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(21) International Application Number: PCT/GB93/01195 (22) International Filing Date: 4 June 1993 (04.06.93) (30) Priority data: 9211966.8 5 June 1992 (05.06.92) GB (71) Applicant (for all designated States except US): THE UNIVERSITY OF LIVERPOOL [GB/GB]; Senate House, P.O. Box 147, Liverpool L69 3BX (GB). (72) Inventors; and (75) Inventors/Applicants (for US only) : BAMFORD, Clement, Henry [GB/GB]; Broom Bank, Tower Road, Prenton, Birkenhead L42 8LH (GB). AL-LAMEE, Kadem, Gayad [IQ/GB]; 22 North Barcombe Road, Childwall, Liverpool L16 7PY (GB).		(74) Agent: W.P. THOMPSON & CO.; Coopers Building, Church Street, Liverpool L1 3AB (GB). (81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: FUNCTIONALISATION OF POLYMERS (57) Abstract A process for the functionalisation of polymers is disclosed. Functionalisation takes place by reacting a polymer with a peroxidant, preferably the peroxydisulphate or monosulphate or sodium or potassium in an aqueous medium. The hydroxylated polymer can then be reacted with other materials, including biomolecules. Using the method of the invention, products e.g. catheters or oxygenators can be produced with improved properties hitherto unobtainable.		

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DESCRIPTION

FUNCTIONALISATION OF POLYMERS

The present invention relates to the functionalisation of polymers. More particularly it relates to the treatment of polymers which do not possess groups normally considered readily reactive. It also relates to the coupling of so-treated polymers with other materials, for example, monomers, polymers, bioactive materials and dyes.

Conventional procedures for activating the surface of, for example, polypropylene include the action of high energy radiation, glow and corona discharges, photoinitiation with the use of a sensitiser such as benzophenone, reaction with ozone, and surface flaming. Some of these procedures have the disadvantage of severely degrading the polymer and the use of non-aqueous media may be necessary.

Early work with polypropylene was aimed at introducing hydroperoxides; thus it was claimed by Jabloner and Mommar (J. Polymer Sci. A-1, 1972, 10, (763-778)) that a cationic surfactant and potassium peroxysulphate could be used to achieve wetting and initiate oxidation of polypropylene powder as slurry. The reaction was carried out in the presence of oxygen (e.g. at 30 p.s.i.), at 100°C. Critical importance was attached to the presence of the cationic

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surfactant and it was stated that an anionic surfactant did not lead to significant hydroperoxidation. Graft copolymerization was subsequently carried out by addition of a redox system (e.g. ferric salt and benzoin) and a vinyl monomer at 65°C.

In many other examples the polymer (polypropylene), initiator (e.g. peroxydisulphate) and monomer were reacted together. This procedure led to a high yield of homopolymer. Any graft copolymer was probably formed by chain transfer involving initial or propagating radicals and the polymer.

It has now been found possible to functionalise many polymers by an inexpensive and simple method. It has been found possible to provide such a method which takes a relatively short time and can be effected in aqueous media.

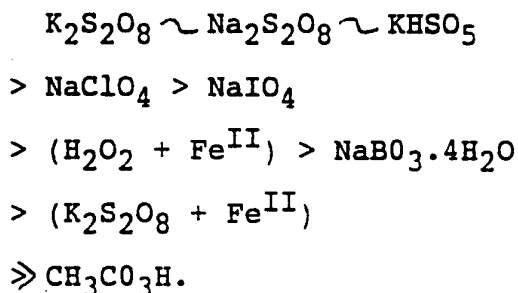
According to the present invention there is provided a method for the functionalisation of a polymer which method comprises reacting the polymer in an aqueous medium with an oxidising agent capable of producing oxygen-centered radicals which are ultimately responsible for introducing hydroxyl groups into the polymer, the reaction being carried out in the absence of any additive which is preferentially oxidised or is reactive towards the radicals produced by the oxidising agent.

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According to a further aspect of the present invention there is provided a method for the functionalisation of a polymer, which method consists essentially of reacting the polymer with a suitable oxidising agent in an aqueous medium.

A suitable oxidising agent is an oxidising agent capable of producing oxygen-centered radicals (i.e. the free radical is on the oxygen atom) in aqueous media. Under appropriate conditions such radicals can be responsible for introducing hydroxyl groups into the polymer, thus producing a functionalisation process. It is important to note that during the oxidation process no additives with readily extractable hydrogen atoms are present.

The oxidising agent usually used in the method of the present invention is a peroxy salt of a metal, preferably a peroxy-disulphate or monosulphate. We have examined the effectiveness of several peroxidants for the hydroxylation of polystyrene and found the following order:-



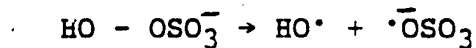
The last compound in the series, that is peracetic

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acid, has been found to be only very weakly active under the test conditions used.

The present invention will be further described for the sake of convenience with reference to (but in no manner limited to) the use of peroxysulphates as the oxidising agents.

