Degradation of Paclitaxel and Related Compounds in Aqueous Solutions III: Degradation Under Acidic pH Conditions and Overall Kinetics

JIAHER TIAN[1,2] VALENTINO J. STELLA[1]

[1]Department of Pharmaceutical Chemistry, The University of Kansas, Lawrence, Kansas 66047

[2]Forest Laboratories, Inc., 220 Sea Lane, Farmingdale, NewYork 11735

ABSTRACT: Paclitaxel and related taxanes are complex molecules with numerous hydrolysable ester groups, possible epimerization at the 7-position, and possessing a strained oxetane ring, a possible site for acid-catalyzed cleavage. Presented here is the stability of paclitaxel, 10-deacetylbaccatin III, baccatin III, and N-benzoyl-3-phenyliso-serine ethyl ester in aqueous solution over a pH range of 1–5 at various temperatures. Analysis of various samples was by HPLC–UV and LC–MS. Baccatin III, 10-deacetyl-baccatin III, and N-benzoyl-3-phenylisoserine ethyl ester were found to undergo acid catalysis since pH-rate profiles all followed a first-order dependency in hydrogen ion concentration. No evidence of any epimerization was noted at acidic pH values. Baccatin III and 10-deacetylbaccatin III showed similar degradation rates with possible products being possible dehydration around the 13-hydroxy group and cleavage of the oxetane ring. Cleavage of the 10-acetyl group of baccatin III was a minor initial pathway. N-Benzoyl-3-phenylisoserine ethyl ester degraded significantly slower than both 10-deacetylbaccatin III and baccatin III. At pH 2, paclitaxel degraded at a rate between that of N-benzoyl-3-phenylisoserine ethyl ester and 10-deacetylbaccatin III. The pH of maximum stability for all compounds appeared to be around pH 4. © 2009 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 99:1288–1298, 2010

Keywords: paclitaxel; 10-deacetylbaccatin III; baccatin III; oxetane ring cleavage; hydrolysis; degradation; pH; stability; acid catalysis

INTRODUCTION

Earlier articles[1,2] in this series examined the kinetics, pathways, and mechanisms of the epimerization and base-catalyzed degradation of paclitaxel and related taxanes in aqueous solution at near neutral and basic pH values. The purpose of the present study was to explore the degradation of these compounds under acidic pH conditions. To our knowledge, the kinetics and major routes of aqueous degradation of paclitaxel and related taxanes under acidic pH conditions have not been published. A number of articles did report the effect of acids and electrophiles on the stability of paclitaxel and related materials in non-aqueous systems. These earlier studies explored the biological activity of various paclitaxel fragments formed under acidic reaction conditions.[3–5]
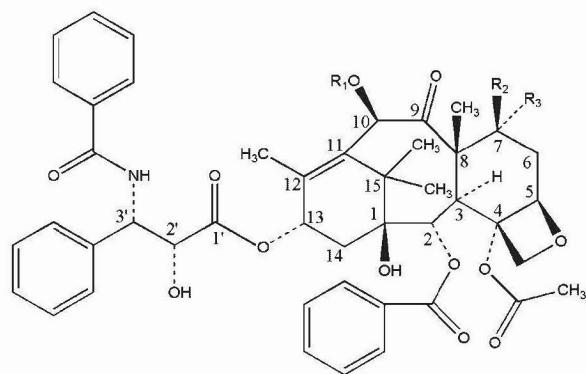
The structures of paclitaxel (1) and its related compounds (2–7) used in this study are shown in Figure 1. These were the same as those reported in our earlier studies.[1,2] By studying the kinetics and pathways to degradation of fragments of paclitaxel and taxotere, it was hoped that the

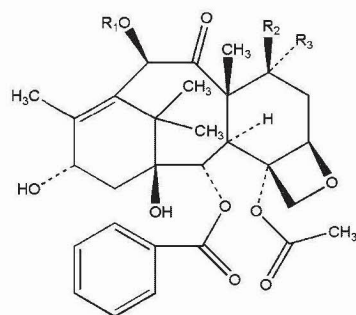Correspondence to: Valentino J. Stella (Telephone: 785-864-3755; Fax: 785-864-5736; E-mail: stella@ku.edu)

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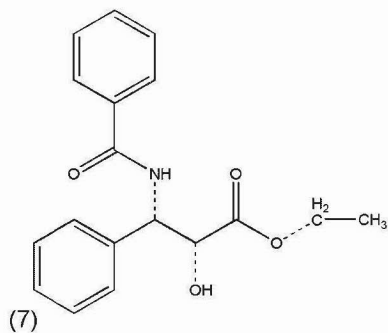InterScience®
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Figure 1. The structures of paclitaxel and related compounds: paclitaxel (**1**) 7-epi-taxol (**2**), 10-deacetyl-taxol (**3**), 7-epi-10-deacetyltaxol (**4**), baccatin III (**5**), 10-deacetylbaccatin III (**6**), and *N*-benzoyl-3-phenyliso-serine ethyl ester (**7**).

degradation complexity seen with larger molecules like paclitaxel would be better understood. Paclitaxel has four hydrolysable ester bonds, which might be expected to undergo hydrolysis promoted by acid. In addition to possible ester hydrolysis, the oxetane ring (D-ring) of paclitaxel

could undergo ring-opening reaction under acidic condition as was seen with some electrophilic reagents.[3–5]

EXPERIMENTAL

Materials

All of the chemicals and solvents were as described in detail earlier.[1,2] The pH of the solution was controlled throughout the reaction by using dilute hydrochloric acid and appropriate buffers. Reactions at pH 1, 2, and 3 were performed in dilute solutions of hydrochloric acid. Acetic acid/sodium acetate buffer was used for pH 4 and 5 and the buffer concentration was 1.0 mM. No significant change of pH was observed throughout the reaction. The ionic strength was maintained at 0.15 with sodium chloride.

