determinations. [b] Second preparation.

Table 2. **Active chlorine content of chloromethylated polystyrene resins**

resin	Merrifield resin[a]	batch A	batch B	batch C
microanal.				
%C	90.0	84.7	76.0	72.0
%H	8.7	7.9	7.9	6.7
%N	1.3	1.8	4.2	3.3
%Cl	0.0	2.1	4.7	16.0
total	100.0	96.5	92.8	95.0
mequiv g^{-1} N	0.9	1.3	3.0	2.4
% initial Cl	3.5	11.4	20.4	31.0
% active Cl	90	82	76	58

[a] Commercial 2% cross-linked with divinyl benzene, 1 mequiv g^{-1}.

resulting white polymer beads were thoroughly washed and dried prior to further transformation. One difficulty faced at this stage was the limited number of analytical techniques available to enable products to be characterised. To this end FTIR, solid-state ^{13}C NMR, and elemental analysis were chosen as main analytical techniques. Initially, we chose to investigate functionalisation of the resins via cobalt acetate-mediated oxidation of the methyl groups to benzyl alcohols or carboxylic acids as described for linear, soluble poly-4-methylstyrene;[7h,i] however, little or no conversion to the desired products could be achieved. More success was achieved with chlorination as a means of functionalisation. Two direct chlorination methods were evaluated on the poly(methylstyrene) resin pre-swollen in the reaction solvent: sulphuryl chloride in chlorobenzene heated in the presence of AIBN[7e] and bleach in dichloromethane/chloroform in the presence of a phase-transfer catalyst (PTC).[7a−d] After reaction, the resulting polymers were thoroughly washed with methanol and dried at 50 °C in vacuo. The resulting resins were analysed to determine the level of chlorine incorporation and location of the active groups. Results are given in Table 1.

Microanalysis results clearly indicate incorporation of chlorine by both bleach and sulphuryl chloride as reported.[7a−e] The level of incorporation varied significantly with the bleach/PTC preparations but was consistent for the SO_2Cl_2 chlorination. The variation in the level of chlorine incorporation with bleach is being investigated. No studies have been carried out at this stage to optimise the level of chlorine incorporation for the preparation of a specific catalyst. FTIR analysis indicates the presence of the $-CH_2-Cl$ moiety by a peak at 1265 cm^{-1} which was not present in the starting cross-linked poly(methylstyrene) resin. Solid-state ^{13}C NMR confirms this assignment by the presence of a peak at 47 ppm ($Ar-CH_2-Cl$), which overlaps with the backbone methine signal, with concomitant decrease in the intensity of the peak at 23 ppm ($Ar-CH_3$). These data indicated that the desired polymer (**3**) had been formed. With higher levels of chlorine incorporation seen in resin C there was some evidence in the solid-state ^{13}C NMR spectrum for the $Ar-CHCl_2$ moiety, by the presence of a peak at ∼73 ppm. Consistent with previous reports,[7a] the ^{13}C NMR spectra for all chlorinated polymers showed little evidence for chlorination of the aromatic rings or the polymer backbone.

Another important parameter for characterising choromethylated polystyrene resins A−C is the quantity of chloromethyl sites readily accessible to reagents. Initially, reaction with pyridine and subsequent displacement of the chloride ion for analysis by nitrate ion was attempted as an analytical method,[9] but inconsistent results were obtained with commercially available Merrifield resin of known active chlorine content. A more accurate method was developed which involved treating a DMF suspension of the resin with excess pyrrolidine at reflux. (It was pointed out by one reviewer that DMF decomposes at reflux, and whilst this would not affect the chloride analysis a more stable alternative such as *N*-methylpyrrolidinone may be more suitable for this analytical method.) The resultant resin was thoroughly washed with methanol, dried, and analysed by microanalysis. Conversion of nitrogen content to mequiv g^{-1} corresponds to the amount of available chlorine. Results using this method are shown in Table 2.

The results in Table 2 indicate that 60−80% of the total chlorine content of the resins formed by chlorination of poly(methylstyrene) is active chlorine. The more heavily chlorinated resins B and C had the lower level of available chlorine, presumably owing to steric problems rendering the sites inaccessible to pyrrolidine.