The decomposition of the peroxy moiety may be considered to be in accordance with the equation:-



The peroxysulphate may be an alkali metal peroxysulphate, preferably potassium peroxysulphate. A particularly useful potassium compound is a triple salt having the composition $2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$ such as that sold under the Trade Name "Oxone". The peroxysulphate is employed as an aqueous solution, particularly in connection with biomaterials. The solution may contain other materials provided they do not affect the solubility of the peroxysulphate and are not themselves easily oxidized or reactive towards radicals.

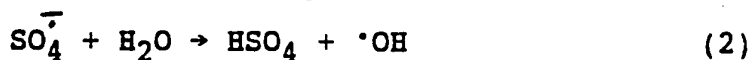
The concentration of the peroxysulphate in the solution is usually of the order of 2 to 50% weight/volume, preferably 2 to 20% weight/volume, and more preferably 5 to 10% weight/volume.

The reaction is usually carried out at a temperature of from 40°C to 100°C, more preferably

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50°C to 100°C. The reaction time required depends upon the nature of the polymer and its physical state of division (as more particularly described hereinbelow). The reaction time and the concentration of the oxidising agent are inversely related and the reaction time and temperature are inter-connected.

Potassium peroxydisulphate has long been used as an initiator of free-radical polymerisation in aqueous solution. The reactions involved have been studied by Kolthoff and Miller (I.M.Kolthoff and I.K.Miller, J.Am.Chem.Soc., 1951, 73 3055) who proposed the following mechanism:-



This proposal was supported by experiments with ^{18}O -labelled water which showed that the oxygen evolved originates from the water.

Various polymers may be functionalised by the method of the present invention. Suitable classes of polymers include:-

(a) Olefin polymers such as, for example, polypropylene;

(b) Aliphatic polyesters such as, for example, polyesters containing (esterified) 1,4-cyclohexane dimethanol units (e.g. the polyester sold under the

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Trade Name "Ecdel");

(c) Polymers containing aromatic rings, such as, for example, poly(ethylene terephthalate);

(d) Polycarbonates;

(e) Vinyl polymers (polymers or copolymers of monosubstituted ethylenes) such as, for example, polystyrene, polyacrylonitrile, poly(vinylchloride) and high density polyethylene;

(f) Polyurethanes such as, for example, aromatic poly(ether urethanes) sold under the Trade Names "Biomer" and "Pellethane" and the aliphatic poly(ether urethane) sold under the Trade Name "Tecoflex";

(g) Nylons, such as, for example nylon 6, nylon 6,6, poly (11-undecanoamide);

(h) Poly(glycols) or polymers or copolymers containing poly(glycol) chain segments. The latter include poly (ether urethanes) which are also included in (f) above, the ether constituent being a poly (glycol); and

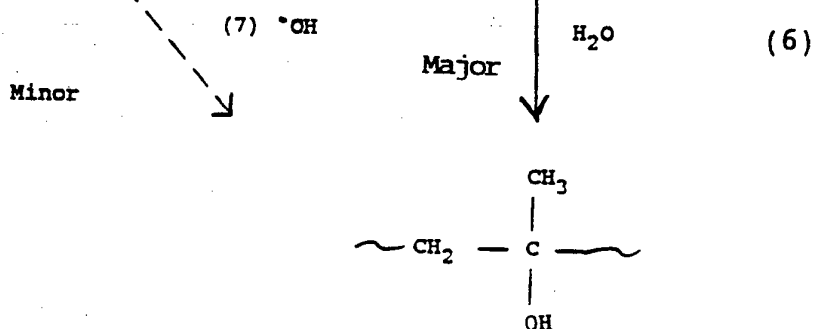
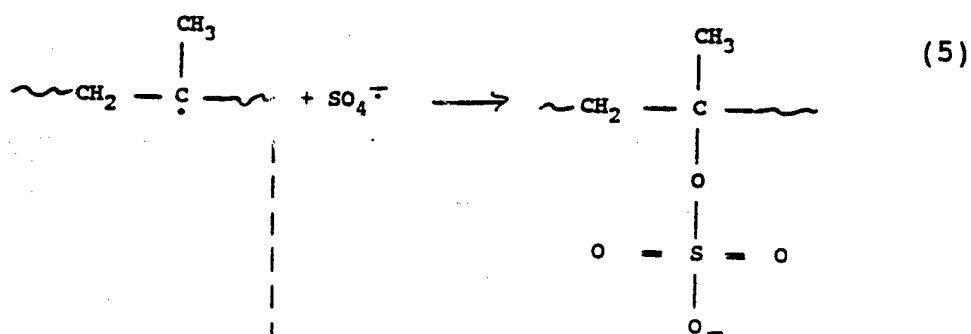
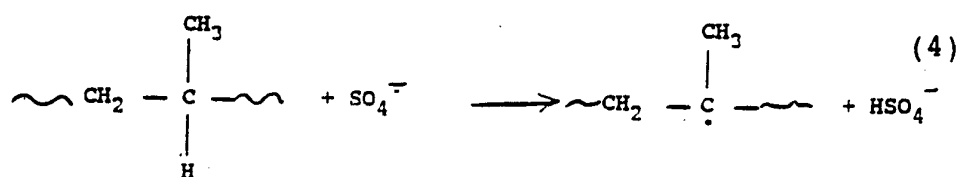
(i) Polyaldehydes.