HPLC and Mass Spectrometry Assays

HPLC–UV was employed to simultaneously detect and quantify the presence of the starting compound and its degradation products. The stability indicating isocratic HPLC–UV assay and the HPLC system operating conditions were described previously,[1,2] as were mass spectrometer conditions and are not repeated here.

Kinetics

The kinetics of the degradation reaction was investigated in aqueous solutions at pH 1–5. For the kinetic experiments at 25°C, 25 mL of the appropriate buffer solutions were equilibrated in a water bath at 25.0 ± 0.1°C, and the hydrolysis study initiated by adding 0.8 mL stock solution (125 µg/mL of the appropriate substrate in acet-onitrile) into the reaction buffer. This resulted in an initial reaction concentration of 2.0 µg/mL (6.4×10^{-6} M for *N*-benzoyl-3-phenylisoserine ethyl ester, 3.7×10^{-6} M for 10-deacetylbaccatin III, 3.4×10^{-6} M for baccatin III, and 2.3×10^{-6} M for paclitaxel). At various time intervals, aliquots (0.8 mL) of the reaction solutions were withdrawn, and assayed immediately by HPLC.

For the stability studies at elevated temperatures at 43.5, 50.0, and 70.0°C respectively, vials containing reaction solutions were placed in thermostatically controlled ovens. Solutions

were prepared at 25°C and the reported pH values were those determined at 25°C. No corrections for temperature effects on pH were applied. The reaction solutions were maintained at the desired temperature throughout the kinetic study. The vials were removed from the ovens at appropriate time intervals and quickly cooled in ice water to quench the reaction, and followed by immediate HPLC analysis.

The individual rate constant values were obtained from the best multi-variance regression of experimental data to various equations using the SigmaPlot program (v 7.101, SPSS, Inc., Chicago, IL). Numbers are reported ± standard deviation (±SD) where statistics could be determined.

RESULTS AND DISCUSSION

Paclitaxel (**1**) is a complex molecule capable of undergoing both epimerization and hydrolysis of various ester bonds under neutral to basic pH conditions in aqueous buffers. Tian and Stella[1,2] were better able to understand the degradation of paclitaxel and taxotere under these conditions by also studying the hydrolysis of 10-deacetylpaclitaxel (**3**), baccatin III (**5**), 10-deacetylbaccatin III (**6**), and N-benzoyl-3-phenylisoserine ethyl ester (**7**) and some of their related epimers (**2** and **4**, see Fig. 1).

Degradation of 10-Deacetylbaccatin III (6)

The degradation of the 10-deacetylbaccatin III (**6**), the taxane fragment of taxotere and 10-deacetyl-paclitaxel (**3**), was monitored in aqueous solutions of pH 1.09, 1.99, 3.05, 4.53, and 5.18 at 25°C and higher temperatures. No epimerization was noted in any studies under acidic pH conditions. This observation held for all the substrates studied under these conditions. In the pH range 1–3, the overall loss of the compound demonstrated good linearity on the semi-logarithmic plots, as shown in Figure 2. For those reactions where only limited degradation occurred, first-order kinetics was assumed based on the observation over many half-lives for the more completely degraded samples. The reactions at pH 4–5 were too slow to follow at 25°C so no reliable results were achieved over the time period of study at this temperature and are, therefore, not reported here.
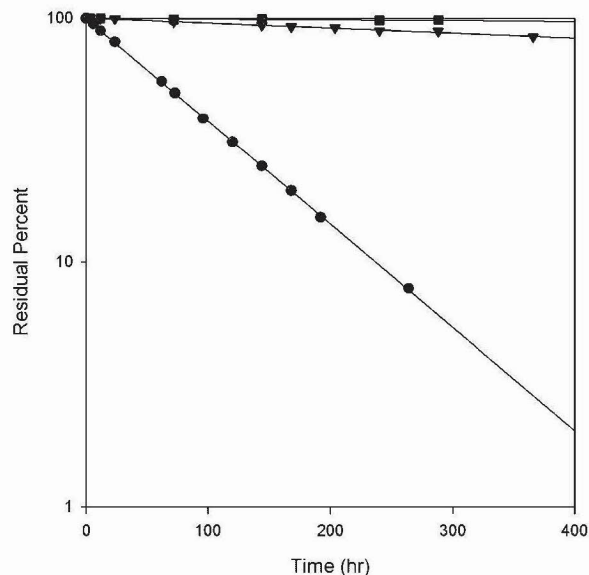

Figure 2. Semi-log plots for the degradation of 10-deacetylbaccatin III in aqueous solution at pH 1.09 (●), pH 1.99 (▼), and pH 3.05 (■), $T = 25°C$ showing the loss of 10-deacetylbaccatin III follows pseudo-first-order kinetics.

Although ester hydrolysis might be expected to be the major route of degradation, HPLC–UV analysis showed the appearance of six quantifiable peaks with time. The peak area for loss of 10-deacetylbaccatin III and formation of the six degradation peaks is shown in Figure 3. For example, at pH 2 and 70°C, two initial products were observed, one eluting before the parent peak (**P₂**) and one eluting later than the parent peak (**P₁**). A sample HPLC–UV–MS chromatogram is shown in Figure 4. These products, **P₁** and **P₂**, were formed by parallel competing reactions from 10-deacetylbaccatin III as shown by the open square and circle symbols. These products were followed by other products with time (open and filled upside down triangles and the filled circle symbols) that are clearly secondary or tertiary (the upside down triangle) products as indicated by the delay in their appearance, that is, they were formed from one or both of the initial products. An effort was only made to identify **P₁** and **P₂** from HPLC–UV–MS data. Unfortunately, because of the low concentrations used and the small quantity of 10-deacetylbaccatin III available to work with, it was not possible to isolate enough of these degradation products to run NMR studies to confirm the proposed structures.