After we achieved good levels of chlorination, the transformation of the resins into other functionalised species was investigated. Treatment of the resin A in DMF at 90 °C in the presence of $Ni(acac)_2$ and potassium iodide gave, after thorough washing and drying, a blue-coloured polymer [10] which gave analytical data consistent with a polymer-bound metal(acac) complex (FTIR showed a peaks at 1586 and 1349 cm^{-1}, and microanalysis indicated 3.7% incorporation of Ni). The derivatised resin obtained was found to be an active catalyst for a Michael addition,[10] giving the desired product in quantitative yield (Scheme 1), and a condensation reaction, giving the desired product in 85% yield (Scheme 2). Reuse of the catalyst in this latter reaction gave the condensation product in 86% isolated yield.

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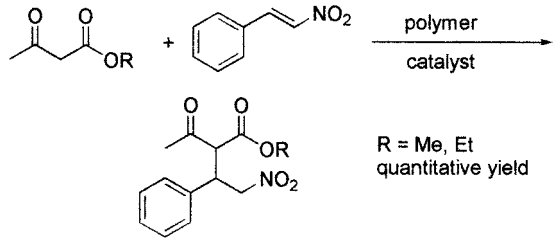
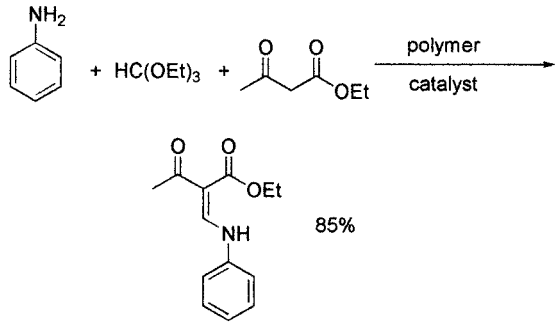
Scheme 1. **Michael addition**



Scheme 2. **Condensation reaction**



We then looked at preparing a solid-supported Lewis acid catalyst.[11a−c] Attempts to displace chloride to produce a polymer containing a supported benzyl diphenylamine ligand using diphenylamine and pyridine in chloroform [11a] failed to produce any of the desired product since recovered resins showed, by elemental analysis, no loss of chloride or incorporation of nitrogen. Reaction of polymer Batch C with diphenylamine and 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU) in dimethylsulphoxide (DMSO)[12] produced a product in which approximately 65% of the chloride had been displaced with diphenylamine. Treatment of the diphenylamine-modified polymer with $TiCl_4$ gave a product which had ~0.2 g of $TiCl_4$ per g of resin as judged by the increase in the chloride assay. This solid-supported $TiCl_4$ catalyst gave results in simple esterification, acetal, and ketal formations comparable to those reported in the literature for a similar catalyst.[11a] We have an interest in the use of solid-supported Ti catalysts for transesterification reactions, especially in the preparation of sensitive methacrylate monomers.[11c] The $TiCl_4$ polymer catalyst did show very weak activity as a transesterification catalyst, but some undesirable side-reactions, formation of oligomers, was apparent when methacrylate esters were used.

We then tried to prepare a milder Ti catalyst for transesterification reactions. Unfortunately, Titanium tetraisopropoxide appeared to have little or no affinity for the diphenylamine-functionalised polymer; however, triisopropoxy titanium chloride did bind to the polymer. Chloride analysis indicated 0.14 g of $(i\text{-PrO})_3TiCl$ per g of polymer. This material did act as an efficient transesterification catalyst

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Scheme 3. **Transesterification reactions**