Whilst again not wishing to be bound by any theory of reaction, the following reaction mechanism may well indicate how the functionalised polymers of the present invention are formed and react with other materials.

Using as an illustration example the polymer

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Using as an illustration example the polymer polypropylene the functionalisation process involves the abstraction of relatively reactive hydrogen atoms from the polymer as shown below - reactions (4), (5) and (6).



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The state of subdivision of the polymer to be functionalised is basically determined by the function and construction of the article. It is however preferred to use as large a specific surface as possible. Therefore, for example, particles are desirably as small as possible and fibres have a small diameter, say of the order of 200 microns.

As mentioned above, the time for the functionalisation method of the present invention can be relatively short, for example ten minutes. It is however dependent on the nature (chemical and physical) of the polymer employed. For example, with microporous polypropylene fibres, the preferred conditions are 10 min. at 100°C (reflux) using 10% w/v aqueous potassium peroxysulphate. Polypropylene and Ecdel films may be functionalised with this reagent; in these cases longer periods of treatment (e.g., up to five hours) are without deleterious effect.

According to the present invention there is also provided a process for the production of a polymer product which comprises reacting a functionalised polymer, formed by the method of the present invention, with another material which could be used for further functionalisation or for coupling to a biomolecular species.

Such other materials may be, for example,

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(a) vinyl monomers, particularly water-soluble vinyl monomers or mixtures of such monomers, which can be grafted on to the functionalised polymers, and

(b) Materials containing other functional groups e.g. those derived from isocyanates, acyl chlorides or acyl anhydrides.

Such reactions include grafting of vinyl monomers by free-radical reactions and/or non-radical introduction of species with various types of functional groups.

Applications include, for example, the treatment of catheters to modify their surface characteristics, notably to reduce friction (Example 10), treatment of hollow-fibre oxygenators and blood filters to improve haemocompatibility (Example 2) and the coupling of a wide range of biomolecules (including antibodies) to polymer supports. Thus molecules to be grafted may include, for example, heparin (Examples 5 and 9), hirudin (Example 8), oligonucleotides and DNA (Example 11), antibacterial agents, the coupling of Cibacron Blue to polymer supports for protein separation and species with groups which promote cell-adhesion.

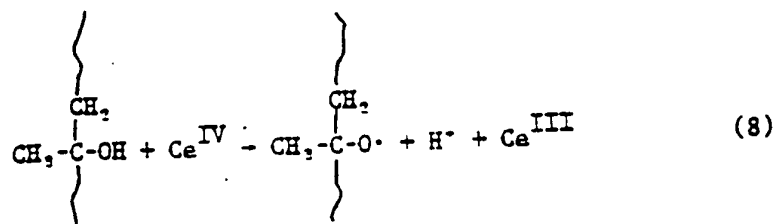
Grafting of vinyl monomers to non-aromatic hydroxylated polymers is subsequently carried out in aqueous solution by the conventional ceric ion technique. (See G.Mino, S.Kaizerman and S.Rasmussen,

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J. Polym. Sci., 1958, 31, 242). Additionally, grafting of acrylamide by this method may be followed by hydrolysis of the amide groups to carboxyl to provide an increased number of sites for further coupling (see, for example, Example 8). Also grafting of monomers which do not propagate rapidly may be promoted by addition of low concentrations of acrylamide to produce a co-graft (see, for example, Examples 5 and 9).

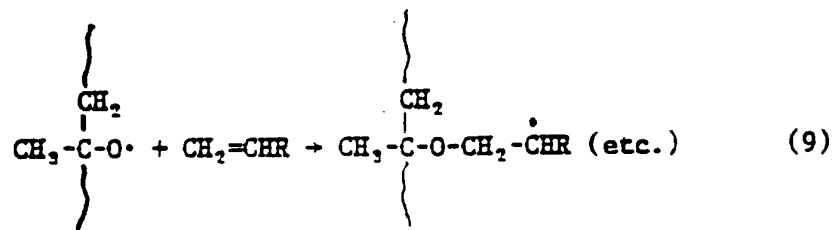
Alternatively, other functional groups may be introduced by further reactions with the hydroxyls; for example the latter may be reacted with molecules carrying isocyanate groups. Hydroxylated aromatic nuclei in polymers do not normally react with ceric ion in the above way, but the hydroxyls may be reacted with standard reagents, which may, however, require non-aqueous media (see, for example, Examples 6, 7).