The late eluting peak (**P₁**, open square symbol in Fig. 3) was not the epimer when compared to a
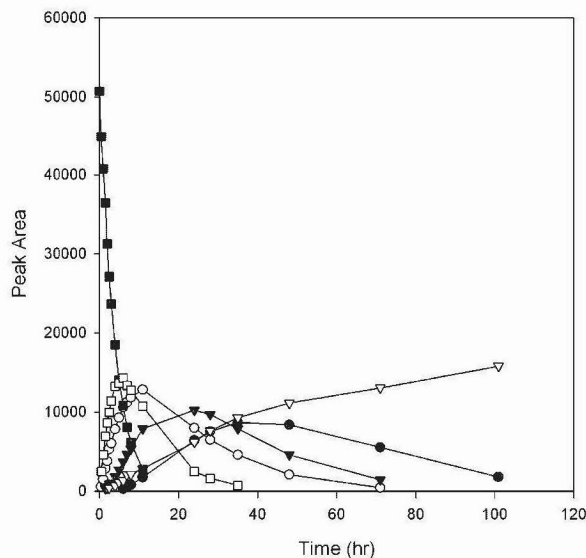
Figure 3. Plot of the peak area versus time course for various peaks seen in the chromatogram for the degradation of 10-deacetylbaccatin III (■) and the appearance of its initial degradation products, P_1 (□) and P_2 (○) in aqueous solution at pH 2, $T = 70°C$. The HPLC–UV chromatogram shows more decomposition products with time. That is, two primary products (P_1, □, mass number = 527 and P_2, ○, mass number = 563, see Scheme 1 for proposed structures) were followed by further degradation to secondary products indicated by the symbols ●, ▼, and ▽.

standard (earlier shown to also elute later than the parent peak) of 10-deacetylbaccatin III (**6**) but showed a loss of mass number 18 (consistent with the loss of water) supporting the conclusion that ester hydrolysis (loss of acetate or benzoate) was not responsible for this product. The longer retention time indicated this intermediate having reduced polarity, thus, it was considered a possible dehydrated product.

By contrast, the mass number of the other initial product (P_2, open circle symbol in Fig. 3), which eluted faster than 10-deacetylbaccatin III, gave a mass number for the addition of 18 mass units, again not consistent with ester hydrolysis. This structure was considered to be the product from the oxetane ring opening, consistent with findings by others under acidic reaction conditions.[3–5] With longer reaction time, both initial products degraded to further products. Among the later products analyzed, no ester hydrolytic products including the presence of benzoic acid were observed. From Figure 3, there did appear to be one major final product but this was an early eluting peak near the solvent front and may have

been made up of multiple products. The contents of this peak were not characterized.

Based on the information gathered, the proposed initial degradation pathways of 10-deacetylbaccatin III (**6**) in the acidic pH range, 1–3, is shown in Scheme 1. The primary reactions were probable dehydration of the C13–OH (P_1) and hydrolytic opening of the oxetane D-ring (P_2). Once the D-ring is opened, two additional –OH groups are formed. Due to the close proximity, it is likely the nearby C4 acetyl group is transferred to either of the two –OH positions. Consistent with this speculation was the observation that two of the additional, but secondary products, showed the same mass number but slightly different HPLC retention times as P_2. Overall, a simplified treatment of the kinetic data can be made for the degradation of 10-deacetylbaccatin III (**6**) in low pH can be defined Scheme 1, where Eq. 1 can define the overall loss of 10-deacetylbaccatin III (**6**)

$$-d[D]/dt = k_1[D] + k_2[D] \tag{1}$$

where the proposed dehydration and D-ring opening are parallel reactions, with constants k_1 and k_2, respectively.

$$[D] = [D]_o \exp[-(k_1 + k_2)t] = [D]_o \exp{-k_{obs}t} \tag{2}$$

The overall rate constant k_{obs} is the sum of k_1 and k_2, and can be obtained by slope of linear fitting of the semi-log plot for the loss of starting material against time. These initial reaction products (P_1 and P_2) degrade further to subsequent products, with apparent constants k_3 and k_4, respectively.

As such, all k values could be estimated from the peak area versus time profiles of products P_1 and P_2 (see Fig. 5) if the assumption were made that the response factors for P_1 and P_2 were identical to that of 10-deacetylbaccatin III. If one makes the assumption that the response factor for P_1 and P_2 are similar, it appears from peak area versus time plot seen in Figure 5 that the dehydration and hydrolytic opening of D-ring have comparable rates at pH 2.