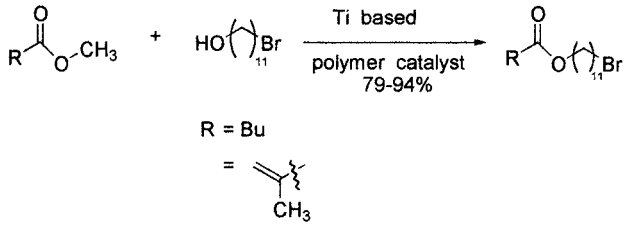

Table 3. **Analysis of N-BOC amino acid resins**

resin	N-BOC amino acid	wt (g)	%Cl	%N	%C	%H
Merrifield	lysine hydrate	6	0.9	1.2	84.0	8.2
batch B	lysine hydrate	4	7.3	2.0	72.0	7.2
batch B	valine	5.5	7.4	2.0	70.0	6.8

for methyl butyrate and 11-bromoundecanol producing the desired product, 11-bromoundecyl butyrate in 86% yield as shown in Scheme 3**.** The $(i\text{-PrO})_3TiCl$ catalyst was reused twice more giving 11-bromoundecyl butyrate in 79 and 94% yields, all reactions taking 6−8 h for completion. Negligible levels of Ti could be detected in reaction mixtures, and if the solid was removed from the reaction mixture, conversion to product ceased. These observations show that catalytic activity is associated with the polymer and is not due to active Ti compounds leaching out of the polymer. Further results with the polymer-supported $(i\text{-PrO})_3TiCl$ catalyst indicate that this is also active as a catalyst in the transesterification of methyl methacrylate with 11-bromoundecanol.[11c]

Finally, we tested the ability of the new chlorinated resins to act as supports for amino acids. Treatment of the chlorinated resin batch A with the cesium salt of N-BOC-glycine in DMF[13] at 55 °C (decomposition of DMF is not anticipated to be significant at this temperature) for 18 h gave, after isolation, washing, and drying, a resin where N-BOC glycine had been incorporated.[7b] FTIR showed strong bands at 1715 cm^{-1} (amide) and 1747 cm^{-1} (ester), and microanalysis showed 1% N and 3% Cl. The presence of the N-BOC glycine was also seen in the ss-^{13}C NMR of the polymer. The methyl signal from the BOC group was seen at 28 ppm, the amide and ester carbonyl groups were clearly seen at 156 and 172 ppm, respectively. The benzyl chloride resonance had diminished and was replaced by a benzylic ester signal at 63 ppm. More conveniently, rather than using preformed cesium salts, amino acids could be directly substituted onto the resins by reacting N-BOC amino acids directly with the chlorinated resins in DMSO and DBU at 60 °C.[12] Chloride analysis before and after reaction showed that ~65% of the chloride had been displaced, a reactivity only slightly lower than that of commercial Merrifield resin under comparable reaction times (see Table 3). Incorporation of amino acid was demonstrated by the presence of nitrogen by microanalysis. The amino acid resins also showed the expected IR and ss-^{13}C NMR signals for the attached amino acids.

Thus, the chlorinated poly(*m*-/*p*-methylstyrene) resin (**3**) shows promise as a starting material for solid-phase peptide

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synthesis, combinatorial chemistry, or the attachment of ligands.

In conclusion, it has been demonstrated that useful functionalised polymers can be prepared from a cheap source of chloromethylated polystyrene resins starting from poly(*m*-/*p*-methylstyrene). Work continues to refine the preparative procedures developed, to give a consistent product, and to identify new polymer-based catalysts.

Experimental Section:

The starting material, cross-linked poly(*m*-/*p*-methylstyrene) was prepared by Courtaulds Fine Chemicals by suspension polymerisation in water−poly(vinyl alcohol).[8] Reactions with the polymers were carried out using air-driven overhead stirrers to avoid breaking up the polymer beads.

IR spectra were run on a Nicolet Avatar 360 instrument and solid-state ^{13}C NMR spectra were obtained as follows. Samples were packed with minimal grinding into a 4 mm magic angle spinning (MAS) zirconia rotor fitted with a Kel-F cap using sufficient material (∼50 mg) to fill the rotor just short of the cap space. Spectra were run at ambient temperature on an AMX360 instrument at a MAS frequency of 10 kHz. ^{13}C MAS spectra (90.55 MHz) were acquired by cross-polarisation (CP) from Hartmann−Hann matched protons at a field of 80 kHz. The CP contact time was 1.8 ms and the repetition time was 15 s. Protons were decoupled at a field of 80 MHz during acquisition by using a two-phase pulse modulated (TPPM) composite sequence (150° flip angle: phase alternation of 7°). Chemical shifts were externally referenced to the carboxylate signal of a glycine test sample at 176.4 ppm relative to TMS and are regarded as accurate to ±0.5 ppm. C, H, and N determinations were obtained via standard combustion analysis. Total chlorine content was measured via digestion and potentiometric chloride ion analysis. Metal content was determined via digestion followed by assay by ICP-AES. The Cs salt of N-BOC glycine was prepared by literature methods.[13] Identity and purity of products from polymer-catalysed reactions were confirmed by TLC, ^1H NMR, and mass spectra. Relevant analytical results have been described in the text.