The functionalised polymer, as exemplified by the product of reaction step (6) or (7) made with reference to the functionalisation of polypropylene, can thus be subjected to grafting in aqueous solution with, for example, the aid of Ce^{IV} . Such a reaction would proceed as follows:

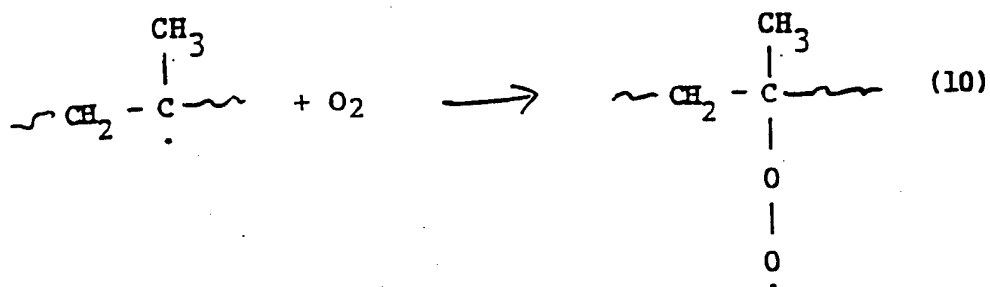


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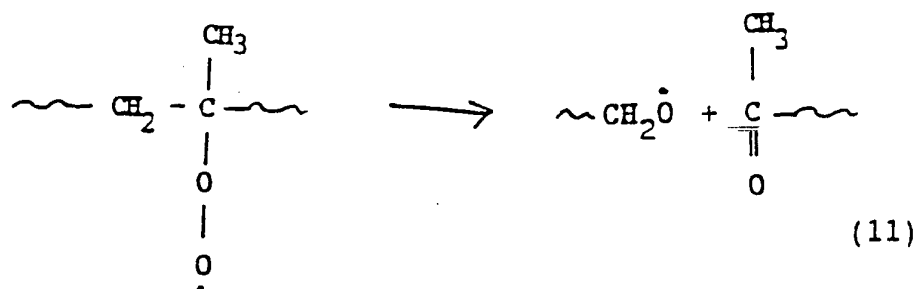
Thus, for example, water-soluble vinyl monomers ($\text{CH}_2=\text{CHR}$) e.g, acrylamide or N-vinyl pyrrolidone could be grafted. Such a reaction is considered to be initiated as follows (9):



As is apparent from equation (3), oxygen is evolved during theolysis of peroxysulphate in water and is probably responsible for causing some degradation in certain polymers. With long treatments this may be significant in some forms for example microporous fibres. It is suggested that this degradation arises from the formation of peroxyradicals by addition of oxygen to radical species. Such a reaction scheme might be as follows: (10;11). This scheme is again exemplified with reference to polypropylene.



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Such radicals could lead to chain scission as in equation (11).

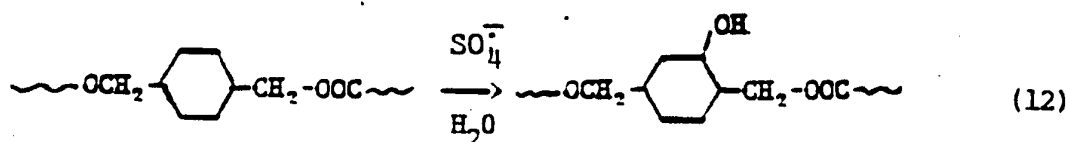
The major process competing with the chain scission in (11) would be hydrogen abstraction forming the hydroxyperoxide, but this is probably less favourable, energetically.

Peroxide has not been detected in the products from polypropylene after hydroxylation. Furthermore, grafting has not been obtained when a film of polypropylene hydroxylated by the method of the present invention is treated with acrylamide in the absence of Ce^{IV} .

It has been observed that passing nitrogen through the liquid during hydroxylation to lower the oxygen concentration reduces the chance of degradation, in support of the reaction scheme shown in (10) and (11).