Theoretically, the oxetane ring structure of paclitaxel should be much less reactive than an epoxide, its three-membered analogue. However, this ring-opening step to form a D-secotaxol derivatives appears to occur quite readily. The estimated acid-catalyzed rate constant is ~10 times faster than the estimated value for the opening of a similar epoxide structure based on previously reported data.[6] The ring-opening reaction to form D-secotaxols results in a tricyclic
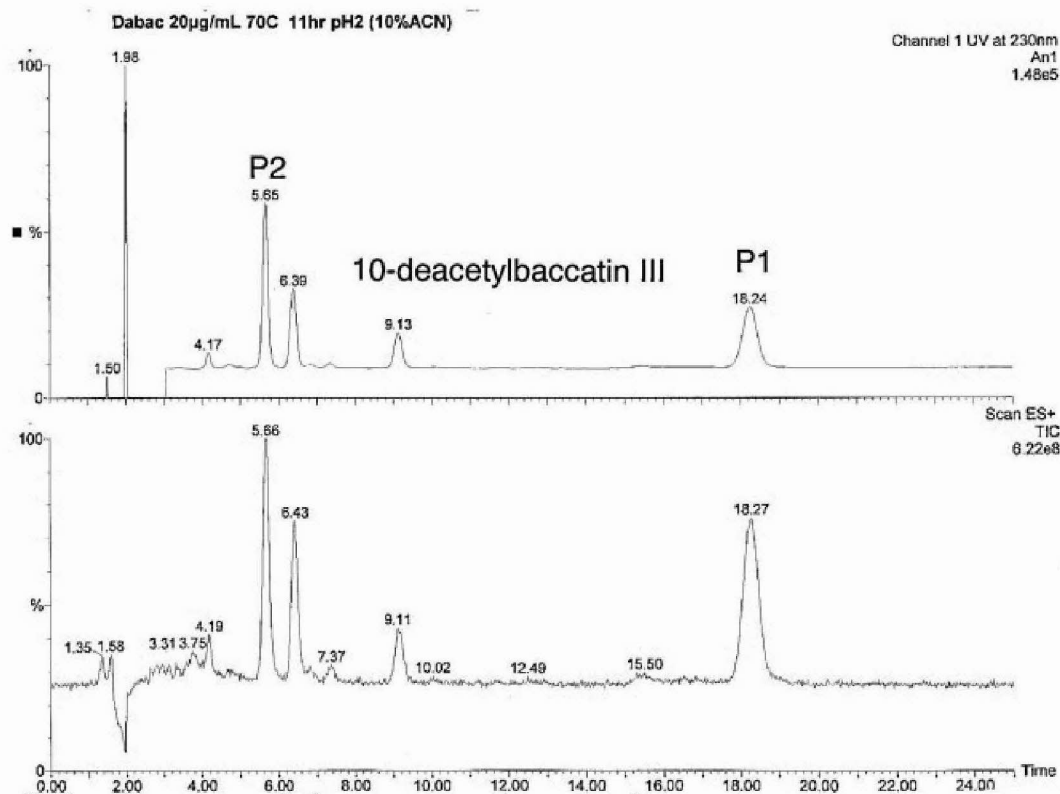
Figure 4. HPLC chromatogram and MS data for the degradation of 10-deacetyl baccatin III (at 9.1 min) and formation of the primary products P_1 and P_2 in aqueous solution at pH 2, $T = 70°C, t = 11$ h. Two primary products (early and late eluting, 5.7 (P_2) and 16.2 (P_1) min, respectively) followed by further degradation to secondary products (the peak at 6.4 min was only seen after the appearance of P_1 and P_2).
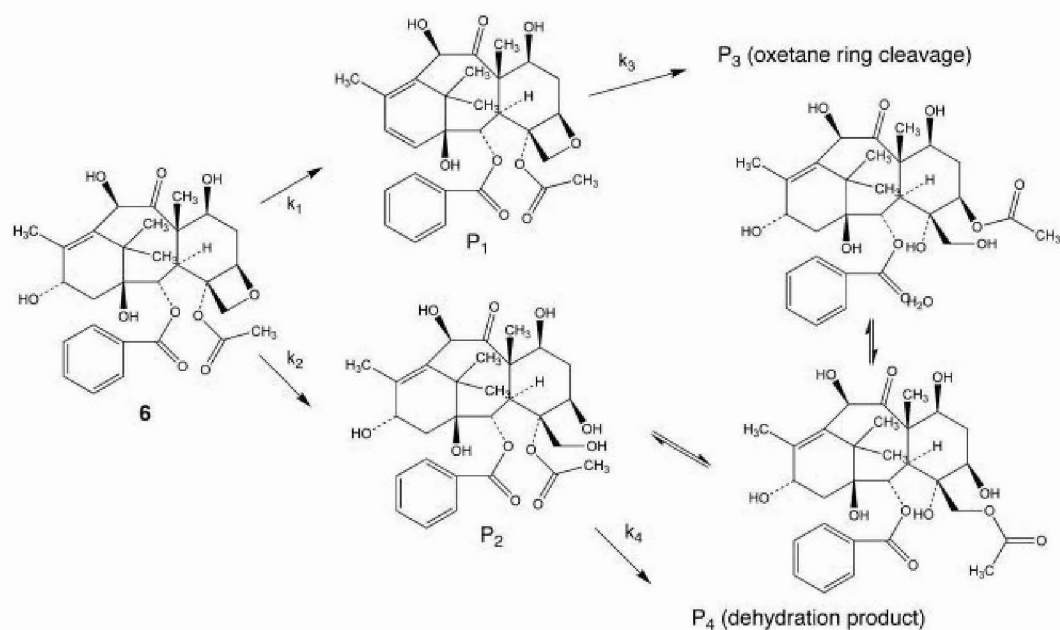
Scheme 1. Proposed degradation pathway for 10-deacetylbaccatin III (6) at low pH values in which the primary reaction pathways resulting in P_1 and P_2, are dehydration of C13–OH and hydrolytic opening of oxetane D-ring, respectively. Once the D-ring is opened, transesterification is proposed with the acetyl group transferred to either of the two newly formed –OH positions followed by other complex reactions.
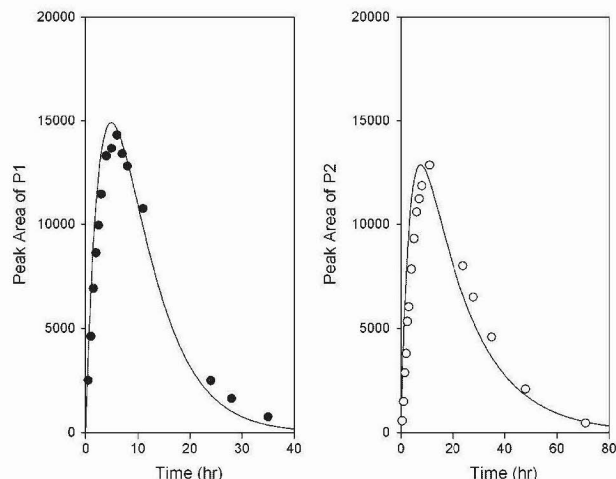
Figure 5. Experimental data and fitted lines describing the appearance of the two initial products P1 (●) and P2 (○) for the degradation of 10-deacetylbaccatin III at pH 2, $T = 70°C$.