Chlorination of Poly(methylstyrene) with Bleach. Cross-linked poly(methylstyrene) (2%, 50.0 g) was swollen for 1 h in a mixture of chloroform (350 mL) and dichloromethane (350 mL) containing benzyltriethylammonium chloride. Bleach (1.0 L, 8% available chlorine) was adjusted to pH = 8.5 using concentrated hydrochloric acid and added to the swollen resin and stirred for 2 days at ambient temperature. The resulting slurry was diluted with methanol (1.0 L) and filtered. The isolated resin was washed with methanol (2 × 500 mL and water (3 × 500 mL) [chloride analysis on the aqueous washing confirmed that the resin was free of residual reagents]. The resulting resin was dried at 50 °C under vacuum for 1 day to give 64 g of the desired chloromethylated polystyrene resin as white beads. See Table 1 for analytical data.

Chlorination of Poly(methylstyrene) with Sulphuryl Chloride. Cross-linked poly(methylstyrene) (2%, 50.0 g) was swollen for 1 h in chlorobenzene (550 mL) containing AIBN (0.7 g). The resultant slurry was heated to 60 °C and treated with a solution of sulphuryl chloride (52 mL, 82.0 g) and AIBN (1.0 g) in chlorobenzene (100 mL) over 1 h. The reaction slurry was then heated at 60 °C for 1.5 h. After this time the mixture was cooled, diluted with methanol (1.0 L), and filtered. The isolated resin was washed with methanol (2 × 50 mL) and dried at 50 °C under vacuum for 1 day to give 70.0 g of the desired chloromethylated polystyrene resin as gray beads. See Table 1 for analytical data.

Reaction of Chlorinated Polymers with Pyrrolidine. Resin (5 g, Batch A) was refluxed in DMF (20 mL) for 20 min. Excess pyrrolidine (5 mL) was added and the mixture refluxed for 5 h. After cooling, the resin was isolated by filtration and washed with DMF (20 mL), water (25 mL), and then acetone (20 mL) and dried under vacuum at 50 °C for 24 h. See Table 2 for analytical data.

Reaction with Ni(acac)$_2$. Polymer A (5 g), nickel acetoacetonate (11 g), and KI (0.3 g) were heated in DMF (50 mL) at 90−100 °C for 18 h. The reaction mixture was cooled, washed with DMF, acetone, and then chloroform and dried under vacuum at 50 °C to give 6 g of a nickel polymer catalyst. Ni by ICP-AES was 3.7%.

Typical Michael Addition with Ni(acac)$_2$ Polymer Catalyst (Scheme 1). β-Nitrostyrene (1.40 g) and ethyl acetoacetate (1.49 g) were refluxed in chlororform (30 mL) with the nickel polymer catalyst (1 g) for 2 days. The reaction was cooled and the polymer catalyst removed by filtration. The solvent was evaporated to leave the desired product (2.93 g) in quantitative yield, as a 1:1 mixture of diastereomers. Proton NMR showed ∼5% residual nitrostyrene. A similar reaction substituting acetylacetone (Scheme 1, R = Me) for ethyl acetoacetate gave the desired product in 93% yield.

Condensation Reaction (Scheme 2). Aniline (0.91 mL), triethylorthoformate (7 mL), and ethyl acetoacetate (1.27 mL) were stirred with the nickel polymer catalyst (1 g) at 100 °C, removing any ethanol formed by distillation. After 18 h the reaction was cooled and filtered and the solids washed with chloroform. The filtrate was evaporated and the residue chromatagraphed on silica with ethyl acetate:hexane 1:9 to give the desired anilino acrylate (1.98 g, 85%) as a white solid. Repetition of this reaction using the same resin catalyst gave the desired anilino acrylate in 86% yield (2.0 g) as a white solid.

