

Synthesis of Polymer-bound Sensitizers and their Applications in the Preparation of Previtamin D₃ from Tachysterol

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Two kinds of polymer-bound photosensitizers were synthesized, in which anthracene acts as sensitizer moiety, polystyrene (PS) and poly(methyl methacrylate) (PMMA) serve as solid phase supports, respectively. The photoisomerization of tachysterol to previtamin D₃ was carried out with these polymer-bound photosensitizers in ethanol and toluene solutions. The experiment results demonstrate that these solid phase photosensitizers are efficient for the photoisomerization with good recycle property and can be simply separated from the reaction mixtures by filtration.

Keywords polymer-bound photosensitizer, tachysterol, vitamin D₃, photoisomerization

Introduction

The photochemistry of 7-dehydrocholesterol (7-DHC) has been studied extensively for many years.¹⁻⁴ As shown in Scheme 1, irradiation of 7-dehydrocholesterol in organic solvent results in its photoisomerization to previtamin D₃ (Pre). Previtamin D₃ can be thermally transferred into vitamin D₃ (VD₃), which is of commercial interests. However, with increasing consumption of 7-dehydrocholesterol the photochemically formed previtamin D₃ competes with 7-dehydrocholesterol in the light absorption. Hereby, previtamin D₃ is photoisomerized into lumisterol (Lumi) and the *E*-triene tachysterol (Tachy) which is toxic and must be separated from the reaction mixture, *e.g.* as a Diels-Alder adduct with maleic anhydride before the thermal transformation of previtamin D₃ to vitamin D₃.⁵ Even when the irradiation conditions are well controlled there is still about 15% formation of tachysterol that lowers the yield of previtamin D₃ (and hence of the vitamin D₃) during the production process.

It is well known that photochemical conversion of tachysterol to previtamin D₃ can be conducted by irradiation with appropriate UV light in the presence of triplet photosensitizers, such as anthracene, 9-fluorenone, benzanthrone, *etc.*^{5,6} All these sensitizers can only be separated from the reaction mixtures by column chromatography, a procedure not feasible for the production of vitamin D series compounds on a large scale. To overcome this difficulty, water-soluble and

non-crosslinked polymeric photosensitizers were used in these reactions.⁷⁻¹⁰ Although column chromatography is not necessary, these methods are not environmentally friendly and not economic for manufacture. The separation of the sensitizer will produce a lot of waste water and need a large amount of solvents for the water-soluble and non-crosslinked polymeric photosensitizers respectively. All these sensitizers have strong photobleaching phenomenon during the photosensitization and cannot be recycled.

In this paper, we synthesize two kinds of crosslinked polymeric sensitizers with anthracene chromophores which photoisomerize tachysterol into previtamin D₃. The sensitizers can be simply separated from the reaction mixtures by filtration with good recycle property.

Experimental

Materials

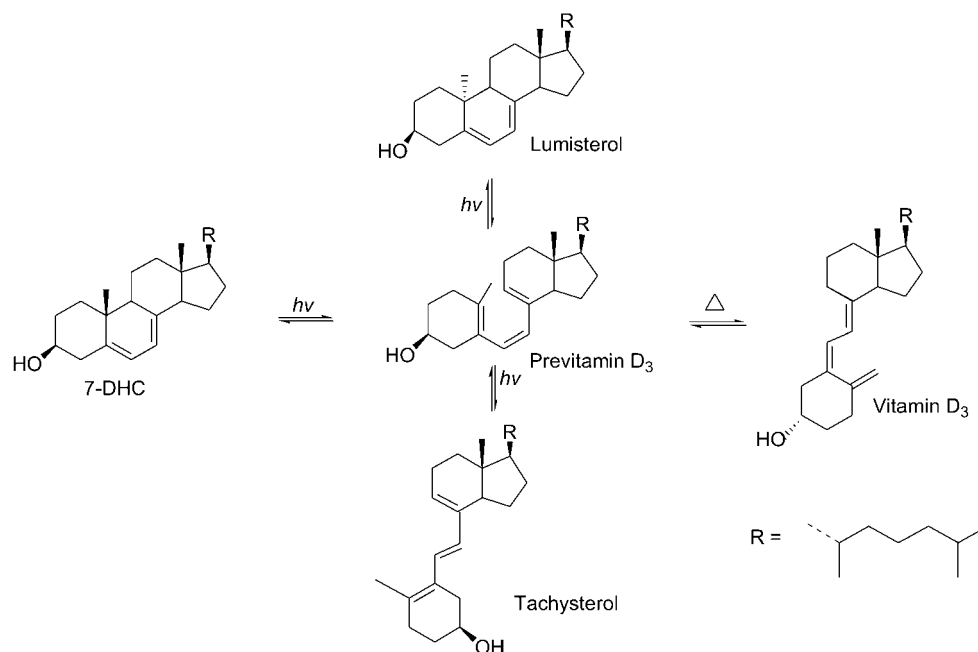
7-Dehydrocholesterol (Acros), Merrifield resin (1% crosslinked 2—2.5 meq. Cl/g, Acros) and 9-anthracene-methanol (Acros) were used without further purification. Methyl methacrylate was purchased from Beijing Chemical Reagent Company and distilled before use. 9-Anthrylmethyl acetate and 9-anthrylmethyl methacrylate with 99% purity were prepared according to the methods reported in the literature.¹¹ All solvents used in this work were purified in usual way before use.