ring system which is considerably more flexible than the rigid, inverted cup-shaped, tetracyclic ring system. It was reported that the ^{1}H-NMR signals of the protons of the A ring underwent a noticeable shift on opening of the D-ring, indicating this increased structural flexibility and conformational change.[5]

The pseudo-first-order degradation rate constants for 10-deacetylbaccatin III under acidic pH increased rapidly with increasing temperature. An Eyring plot (not shown) of 10-deacetylbaccatin III degradation at pH 1.96 was performed. The enthalpy of degradation, $\Delta H^{\neq}$, was determined to be $28 \pm 2 \, \text{kcal mol}^{-1}$ from the slope of the straight line, and the entropy of activation, $\Delta S^{\neq}$, was found to be 4.2 ± 0.6 e.u.

Degradation of Baccatin III (5) and Comparison to 10-Deacetylbaccatin III (6)

The time courses of degradation of baccatin III (**5**) were measured in aqueous solutions of pH 1.12 and 1.98 at 25°C. Linear semi-logarithmic plots indicated that the overall degradation followed pseudo-first-order kinetics, while again no epimerization was observed. Upon analysis of the final products, hydrolysis of the ester bonds was considered insignificant under these acidic pH conditions compared to other reactions as seen with 10-deacetylbaccatin III with the products showing similar relative retention times to those seen with 10-deacetylbaccatin III.

Moreover, the pH dependency for 10-deacetylbaccatin III (**6**) and baccatin III (**5**) degradation, Figure 6, shows that both compounds undergo apparent acid catalysis since the slopes of the pH-rate profiles are close to minus unity. The degradation rates for the two compounds are almost identical, indicating the hydrolysis of the additional acetyl ester group on 10-position seen with baccatin III is minimal compared to the two other reactions seen with 10-deacetylbaccatin III although a small peak for 10-deacetylbaccatin III was observed. This indicates that ester hydrolysis does not contribute significantly to the overall initial degradation in the acidic pH range. That is, if hydrolysis of the 10-acetate group was faster than the dehydration of the C13–OH group or the D-ring opening seen with 10-deacetylbaccatin III, baccatin III should exhibit faster degradation than 10-deacetylbaccatin III at the same acidic pH value.

From these results, the concentration-time profiles at acidic pH values are thought to be a consequence of reactions pathways illustrated in Scheme 2 where three reactions occur in parallel: dehydration at the C13–OH, opening of oxetane ring (D-ring), and minor hydrolysis of the 10-acetyl group. With longer reaction time, these initial products P_5, P_6, and P_7 (**6**), degrade further to secondary products (profiles not characterized).
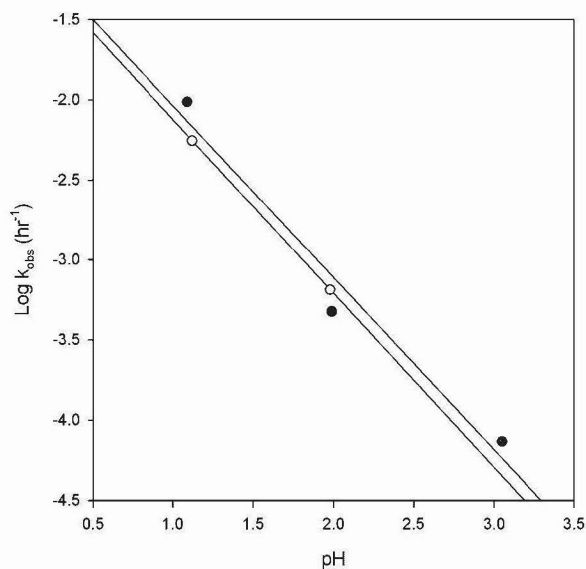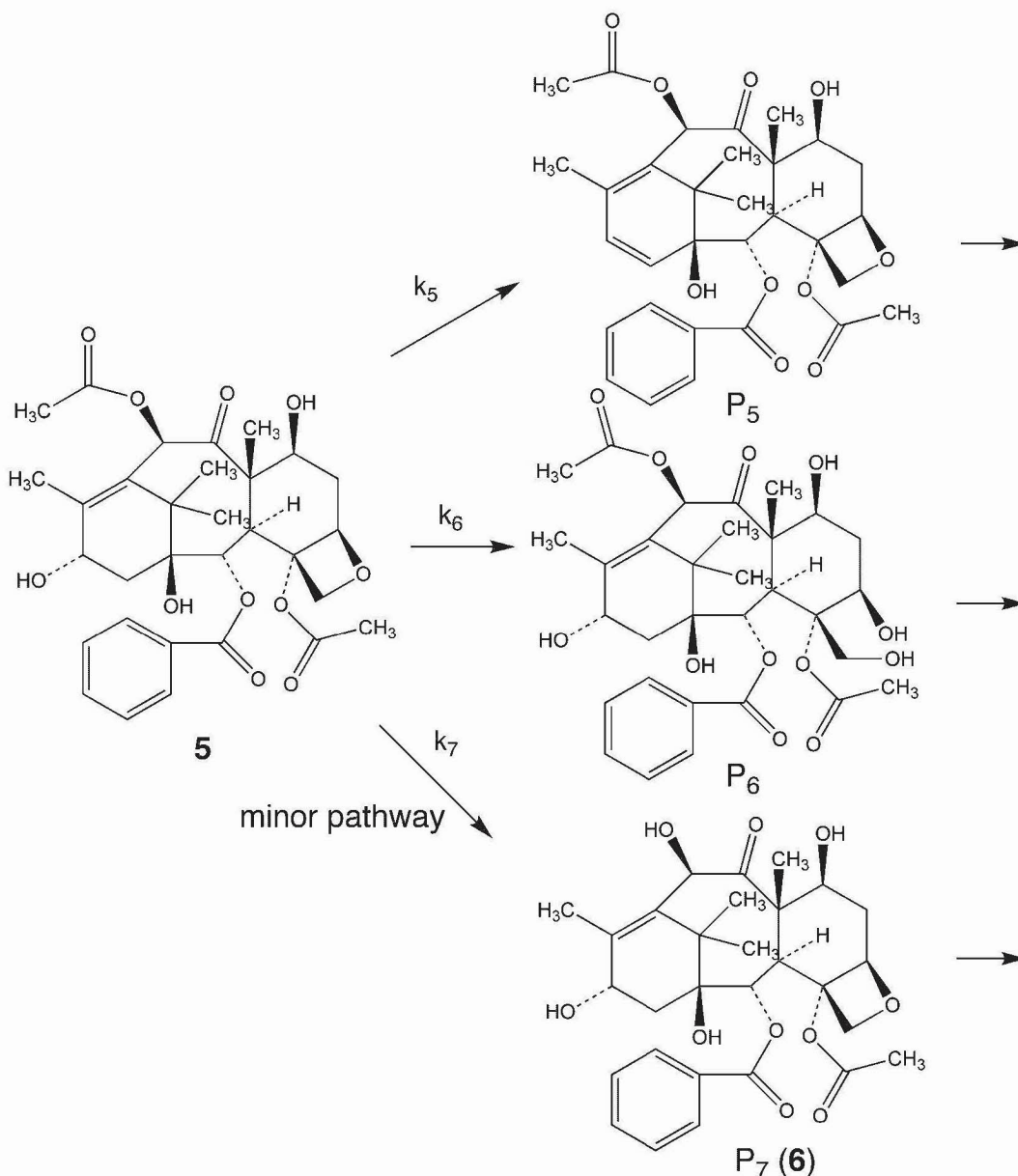