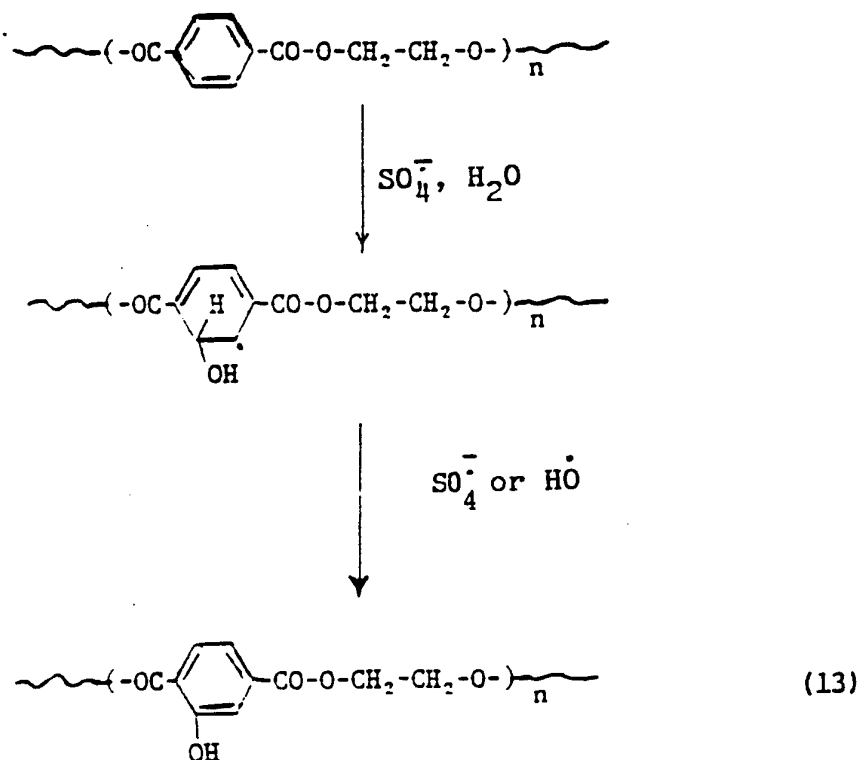
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Functionalisation of an aliphatic polyester containing (esterified) 1,4-cyclohexane dimethanol units (sold under the Trade Name "Ecdel"), has been carried out similarly. A typical reaction could be:



Grafting of a vinyl monomer to the hydroxylated polyester formed in (12) may be carried out in aqueous medium by the ceric ion technique as outlined (cf. equation (8)).

With aromatic polymers hydroxylation may proceed as indicated in (13) for poly(ethylene terephthalate).



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The phenolic OH does not react readily with Ce^{IV} but may be reacted with isocyanates etc., for further functionalisation. Polycarbonates containing aromatic rings behave similarly.

The present invention will now be further described with reference to, but is in no manner limited to, the following Examples.

EXAMPLES

EXAMPLE 1 - Hydroxylation of polypropylene

Bundles (18 cm x 4 cm) of microporous hollow polypropylene fibres, having a diameter of approximately 200 microns, from an oxygenator were heated under reflux with an aqueous solution of potassium peroxydisulphate under the conditions shown in Table 1. In each case a stream of nitrogen was passed through the liquid continuously. Weight and number-average molecular weight after treatment (M_w , M_n , respectively) are presented in Table 1 and show reductions which are rather small, especially for the shorter reaction time (numbers 2 and 3).

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TABLE 1 Molecular weights of hydroxylated polypropylene fibres.

Sample number	Concentration of $K_2S_2O_8$, % w/v	Reaction time, min.	$\bar{M}_w$ $\times 10^{-3}$	$\bar{M}_n$ $\times 10^{-3}$
1	Control		567 566	86 85
2	5	10	450 447	80 80
3	10	10	423 422	84 77
4	10	60	361 359	64 63
5	5	60	259 258	58 56

Some mechanical properties (measured with the aid of a NENE Instron instrument) are shown in Table 2.

These results suggest that concentrations up to 10% w/v with reaction times twenty minutes or less do not produce serious degradation or deterioration in mechanical properties of these specimens.

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TABLE 2 - Mechanical properties of single hollow
fibres of polypropylene after hydroxylation.

Sample number	Conditions of hydroxylation		Stress at peak MPa	% Strain at peak
	Concentration of $K_2S_2O_8$, % w/v	Reaction time, min.		
1	Control		36 42	630 807
3	10	10	49 42	746 792
4	10	60	24	464
5	5	60	31 29	545 498
6	10	20	30 33	747 686

EXAMPLE 2 - Grafting to hydroxylated polypropylene fibre

A sample of hydroxylated polypropylene hollow fibres prepared as for Sample number 3, Tables 1 and 2, was submitted to grafting with acrylamide. 0.2 g of the hydroxylated sample was placed in a solution (100 ml) of acrylamide (20% w/v) in 0.04 M nitric acid containing ceric ammonium nitrate (0.15 g). The

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solution was flushed with nitrogen then heated at 50°C for three hours. The grafted specimen was then washed copiously with water to remove any ungrafted polyacrylamide. The (hydrated) hydrophilic polymer produced in this way had a surface so slippery that handling was difficult. It dyed strongly with Trypan Blue.

A control of non-hydroxylated polypropylene fibres submitted to the same treatment did not show any grafting.

EXAMPLE 3 - Grafting to hydroxylated polypropylene films

A polypropylene film (obtained from Goodfellow) (5 cm x 5 cm x 0.0013 cm) was heated at 80°C with aqueous potassium peroxydisulphate solution (10% w/v) for two hours. After washing, the film was grafted with acrylamide as in Example 2, then again washed copiously with water. The film so obtained was very hydrophilic and stained strongly with Trypan Blue. The infrared spectra of the film showed strong absorption at 3351 and 3199 cm^{-1} (N-H stretch, Amide A) and 1662 cm^{-1} (C=O stretch) arising from grafted polyacrylamide. No such bands were observed with the control film of polypropylene.