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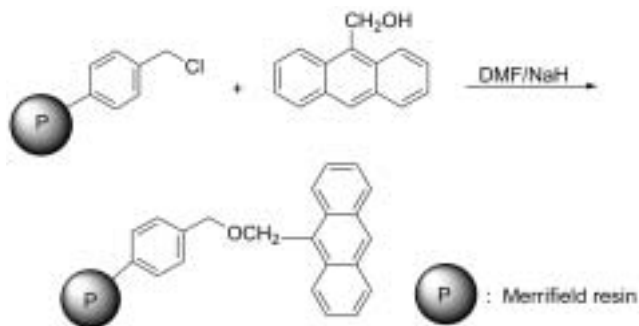
Scheme 1 Photochemical reaction of 7-DHC



Synthesis of solid phase photosensitizers

PS-An The procedure for preparation of polystyrene-bound sensitizer was shown in Scheme 2.¹² To a slurry of sodium hydride in DMF, a solution of 9-anthracenemethanol in DMF was added with stirring. After 1 h stirring at room temperature, Merrifield resin was added. The reaction mixture with stirring was heated to 80 °C for 48 h. The resin was filtrated and washed, then dried in vacuum oven at 60 °C for 12 h. The amount of the sensitizer on the backbone was determined by UV absorption intensity of the 9-anthracene derivative which was yielded by Schaap's cleavage procedure with TiCl_4 as cleaving agent.^{12,13} The polymeric sensitizers, PS-An-I and PS-An-II with different loadings, were synthesized by this procedure.

Scheme 2 Synthesis of PS-An



PMMA-An The poly(methyl methacrylate)-bound anthracene, PMMA-An, was synthesized by the following procedure. Methyl methacrylate, 9-anthrylmethyl methacrylate, divinylbenzene (1 mol% of methylacrylate), BPO and toluene were placed in a polymerization reactor. The mixture was bubbled by argon for 40 min. The reaction temperature was maintained at 80

°C for 24 h. After the polymerization was completed, the polymer was crushed and washed until there was no more anthracene absorption in the solvent. The loading of the anthracene moieties was determined by UV absorption intensity of the 9-anthracene derivative that was yielded by saponification of the polymer with NaOH as base and PMMA-An is about 1% crosslinked.

General procedure for the production of tachysterol and photosensitization

The photochemical reactions were carried out using a 450 W medium pressure Hanovia lamp in a water-cooled quartz immersion well. The first irradiation (a solution of 7-DHC) was performed in a quartz reactor for 30 min and the second (photosensitization) in glass reactor to cut off the light with wavelength below 300 nm. Argon was bubbled prior to and during irradiation.

In the recycle experiments, the solid phase photosensitizer was filtered from the reaction mixture and washed by THF and methanol. After dried under vacuum, it was reused directly in the next irradiation.

