

Conformer-Specific Photoconversion of 25-Hydroxytachysterol to 25-Hydroxyprovitamin D₃: Role in the Production of Vitamin Ds

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Photochemistry in the vitamin D field is relatively well-understood, due in large part to contributions by Havinga¹ and Dauben² and their co-workers. It inspired Havinga's principle of the nonequilibration of excited rotamers (NEER) to explain the excitation-wavelength dependence of the photoproduct quantum yields and distributions.³ Excitation wavelength effects due to differential excitation of a forbidden lowest-excited 2^1A_g singlet state⁴ and due to involvement of hot excited states⁵ of individual conformers have also been advanced. The interconversion of previtamin D (Pre) and tachysterol (Tachy) continues to command center stage because it has recently been proposed⁶ that, in a rigid glass at low temperature, it provides the first experimental demonstration of the Hula-Twist mechanism for *cis*–*trans* photoisomerization.^{7,8} From a practical standpoint it is important because of its key role in the industrial-scale syntheses of the vitamin (Vit) Ds.⁹

The photochemical goal in the production of Vit Ds is to maximize the conversion of the provitamins (Pros) to the (Pres) while minimizing stoichiometric losses to undesirable overirradiation products. The last step in the syntheses, the [1,7]-sigmatropic rearrangement of the Pres to the Vits, Scheme 1, is thermally induced.¹⁰ Only the Pre/Tachy interconversion can be sensitized by a triplet energy donor.¹¹ High Pre yields have been achieved by single- and double-stage approaches.¹² In the first, a Pre-rich quasi-photostationary state (Q-PSS) is obtained by selecting λ_{exc} close to 296 nm.¹³ In the second, a convenient λ_{exc} (e.g., 254 nm) converts Pro to a Tachy-rich Q-PSS, which is converted to a Pre-rich Q-PSS by means of triplet sensitization¹⁴ or direct excitation with a longer λ_{exc} .¹⁵ The two photochemical steps have also been combined.¹⁶

The set of spectra for the 25-hydroxyvitamin D₃ isomers is typical, Figure 1.^{13c,15c,16d} The strong dependence of Pre \rightarrow Tachy, Pre \rightarrow Pro, and Pre \rightarrow Lumi quantum yields on λ_{exc} is well documented.^{4,17} It is in contrast to the quantum yield for Tachy \rightarrow Pre that has been reported to be inefficient and insensitive to changes in λ_{exc} (~ 0.1 at 254 and 313 nm in ether^{1a,17} and in ethanol^{16a}). Curiously, λ_{exc} (337–355 nm)^{15,16} used for the Tachy \rightarrow Pre step in the sequential direct excitation procedure are barely absorbed by Tachy.

The shoulder at the onset (330–300 nm) of the HOTachy spectrum suggests that excitation at 313 nm selectively excites a minor conformer, whereas excitation at 254 nm probably excites the more abundant tEc conformer (shown in Scheme 1).^{1a,18} A recent molecular mechanics-based (MMX) conformational search confirms the placing of tEc as the most abundant conformer (63%) and predicts cEc (18%) to be slightly more abundant than tEt (13%).¹⁹ The weak structureless band at the onset of the UV spectrum of HOTachy should then be assigned to either the cEc or the tEt

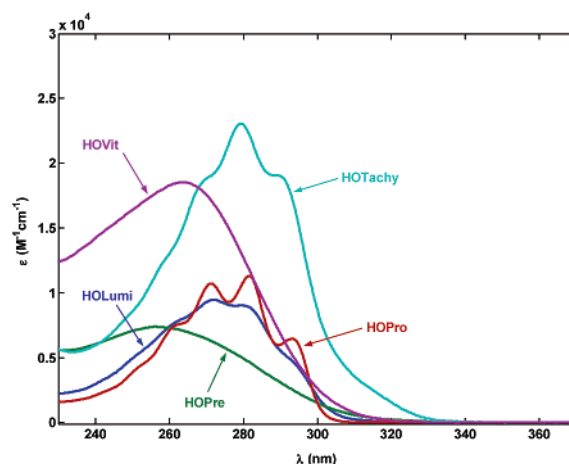
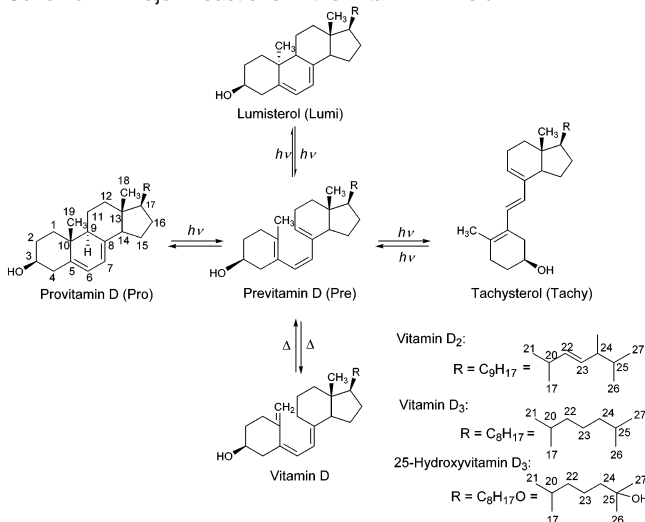


Figure 1. Absorption spectra of HOvit isomers (methanol, 20 °C).