EXAMPLE 4 - Hydroxylation of Ecdel

Hydroxylation of the polyester sold under the Trade Name Ecdel (obtained from Kodak) was carried out

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on films (3 cm x 3 cm x 0.014 cm) refluxed in aqueous potassium peroxydisulphate solution (10% w/v for half an hour. After washing, the films were grafted with acrylamide (20% w/v) in 0.04 M HNO_3 with 2×10^{-3} M ceric ammonium nitrate at 40°C for times ten minutes, thirty minutes, one hour, two hours and three hours. The grafted films were washed copiously with water and dried in vacuum at 40°C. All the films were found to be stained strongly with Trypan Blue; under comparable conditions the depth of colour appeared proportional to the time of grafting. The ten-minute film showed intense absorption in the infrared, corresponding to the N-H and C=O stretching bands mentioned in Example 3. Percentage weights of polyacrylamide grafted on to hydroxylated Ecdel film are shown in Table 3.

TABLE 3 - Grafting of polyacrylamide to hydroxylated Ecdel. Hydroxylation time 1/2 h. with 10% w/v aqueous $\text{K}_2\text{S}_2\text{O}_8$. Film dimensions 3 x 3 x 0.014 cm.

Sample number	Grafting time, h	% weight increase, w/w
1	1	30.4
2	2	49.3
3	3	60.0
Control	3	0.33

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Molecular weights of Ecde1 in films before and after hydroxylation are shown in Table 4. They indicate that negligible change has occurred during the process of hydroxylation.

TABLE 4 - Molecular weights of Ecde1 in hydroxylated

Sample number	Concentration of $K_2S_2O_8$, % w/v	Reaction time, min	$\bar{M}_w$ $\times 10^{-3}$	$\bar{M}_n$ $\times 10^{-3}$
1	Control		117 114	37 38
2	5	10	117 107	36 41
3	5	60	112	37
4	10	10	113 117	39 38
5	10	60	118 118	37 37

Some mechanical properties of the hydroxylated Ecde1 films are presented in Table 5. The hydroxylation process apparently had little effect on these properties.

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TABLE 5 - Mechanical properties of hydroxylated Ecdel

Sample number	Conditions of hydroxylation		Stress at peak MPa	% Strain at peak
	Concentration of $K_2S_2O_8$, % w/v	Reaction time, min.		
Control			31	488
			32	503
			32	533
1	10	10	26	387
			32	514
			32	506
2	10	60	30	509
			27	427
			30	530

EXAMPLE 5 - Grafting of heparin macromer on to Ecdel

Heparin macromer (as described in International Patent Application GB91/00679) and acrylamide were co-grafted at 25°C to hydroxylated Ecdel film using the ceric ion technique already outlined. Hydroxylation had been performed on a 4 cm x 3 x 0.014 cm Ecdel film, by treatment with 10% aqueous $K_2S_2O_8$ for four hours under reflux. The subsequent co-grafting was carried out with 0.1 g acrylamide, 0.3 g heparin macromer in a total volume of 6 ml for two hours. After very copious and prolonged washing of the film, the bioactivity was assessed by standard measurements

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of the partial thromboplastin time (PTT). Two controls were used - untreated Ecdel, and Ecdel grafted with acrylamide without heparin.

The following PTTs were recorded for films 1.5 x 0.5 x 0.014 cm in 200 μ l human plasma plus 200 μ l platelet substituent plus 200 μ l CaCl₂ solution 25 mM.

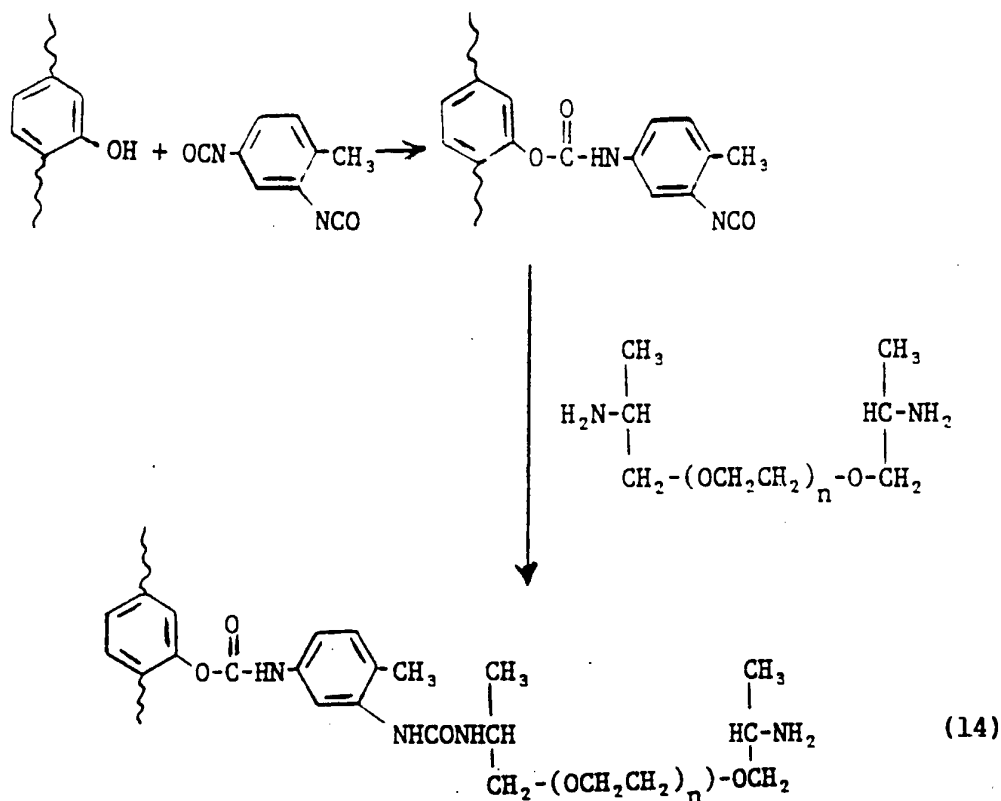
Ecdel film, untreated	: 330 seconds
Ecdel grafted with acrylamide	: 460 seconds
Ecdel grafted with heparin and acrylamide	: 1400 seconds