The photochemical reaction was followed by a Hitachi HPLC system, equipped with L-7110 pump and L-7420 UV/Vis detector. An Alltima LC-Si 5 μm column (4.6 mm ID, 25 cm) was used with a mobile phase of 0.3% pentanol in hexane. The samples were monitored at 254 nm with flowing rate 2 mL/min. Retention time and independent samples established peak identities.

The conversion of tachysterol can be obtained by comparison the peak areas of tachysterol before and after second irradiation: $\text{Conversion\%} = (A_0 - A_t) / A_0 \times 100\%$, A_0 is the peak area of tachysterol before the second irradiation and A_t is that after "t" minutes irradiation.

Results and discussion

The photosensitizers with different polymer backbones, polystyrene (PS) and poly(methyl methacrylate) (PMMA), and different loadings were synthesized according to the procedures described in the experimental section. The loadings of these photosensitizers are listed in Table 1.

Table 1 Loadings of the photosensitizers

Photosensitizer	PS-An-I	PS-An-II	PMMA-An-I	PMMA-An-II
Loading/(mol·g ⁻¹)	1.2×10 ⁻⁵	2.0×10 ⁻⁵	6.0×10 ⁻⁵	3.7×10 ⁻⁵

The photochemical reaction was followed by HPLC. Figure 1 shows the HPLC traces of the reaction mixture formed during the first irradiation (a) and the second irradiation (b) in the presence of PS-An-II in toluene. Table 2 shows the conversion of tachysterol during irradiation in ethanol sensitized by PS-An and PMMA-An with two different loadings respectively. The same amounts of anthracene moieties were used in these

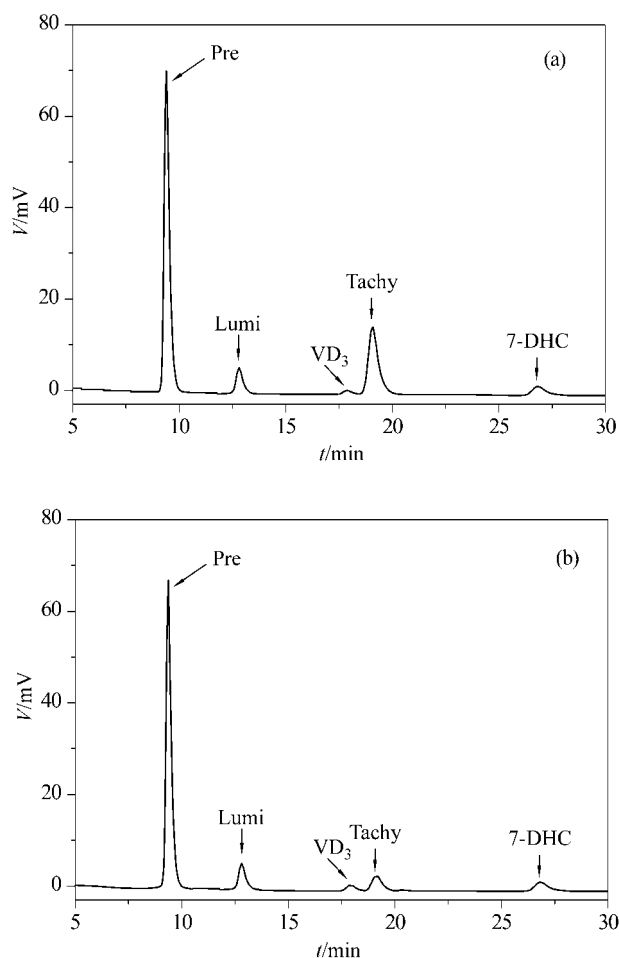


Figure 1 HPLC traces of the reaction mixture for the first irradiation (a) and the second irradiation in the presence of PS-An-II in toluene (b).