Figure 6. Partial pH-rate profiles for the degradation of 10-deacetylbaccatin III (●) and baccatin III (○) in the acidic pH range 1–3, $T = 25°C$. The solid line for 10-deacetylbaccatin III is the best fit to Eq. 4 while the line for baccatin III is the straight line joining the two points.

Scheme 2. Proposed degradation profile for baccatin III in the acidic pH range. The degradation of baccatin III at low pH undergoes three pathways in parallel: apparent dehydration, D-ring opening, and hydrolysis of acetyl groups followed by a series of secondary reactions. Formation of 10-deacetylbaccatin III constituted a minor initial pathway as little 10-deacetylbaccatin III was detected in the HPLC assay.

The overall loss of the starting compound follows pseudo-first-order kinetics

$$[D] = [D]_o \exp[-(k_5 + k_6 + k_7)t]$$
$$= [D]_o \exp[-k_{obs})t] \qquad (3)$$

where the overall rate constant k_{obs}, the sum of k_5, k_6, and k_7, can be readily obtained from the slope of the linear semi-logarithmic plot of degradation of the starting material.

In the acidic pH range, 1–3, acid-catalyzed degradation is dominant compared to water catalysis, and the total shape of log k_{obs} versus pH profiles can be expressed by the following equation:

$$k_{obs} = k_H a_H \qquad (4)$$

where k_H is an acid catalysis second-order rate constant and a_H is the activity of hydrogen ion that was approximated to concentration. In Figure 6, the solid line for 10-deacetylbaccatin III represent the theoretical line calculated from a linear fit to Eq. 4, while the data points are the experimental results. The slope of this line is close to unity. For baccatin III, the solid line is just the straight line joining the two experimental values with again the slope being very close to the expected unity value. The apparent second-order rate constants for the acid-catalyzed degradation, k_H, are 7.7×10^{-2} and $6.8 \times 10^{-2} M^{-1} h^{-1}$ at 25°C, for 10-deacetylbaccatin III (**6**) and baccatin III (**5**), respectively. No statistical analysis was performed due to the limited quantity of data.

Obviously, the apparent dehydration reaction seen with baccatin III and 10-deacetylbaccatin III cannot be a primary pathway for paclitaxel and taxotere degradation under acidic pH conditions without first hydrolysis of the side chain ester group. Once the side chain is cleaved, however, the apparent dehydration reaction is possible and such a reaction pathway would be seen in secondary degradation products. This points out one of the occasional dangers in using model compounds such as baccatin III and 10-deacetylbaccatin III in studying and predicting the degradation rate of more complex molecules such as paclitaxel and taxotere, that is, a pathway seen in the model compounds that are not possible in the more complex molecule.

Figure 7. Partial pH-rate profile for the degradation of N-benzoyl-3-phenylisoserine ethyl ester at acidic pH values at 70°C. The filled symbol (●) represents the experimental data determined at 70°C, while the open symbol (○) represents the experimental point determined at 50°C.

was $0.958 \pm 0.138 M^{-1} h^{-1}$. If one were to use the 70 and 50°C data points generated at pH 0.96 a value $1.7 \times 10^{-2} M^{-1} h^{-1}$ for k_H at 25°C can be estimated. This value is lower compared to a value of $6.8 \times 10^{-2} M^{-1} h^{-1}$ for baccatin III degradation under similar acidic pH conditions.

Degradation of N-Benzoyl-3-Phenylisoserine Ethyl Ester

N-benzoyl-3-phenylisoserine ethyl ester (**7**) is selected as a mimic of the side chain of paclitaxel. The loss of the compound was followed kinetically at pH 0.96, 1.94, and 2.68 at 70°C, as well as pH 0.96 at 50°C. The semi-logarithmic plots of the concentration of the starting compound versus time were linear and indicated that the overall degradation followed pseudo-first-order kinetics.