Clearly the thrombogenicity of the film has been markedly reduced by coupling heparin.

EXAMPLE 6 - Functionalisation of polycarbonate

Films of polycarbonate (obtained from Goodfellow) (5 cm x 5 cm x 0.075 cm) were refluxed with 10% w/v aqueous K₂S₂O₈ for five hours, then copiously washed in water. The hydroxylated films could not be grafted with the aid of the normal ceric ion technique (equation (8)). However, the hydroxyl groups were found to react readily with tolylene 2,4-diisocyanate (TDI) at 50°C. The product was reacted with Jeffamine (O,O'-bis(2-aminopropyl)ethylene glycol 400) to give a basic polymer:

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The final aminated polymer was found to dye very strongly with Eosin-Y. A non-hydroxylated polycarbonate treated with Jeffamine as above failed to give any stain with the dye.

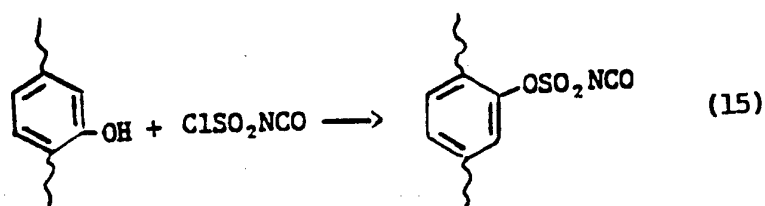
The aminated polymer is clearly suitable for further direct coupling e.g., of biomolecules containing carboxyl.

EXAMPLE 7 - Functionalisation of poly(ethylene terephthalate)

Granules (approximately 1mm in diameter) of a poly(ethylene terephthalate) sold under the Trade Name Dacron were refluxed in aqueous solution of $\text{K}_2\text{S}_2\text{O}_8$

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(10% w/w), washed and dried. The product, like the polycarbonate in Example 6, could not be grafted by the ceric ion technique. It was treated with bulk chlorosulphonyl isocyanate (CSI) (W.A.Szabo, Aldrichimica Acta, 1977, 10, 23) for two hours at 90°C. The product, after washing with petroleum ether was reacted with Jeffamine. After washing it was found to dye strongly with Eosin-Y. The reaction which occurs with CSI is probably that shown in (15).



Coupling with Jeffamine then proceeds as in equation (12).

Alternatively, the hydroxylated Dacron could be reacted with a diisocyanate as described in Example 6.

Example 8

A polystyrene film was hydroxylated according to the method of the present invention (described for polypropylene in Example 3) then grafted with

acrylamide by the ceric ion technique. The polyacrylamide was then hydrolysed by treatment with 1 N NaOH at 60°C for 15 minutes, after which the film was washed extensively with water. The resulting material gave a positive test for COOH with Toluidine

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Blue. 10cm² of the film was activated by reaction with carbonyl diimidazole (2g in 50 ml acetonitrile, 4 hours at 25°C then washed, dried in vacuum and coupled with hirudin (10 mg in 1ml sodium borate buffer, pH, overnight). After prolonged washing with water a portion of the film (1.5 x 0.5 cm) was submitted to the PTT test (as described in Example 5) with the following result.

After hirudin coupling: 1300 seconds

Control (activated polystyrene): 300 seconds

Example 9

A hydroxylated film of Ecdel (Example 4) was grafted with a mixture of acrylamide (0.2g) and 3-aminopropyl methacrylamide hydrochloride (0.8g) by the ceric ion technique. After washing with 0.5N NaOH the film gave a positive test for amino with Eosin Y. A portion (3 x 1 cm) was coupled with heparin (0.3g) in 5ml water with the aid of 0.3g EDC (1-ethyl-3-(3-dimethyl aminopropyl carbodimide hydrochloride) (25°C, 17 hours). It was then washed extensively with water and PBS; a piece of the film (2 x 1 cm) submitted to the PTT test gave the following result.