Table 2 Conversion of tachysterol with different solid phase photosensitizers^a

Irradiation time/min	Conversion of tachysterol/%			
	PS-An-I	PS-An-II	PMMA-An-I	PMMA-An-II
0	0	0	0	0
5	57	64	64	56
15	78	80	93	92
30	83	84	93	95

^a Concentration of anthracene moiety: 1×10⁻⁴ mol/L, [7-DHC]=1 mg/mL.

experiments. The results show that the tachysterol can be isomerized to previtamin D₃ by these polymeric photosensitizers. During 30 min irradiation, the conversions of tachysterol photosensitized by different solid phase sensitizers are similar for the same polymer support. This indicates that the amount of anthracene plays the main role for the rate of photoisomerization and the effect of loading in the range of our experiments can be ignored. The little difference between PS and PMMA backbone may be caused by the unlikeness of the interaction between polymer support and substrate.

The photoisomerizations with different amount of polymer bound anthracene were also investigated. As expected, the reaction rate increases with more sensitizer being used for both PS-An and PMMA-An because it will enhance the probability of the reactant encountering the anthracene moieties.

The solvent effect on the photoisomerization with polymer-bound photosensitizer was also examined. The backbone of Merrifield resin is crosslinked polystyrene, which can be swelled very well in toluene but poor in ethanol. It was expected that the photoisomerization in toluene would proceed faster than in ethanol because the anthracene moieties might have more chance to encounter the reactant. However, the result of PS-An is on the contrary. After 5 min irradiation the conversion of tachysterol shows about 50% higher in ethanol than in toluene. It is suggested that almost all the anthracene moieties are located on the periphery of the resin bead. When the resin is swelled the chain segments of crosslinked polymer have more room to move and some of the anthracene moieties are wrapped inside the crosslinked polymer that inhibits the contact with the substrate.¹⁴ The PMMA-An is obtained by copolymerization, the anthracene moieties are randomly distributed in the PMMA array, and as a consequence it is more affected by solvents. After 15 min irradiation the conversion of tachysterol is about 70% higher in ethanol than in toluene.

The distribution of the anthracene moieties also influences the recycle property of polymeric photosensitizers. Generally the photodimerization is considered as the reason for the bleach of anthracene.¹⁵ When anthracene chromophores were anchored on the polymer supports, the photobleaching was evidently suppressed. The

recycle property for both PS-An-II and PMMA-An-I was tested. The same amounts of anthracene moieties for different polymeric photosensitizers were used and irradiation time kept constant (30 min) for each cycle. PMMA-An-I shows better recycle property than PS-An-II. The difference may be caused by lower local concentration of sensitizer moiety that inhibits the dimerization of anthracene in more degree for PMMA-An-I than PS-An-II. After eight cycles the sensitization efficiency only decreases by about 10% (the conversion of tachysterol is decreased from about 90% to about 80%). When we prolong the irradiation time the conversion of tachysterol will reach the level of the first run. Taking these results into account, the solid phase photosensitizers with better recycle property can be obtained by lower loading and well dispersing of sensitizer moieties.

Generally the efficiency of insoluble photosensitizer is much lower than that of the corresponding small molecule photosensitizer, and this restricts the application of hetero-sensitization.¹⁶ The results for the comparison of the polymer-bound photosensitizer with small molecule photosensitizer are listed in Table 3. After 15 min irradiation the conversions of tachysterol with PS-An-I and 9-anthrylmethyl acetate as the photosensitizer can reach similar level, about 85%. It indicates that by increasing the amount of polymeric photosensitizer the efficient photosensitization can proceed with compatible reaction rate of homogeneous sensitization. Considering the recycle property and simplified separation process of the polymer-bound photosensitizers the heterogeneous sensitizers can be possibly applied on

large-scale industrial productions.

Conclusions

The results presented in this paper prove that the polymer-bound sensitizers are efficient in the photoisomerization of tachysterol to previtamin D₃ and feasible to the industrial production because of its easy separation from the reaction mixture. The solid phase photosensitizers show good recycle property because the anthracene chromophores are separated from each other by polymer support.

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Table 3 Conversion of tachysterol with polymer-bound photosensitizer PS-An-I and 9-anthrylmethyl acetate^a

Irradiation time/min	Conversion of tachysterol/%	
	PS-An-I	9-Anthrylmethyl acetate
0	0	0
5	57	86
15	85	87
30	86	87

^a Concentration of anthracene moiety of PS-An-I: 1.0×10^{-4} mol/L; 9-anthrylmethyl acetate: 1.2×10^{-5} mol/L.