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Synthesis of a Polymer-bound Sensitizer and its Application in the Photoisomerization of *trans*-Vitamin D_3 to *cis*-Vitamin D_3

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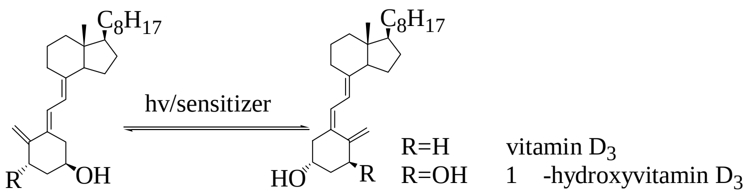
Abstract: A polymer-bound photosensitizer was synthesized by the reaction of Merrifield resin with 9-anthracenemethanol in the presence of potassium hydride. The photoisomerization of *trans*-vitamin D_3 to *cis*-vitamin D_3 was carried out with this polymer-bound photosensitizer in ethanol and toluene solutions. The experiment results demonstrate that this solid photosensitizer is efficient for the photoismerization and easy for separation from the reaction mixtures.

Keywords: Photoisomerization, solid phase sensitizer, vitamin D_3.

The photochemistry of the vitamin D family and their precursors has been the subject of extensive studies for many years[1-4]. Most of the studies focus on the photoisomerization of 7-dehydrocholesterol and that of tachysterol to previtamin D_3, which is of commercial importance in the synthesis of vitamin D_3[4, 5]. Recently the *cis/trans* isomerization of vitamin D analogs (**Scheme 1**) draws attention because of its importance in the synthesis of hydroxylated vitamin D metabolites[6]. However, only a few literatures are dealing with this aspect[3, 7].

Scheme 1



It is well known that photochemical conversions of tachysterol to previtamin D, and *trans*-vitamin D into *cis*-vitamin D_3 are conducted by irradiation with appropriate UV light in the presence of photosensitizers, such as anthracene, 9-fluorenone, benzanthrone, *etc*. 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, non-crosslinked polymeric

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photosensitizers[1-3] were used in these reactions. Although column chromatography is not necessary, this method is not economic for a manufacturing process because the separation of the sensitizer needs a large amount of mixed solvent. Taking these facts into account, we synthesize a crosslinked polymeric sensitizer –Merrifield resin-bound anthracene as the sensitizer to photoisomerize *trans*-vitamin D_3 into *cis*-vitamin D_3. This photosensitizer can be simply separated from the products by filtration.

Scheme 2

Experimental

The solvents were purified in the usual way *prior* to use. Commercial vitamin D_3 (Acros), Merrifield Resin (1% crosslinked 2-2.5meq. Cl/g, Acros) and 9-anthracenemethanol (Acros) were used without further purification. *trans*-Vitamin D_3 and 9-anthrylmethylacetate with 99% purity were prepared according to the literatures[8, 9] respectively.

The procedure for preparation of polymer bound sensitizer was shown in **Scheme 2**[10]. To a slurry of potassium hydride in DMF, a solution of 9-anthracenemethanol in DMF was added with stirring. After 1 hour stirring at room temperature, a slurry of Merrifield resin in DMF was added. The reaction mixture with stirring was heated to 80°C for 48 hours. The resin was filtered and washed, then dried in vacuum oven at 60°C for 12 hours.

The photochemical reactions were carried out using a 450 W medium pressure Hanovia lamp in a water-cooled quartz immersion well. All the samples were in glass reactors to cut off the light with wavelength below 300 nm and were bubbled with argon *prior* to and during irradiation.

The photochemical reaction was followed by a Hitachi HPLC, equipped with L-7110 pump and L-7420 UV/Vis detector. An Alltima LC-Si 5μm column (4.6 mm ID, 25 cm) was used with a mobile phase of 0.6% pentanol in hexane. The samples were monitored at 254 nm with flowing rate 2 mL/min. Retention time and independent samples established peak identities.