Reaction with Diphenylamine. Chlorinated resin (batch C, 31% chlorine), 5 g, was slurried in DMSO (100 mL), and DBU (10 g) and diphenylamine (9.5 g) were heated to 130 °C for 5 min and then cooled to 70 °C and stirred for 18 h. The reaction mixture was cooled to ambient temperature and filtered. The residue was washed with DMSO (4 × 50 mL), MeOH (3 × 30 mL)—no ionic chloride ($AgNO_3$ test) or diphenylamine (TLC) could be detected in the final MeOH wash. The resin was then washed with acetone (2 × 50 mL) and dried at 50 °C in vacuo overnight to give 4.9 g of a brown solid (Cl = 11.2%, C = 70%, N = 5%, H = 7.3%)

Reaction of Diphenylamine Resin with $TiCl_4$. The diphenylamine-functionalised resin from above (4 g) was suspended in ethanol-free chloroform (50 mL) and heated at reflux for 1 h. The reaction was cooled and $TiCl_4$ (3 mL)

added. The reaction was stirred under nitrogen for 2 days, filtered under nitrogen, and washed with chloroform (50 mL portions) until no $TiCl_4$ could be detected in the liqours. The resulting resin was dried in vacuo at ambient temperature. Yield 6 g of a brown solid. The chloride assay was 27%.

Reaction of Diphenylamine Resin with Chlorotitanium Triiospropoxide. Diphenylamine-functionalised resin (3 g, 11.2% chlorine) was stirred with $(i\text{-PrO})_3TiCl$ (3 g) in ethanol-free chloroform (60 mL) for 16 h. The polymer was filtered and washed with chloroform (50 mL portions) until the filtrate showed no $(i\text{-PrO})_3TiCl$ present. The resulting product was then dried in vacuo at ambient temperature. Yield 3.6 g. Chloride analysis 13.6%.

Transesterification Reactions. $(i\text{-PrO})_3TiCl$ resin (0.5 g) and 11-bromoundecanol (2 g, 0.008 mol) were heated at reflux in methyl butyrate (10 mL). A small amount of distillate was removed to displace MeOH and replaced by a similar volume of methyl butyrate. Typically, after 6 h the conversion was better than 90%. The reaction was cooled and the liquid decanted. The resin was washed with methyl butyrate (2 × 5 mL) and the solvent evaporated. The product was isolated by chromatography on silica with hexanes−ethyl acetate (9:1). Typical yield 2.3 g of 11-bromo-undecyl butyrate (86%). The reaction vessel could be recharged and the reaction repeated, giving 11-bromo-undecyl butyrate in 79% yield (2.1 g) and 94% yield (2.5 g).

Reaction of Chlorinated Resins with Cs N-BOC Glycine. Chlorinated resin (batch A, 11.4% chlorine, 1 g) was suspended in DMF (18 mL) and N-BOC glycine cesium salt added (1.18 g). The reaction was heated at 55 °C for 90 h and cooled, and the resin was filtered off. The resin was washed with DMF (2 × 25 mL), 9:1 DMF−water (4 × 25 mL), and ethanol (4 × 25 mL). The resin was dried in vacuo at 50 °C. Yield: 0.90 g of a pale yellow solid. Found C = 75.4%, H = 6.8%, N = 1.0%, Cl = 2.9%.

Reaction of Chlorinated Resins with N-BOC Amino Acids and DBU in DMSO. The chlorinated resin (commercial Merrifield, 3% chlorine, 5 g) or resin batch B (20% chlorine 5 g for reaction with N-BOC alanine and 3.5 g for reaction with N-BOC lysine hydrate) was suspended in DMSO (100 mL). The N-BOC amino acid (1.6 equiv based on chloride content) and DBU (1.6 equiv based on chloride content) were added. The reaction was heated at 60 °C for 18 h, cooled, filtered, and washed with DMSO (3 × 40 mL), MeOH (4 × 40 mL). The last MeOH wash contained no ionic chloride or amino acid ($AgNO_3$ test). The products were washed with acetone (2 × 40 mL) and dried in vacuo at 50 °C overnight.

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