After heparin coupling: 750 seconds

Control: 230 seconds

Example 10

Catheters were of three types:

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(1) composed of nylon-11, (2) having a shaft of Pellethane and a balloon of Tecoflex, and (3) constructed of poly(ether-ester). All were heated at 60°C in a 10% solution (w/v) of potassium peroxy disulphate for 1 hour then washed extensively. They were then grafted with polyacrylamide by immersion in a solution at 40°C of acrylamide (10%w/v), ceric ammonium nitrate $5 \times 10^{-3} \text{M}$ in 0.04M nitric acid. After washing the catheters extensively with hot water, the surface friction was found to be very greatly reduced so that the catheters were very slippery.

Example 11

A disc 2.54 cm in diameter was cut from a membrane of polyacrylonitrile produced by electrostatic spinning or the precipitation technique and hydroxylated by treatment with 10% aqueous potassium peroxydisulphate at 80°C for 1 hour. It was then washed copiously with hot water. Oligodeoxythymidine (oligo(dT)) radiolabeled with p^{32} was converted to a polymerisable monomer by esterification with 2-hydroxyethyl methacrylate in pyridine solution in the presence of dicyclohexyl carbodiimide. The resulting monomer was grafted to the polyacrylonitrile membrane with acrylamide as comonomer, with the aid of the ceric ion technique described in earlier Examples. The membrane was

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washed and found to have high radioactivity, indicating that coupling of the oligo(dT) had been achieved.

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CLAIMS

1. A method for the functionalisation of a polymer, which method comprises reacting the polymer in an aqueous medium with an oxidising agent capable of producing oxygen-centered radicals which are ultimately responsible for introducing hydroxyl groups into the polymer, the reaction being carried out in the absence of any additive which is preferentially oxidised or is reactive towards the radicals produced by the oxidising agent.

2 A method as claimed in claim 1, in which the oxidising agent is a peroxidant.

3. A method as claimed in claim 2, wherein the peroxidant is a peroxydisulphate or a peroxymonosulphate.

4. A method as claimed in claim 3, wherein the peroxydisulphate or peroxymonosulphate is the salt of an alkalimetal.

5. A method as claimed in claim 4, in which the salt of the alkalimetal is the potassium or sodium salt.

6. A method as claimed in any of the previous claims in which the oxidising agent is used in an amount of from 2 to 50% wt/vol.

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7. A method as claimed in any of the preceding claims wherein the method is conducted at a temperature of from 40 to 100°C for a period of from 10 minutes to 5 hours.

8. A method as claimed in any of the preceding claims in which the polymer is selected from olefin polymers, aliphatic polyesters, polymers containing aromatic rings, carbonate polymers, vinyl polymers, polyurethanes, nylons, polyglycols and polyaldehydes.

9. A method as claimed in any of the preceding claims, wherein nitrogen is passed into the aqueous medium during the reaction.

10. A process for the production of a polymer product comprises reacting a functionalised polymer produced according to any of claims 1 to 9 with another material which could be used for further functionalisation, or for coupling to a biomolecular species.

11. A process as claimed in claim 10, wherein the biomolecular species is coupled by a free radical reaction or a non radical reaction.

12. A process as claimed in claim 10 or 11 wherein the polymer product is a catheter and the functionalised polymer is reacted with acrylamide or N-vinyl pyrrolidone.

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13. A process as claimed in claim 10 or 11, wherein the polymer product is a hollow fibre oxygenator or a blood filter and the functionalised polymer is reacted with acrylamide or N-vinyl pyrrolidone.

INTERNATIONAL SEARCH REPORT

PCT/GB 93/01195

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. 5 C08F8/06; C08G85/00; C08F8/30; C08G81/00		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C08F ; C08G	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ^o	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	US,A,4 042 644 (F. HRABAK) 16 August 1977 see column 2, line 18 - line 35; claims 1-4	1-11
X	DE,A,1 595 808 (HERCULES INC.) 23 April 1970 see page 3, paragraph 2 - page 4, paragraph 1 see page 6, paragraph 2 - page 7, paragraph 1 see page 11, paragraph 2 - page 12, paragraph 1; claims 1-5	1-8
A	US,A,4 311 573 (K. G. MAYHAN) 19 January 1982 see column 1, line 32 - line 51 see column 6, line 18 - line 35; claims 1-18	1, 12, 13
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^o Special categories of cited documents : ¹⁰ "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
12 OCTOBER 1993		
International Searching Authority		Signature of Authorized Officer
EUROPEAN PATENT OFFICE		PERMENTIER W.A.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
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A	US,A,4 011 380 (C. T. WEST) 8 March 1977 see claims 1-21 ---	1
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**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

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The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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