Figure 7 is the pH-rate profile for the degradation generated by plotting the rate constants determined at 70°C and the data point generated at 50°C. In the pH range, 1–3, acid-catalyzed degradation seems the dominant pathway at 70°C (and is expected to be similar at 25°C) and is adequately defined by Eq.4. The second-order rate constant for the acid-catalyzed degradation, k_H, at 70°C, determined from the experimental data,
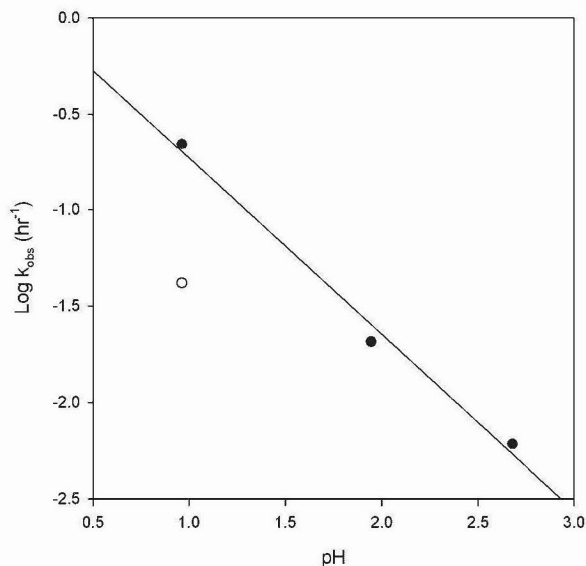
Degradation of Paclitaxel Under Acidic pH Conditions

Because of its low solubility ($<1\,\mu g/mL$) in water at 25°C, it is difficult to follow the stability of paclitaxel at this temperature. When the time course of paclitaxel at pH 2.03 was followed at 50 and 70°C, the increased solubility at these elevated temperatures was sufficient for quantitative analysis. Semi-logarithmic plots of the total loss of the starting compound versus time were linear and indicated that the overall degradation followed pseudo-first-order kinetics, unlike those seen under basic pH conditions where the reversible epimerization reaction leads to complex kinetics.[1,2] The experimental data yielded rate constant values of $3.62 \pm 0.19 \times 10^{-3}$ and $2.63 \pm 0.13 \times 10^{-2} h^{-1}$ at 50 and 70°C, respectively, at pH 2.03. Figure 8 illustrates the comparison of the degradation of 10-deacetylbaccatin III, N-benzoyl-3-phenylisoserine ethyl ester,
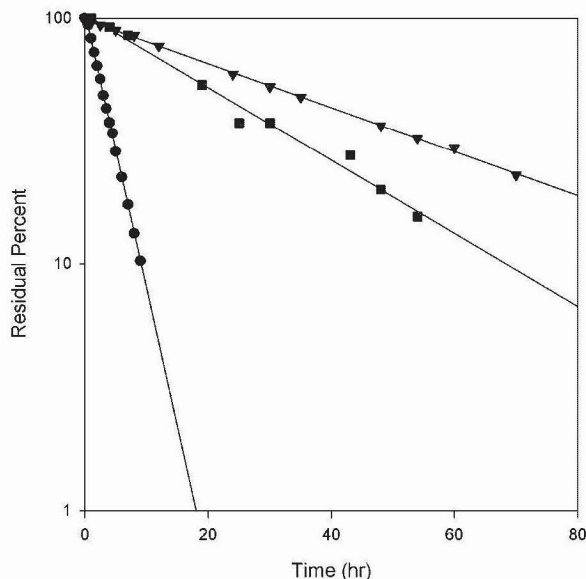
Figure 8. Semi-log plots showing the degradation of *N*-benzoyl-3-phenylisoserine ethyl ester (▼), paclitaxel (■), and 10-deacetylbaccatin III (●) in pH 2 aqueous solution maintained at 70°C

and paclitaxel at pH 2.03 and 70°C. If one were to correct for the fact that paclitaxel cannot undergo the dehydration reaction seen with 10-deacetylbaccatin and baccatin III, one would conclude that

oxetane ring cleavage is probably the predominant reaction under this condition.

The acid-catalyzed degradation of 10-deacetylbaccatin III and baccatin III were discussed earlier. Both compounds can undergo apparent dehydration and oxetane ring opening, and the overall reaction is fast. By contrast, the *N*-benzoyl-3-phenylisoserine ethyl ester goes through a slower acid-catalyzed ester hydrolysis. Paclitaxel shows a reaction rate in between, indicating multiple pathways that are faster than side chain ester hydrolysis alone under these conditions. These results suggest paclitaxel follows the reaction pathways described in Scheme 3. Degradation of paclitaxel under acidic pH undergoes hydrolysis of the side chain and D-ring opening simultaneously. Once the side chain is cleaved, the baccatin III being produced degrades through dehydration and hydrolytic D-ring opening and a small contribution from 10-deacetylation.