Scheme 1. Major Reactions in the Vitamin D Field



conformer with the former more likely since *s-cis* diene moieties normally absorb at longer wavelengths.²⁰

We, therefore, remeasured the Tachy \rightarrow Pre quantum yields (ϕ_{TP}). HOTachy, prepared by 254-nm (low-pressure Hg lamp) irradiation of deaerated HOPro in methanol (MeOH), was isolated by preparative HPLC. Degassed methanol solutions in 13-mm o.d. ampules (quartz for 254 and Pyrex for 313 nm) were irradiated in a merry-go-round apparatus at 20 °C. Some ampules were provided with sidearms attached to 3-mm UV cells. Analysis of the time evolution of UV spectra by singular value decomposition (SVD)²¹ complemented HPLC analysis.²² The *trans*–*cis* photoisomerization of stilbene was used for actinometry, and conversions were corrected for back-reaction.²³ We find $\phi_{TP} = 0.12 \pm 0.02$ at 254 nm as expected,^{1a,16a,17} but $\phi_{TP} = 0.42 \pm 0.02$ at 313 nm, a factor

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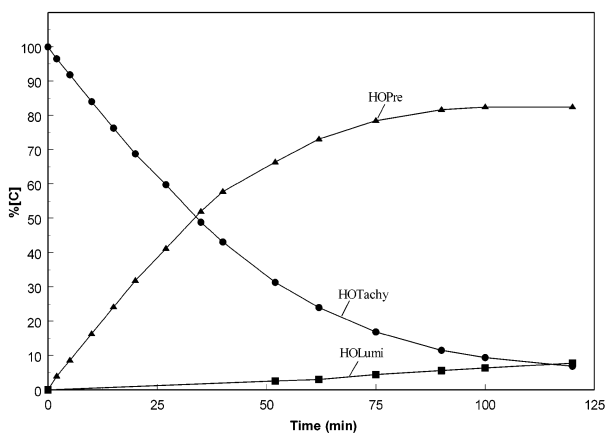


Figure 2. Irradiation of HOTachy at 313 nm (SVD analysis).

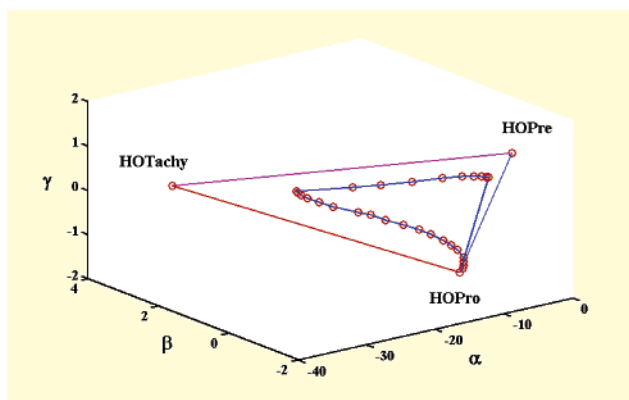


Figure 3. Combination coefficients for the two-stage 254/313-nm conversion of HOPro to a HOPre-rich mixture.

of ~ 4 larger than previously reported values ($[HOTachy]$ in the $3.2\text{--}9.0 \times 10^{-4}$ M range). On the basis of predicted conformer energetics¹⁹ and absorption spectra,²⁰ it follows that *cEc*-Tachy gives Pre much more efficiently than does *tEc*-Tachy. The product evolution from a 3-component SVD analysis of UV spectra of a typical run is shown in Figure 2. It neglects small amounts of HOPro and HOvit present at longer times.

HPLC analysis of the final reaction mixture gave 5.7% (6.9) HOTachy, 81.9% (82.4) HOPre, 8.3% (7.8) HOLumi, 2.4% HOPro, and 1.8% HOvit (values in parentheses are from the SVD analysis in Figure 2). Nearly identical product compositions are reached much faster without the use of the 313-nm filter solution because 313 nm is the only Hg line (medium pressure Hg lamp) transmitted by Pyrex that is significantly absorbed by the mixture, Figure 1. The large HOPre/HOTachy Q-PSS ratio disagrees with previous expectations.^{3a,13c} Our results explain the Pre D₃-rich Q-PSS (59%) that was obtained recently upon 308-nm excitation of 7-dehydrocholesterol (Pro D₃) in ethanol.^{15c}

Similar conversions to HOPre were achieved starting from either HOTachy (313-nm) or HOPro (254/313-nm stepwise sequence). In a typical experiment, 4.5×10^{-4} M HOPro in MeOH was irradiated at 254 nm for 300 min to a mixture of 14.8% HOPro, 23.2% HOPre, 59.3% HOTachy, 2.0% HOLumi, and 0.6% HOvit and afterward, at 313 nm for 150 min to a final composition of 11.8% HOPro, 74.3% HOPre, 6.1% HOTachy, 5.4% HOLumi, and 2.4% HOvit (HPLC). UV spectra recorded during the course of these irradiations were treated by SVD as a four-component system (HOvit was neglected). The plot of the combination coefficients of the three major eigenvectors, Figure 3, is revealing. Points for the experimental spectra fall close to the stoichiometric plane

defined by the spectra of the pure components HOPro, HOPre, and HOTachy. Initially, irradiation at 254 nm moves the system from the HOPro corner toward HOPre, but it soon turns toward HOTachy. The switch to 313-nm irradiation causes the sharp turn toward HOPre. The second step of the 254/313-nm two-step sequence achieves high, clean Tachy-to-Pre conversion with minimal competing Pre photocyclizations to Pro and Lumi without requiring high excitation intensities due to the low absorbances at previously used λ_{exc} .^{15,16}

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