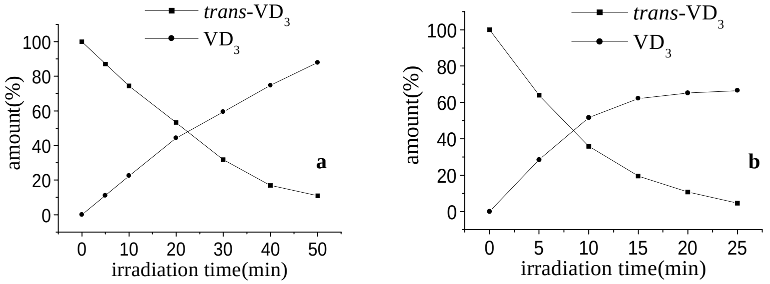
Results and discussion

The preparation of polymer bound sensitizer was described in the experimental section. The amount of the sensitizer in the backbone was determined by UV absorption intensity of the 9-anthracene derivative which was yielded by Schaap's[11] cleavage procedure with $TiCl_4$[10] as cleaving agent. The loading was found to be 2.0×10^{-5} mol/g.

The photoisomerization was followed by HPLC. **Figure 1a** shows the concentration change of *trans*-vitamin D_3 and *cis*-vitamin D_3 during irradiation for the sample sensitized by Merrifield-bound anthracene in ethanol. The yield of *cis*-vitamin D_3 was almost 100% based on the consumption of the *trans*-vitamin D_3. After 50min irradiation, about 90% of *trans*-vitamin D_3 was converted into *cis*-vitamin D_3.

Figure 1 The change of the concentration of *trans*-vitamin D_3 and *cis*-vitamin D_3 as a function of irradiation time

a. sensitized by polymer-bound anthracene; **b**. sensitized by 9-anthrylmethyl acetate.



(concentration of sensitizer moiety: 1.8×10^{-5} mol/L; initial concentration of *trans*-vitamin D_3: 2.20×10^{-3} mol/L).

Generally the efficiency of insoluble photosensitizer is much lower than that of the corresponding non-polymer-supported photosensitizer[12], and this restricts the application of hetero-sensitization. **Figure 1a** and **1b** give the results of isomerization sensitized by polymer-bound anthracene and 9-anthrylmethyl acetate respectively. The same amounts anthracene moieties were used in these experiments. The photoisomerization with 9-anthrylmethyl acetate shows a totally different tendency from the Merrifield resin-bound sensitizer. The photoisomerization rate with polymer-bound sensitizer keeps almost constant through the reaction. However, in the case of 9-anthrylmethyl acetate as photosensitizer, even *trans*-vitamin D_3 is continuously consumed, there is no more *cis*-vitamin D_3 formed after the yield reaching 60%. This is attributed to the bleaching of the sensitizer. When the sensitizer is consumed, *trans*-vitamin D_3 and *cis*-vitamin D_3 are irradiated directly and they are converted into undesirable byproducts[13]. Although the reaction rate for the sample sensitized by heterogeneous sensitizer is a little bit lower than that by homogeneous sensitizer, it is still acceptable in practice.

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 not in ethanol. We 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, in our experiments the photoisomerization efficiency did not show any difference in toluene and ethanol. This result suggests that almost all the anthracene moieties are located on the periphery of the resin bead.

Generally the photodimerization is considered as the reason for the bleach of anthracene[14]. The solid phase polymer support can separate anthracene chromophores from each other, this photodimerization is forbidden. As a consequence the Merrifield-bound sensitizer can be used for many recycles. It is needed to point out that the polymer-bound sensitizer efficiency still decreases to some extent after each run of photosensitization. This means that the bleach of anthracene is not only caused by dimerization.

Table1 Conversion of *trans*-vitamin D_3 in ethanol (8×10^{-4} mol/L) with different amount of polymer-bound anthracene at ambient temperature after irradiation for 5 min

Polymer-bound anthracene (mg)	10	20	30
trans-VD_3 (%)	56.6	46.0	35.5
VD_3 (%)	41.2	49.2	58.4

The photoisomerizations with different amount of polymer-bound anthracene were also investigated. To avoid over irradiation, the reaction time was fixed at 5 minute. The results are shown in **Table 1**. As expected, the reaction is faster with more sensitizer. The rate increase is proportional with the amount of photosensitizer.

Conclusion

The results presented in this paper proved that the Merrifield resin-bound anthracene photosensitizer is efficient in the photoisomerization of *trans*-vitamin D_3 to *cis*-vitamin D_3 and feasible to the industrial production because of its easy separation from the reaction mixture.

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