Dehydration of C13–OH and the hydrolysis opening of oxetane ring (D-ring) are the primary steps for the degradation of 10-deacetylbaccatin III and baccatin III at pH values <3, while no epimerization is observed under these conditions. These two reactions are acid-catalyzed, with comparable rate constants at the same pH value.
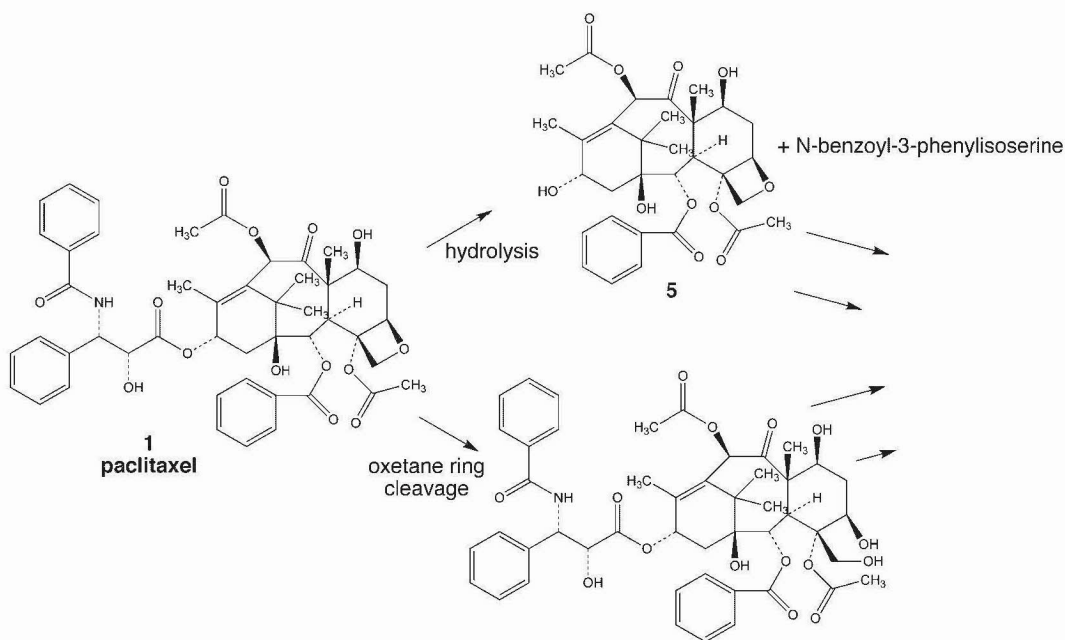
Scheme 3. Proposed degradation scheme for paclitaxel in the acidic pH range. Paclitaxel undergoes hydrolysis of the side chain and D-ring opening simultaneously. Once the side chain is cleaved, the baccatin III being produced degrades further through apparent dehydration and hydrolytic D-ring opening as indicated in Scheme 2.

Acid-catalyzed hydrolyses of ester bonds on C2, C4, and C10 positions are relatively slow under acidic pH conditions and make little to no major contribution to the overall degradation kinetics. Paclitaxel undergoes some hydrolysis of its side chain and oxetane ring opening simultaneously, without epimerization. After the side chain is cleaved, the initial product baccatin III degrades further through the pathways described above.

Overall pH Dependency of the Degradation of Paclitaxel-Rated Compounds

The epimerization of paclitaxel and several related taxanes have been examined in aqueous solution, and the rate constants of the interconversion of the R- and S-epimers determined in near neutral and basic pH range.[1,2]

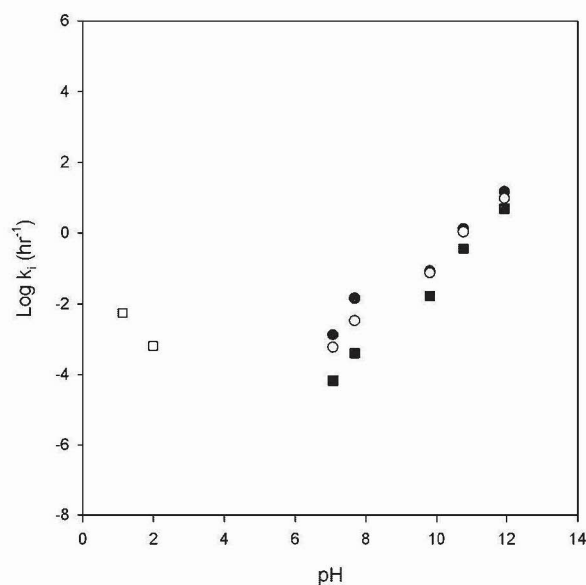Figure 9 shows the overall pH-rate profile for the epimerization and degradation of baccatin III from pH 1–12 at 25°C. The data for the neutral to basic pH range was those determined experimentally from earlier work.[1,2] A very similar plot is seen in the neutral to basic pH range for 10-deacetylbaccatin III (not shown) and from more limited data for paclitaxel.[1,2] The plots show a V-shape profile, with base-catalyzed reversible epimerization to C7–OH and hydrolytic degradation of ester groups at high pH. Compared to basic condition, the compounds are much more stable under acidic pH conditions, in which the primary degradation appears to be through dehydration at the C13–OH and hydrolytic opening of the oxetane ring. The maximal stability is obtained near pH 4–5.

Based on the similarity of the chemical structure, the measured kinetic data of smaller partial structures such as 10-deacetylbaccatin III and baccatin III allows one to make reasonable and reliable assumptions about the chemical stability of the more complex molecules. Paclitaxel, taxotere, and their other derivatives likely have similar V-shape profiles. The rates for epimerization of paclitaxel and taxotere are comparable to baccatin III and 10-deacetylbaccatin III, respectively, while paclitaxel showed faster hydrolysis under basic pH due to the more labile side-chain ester bond. Lacking the dehydration reaction seen with 10-deacetylbaccatin III, paclitaxel showed better chemical stability at pH values <3.

Figure 9. pH-rate profile for baccatin III degradation in aqueous solution, pH 1–12, at 25°C where k_i is the rate constant used to describe each of the pathways defined by each of the appropriate symbols. The open circle (○) and the filled circle (●) represent the pseudo-first-order rate constants (forward and reverse, respectively) for the base-catalyzed reversible epimerization, while the filled square (■) represents the total hydrolytic degradation of the ester groups (from Refs. 1,2). The open square (□) represents the total degradation (apparent dehydration, oxetane ring opening, and ester hydrolysis) under acidic condition generated in the present study.

ACKNOWLEDGMENTS

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