

# Crystal Structure of 2-Debenzoyl, 2-Acetoxy Paclitaxel (Taxol®): Conformation of the Paclitaxel Side-Chain

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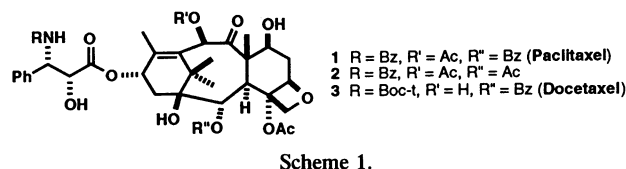
Crystals of the C2-acetate analog of paclitaxel, grown from a mixture of isopropyl alcohol and methanol, belong to the space group  $P2_1$  with  $a = 9.058(3)$ ,  $b = 18.306(5)$ ,  $c = 15.043(1)$  Å,  $\beta = 97.09(1)^\circ$ ,  $Z = 2$ ,  $V = 2475.1(9)$  Å<sup>3</sup>,  $D_{calc} = 1.269$  g cm<sup>-3</sup> and  $\mu = 0.75$  cm<sup>-1</sup>. The structure was determined by direct methods and refined to  $R(F) = 0.054$  and  $wR(F) = 0.057$  for 605 variables and 3496 observed reflections. The paclitaxel side chain possesses a conformation similar to that observed in the crystal structure of docetaxel (Taxotere®). A three dimensional network of hydrogen bonds is formed through solvent molecules and stabilizes the crystal lattice.

**KEY WORDS:** 2-debenzoyl, 2-acetoxy paclitaxel; docetaxel; paclitaxel side-chain; crystal structure; solid state conformation; intramolecular hydrogen bonding; intermolecular hydrogen bonding.

## INTRODUCTION

The highly oxygenated diterpenoid paclitaxel (1), a mitotic spindle poison (2), has been recently approved for the treatment of refractory ovarian and breast cancer by FDA. Paclitaxel has also shown very promising activity against lung cancer in the recent clinical evaluation (3). In striking contrast to other plant-derived antimitotics, such as podophyllotoxin and colchicine, paclitaxel promotes the assembly of microtubules and stabilizes them against depolymerization. Through such an unique mechanism, paclitaxel interferes with cell mitosis (2).

Paclitaxel has been the target of intensive synthetic (4,5) and structure-activity relationship (SAR) studies (6,7,8,9) due to its excellent biological profile and structural complexity. In order to assess the contribution of each functional group to binding at the active site in tubulin, we have prepared various deoxygenated paclitaxel analogs, including both C-7 and C-10 deoxy paclitaxel and C-7,10 dideoxy paclitaxel (10,11). Interestingly, all of these deoxy paclitaxel analogs retain substantial antitumor activity, thus indicating that functional groups at both C-7 and C-10 are not essential tubulin binding elements. However, several C-2 analogs we have prepared without an ester linkage all fail to promote



Scheme 1.

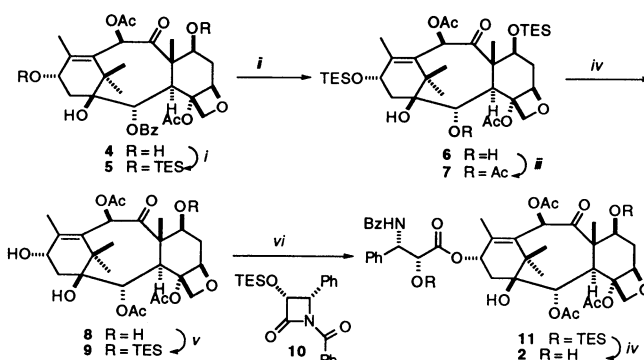
tubulin polymerization (12,13) thus confirming the importance of the C-2 benzoate for tubulin binding.

In conjunction with our SAR study, we were also interested in the possible correlation (if any) between the conformation of the paclitaxel-like compound and its *in vitro* activity (14,15). Recently, we have reported that certain C-ring modified paclitaxel analogs, such as bicyclic C-ring bearing compounds, not only possess a different B,C-ring conformation but also possess substantially reduced biological activity. Similarly, modifications at the C2 position such as C2-deoxy paclitaxel and C1,2-cyclic carbonate paclitaxel have thus far led only to bioinactive analogs (12,13). We then speculated that certain structural modifications might result in conformation changes, either at the side chain or at the baccatin core, which compromise biological activity. Along the same line, Guénard (14) has recently proposed the existence of hydrophobic interactions between C2-benzoate and the side chain aromatic groups. In order to further probe conformation changes induced by C2 modification and to have a better understanding, at the molecular level, of the role of C2-benzoate in receptor binding, we have prepared the 2-debenzoyl, 2-acetoxy paclitaxel analog and have determined its structure and solid state conformation using X-ray crystallography. In this paper, we wish to report the synthesis and the X-ray structure of 2-debenzoyl, 2-acetoxy paclitaxel 2. A detailed comparison between crystal structures of 2-debenzoyl, 2-acetoxy paclitaxel 2 and docetaxel 3 (16) will also be provided.

## MATERIALS AND METHODS

### Synthesis

Our synthesis of 2-debenzoyl, 2-acetoxy paclitaxel 2



**Scheme 2. Reagents and conditions:** (i) TESCl/imidazole/DMF/r.t., (86%); (ii) Red-A1/THF/0°C, (77%); (iii) DCC/DMAP/AcOH/Toluene/r.t. (92%); (iv) Pyridine/48%HF/CH<sub>3</sub>CN/5°C, for 7 to 8 (65%), for 11 to 2 (58%); (v) TESCl/imidazole/DMF/0°C, (87%); (vi) LHMDs/THF/0°C, then 10, (52%).

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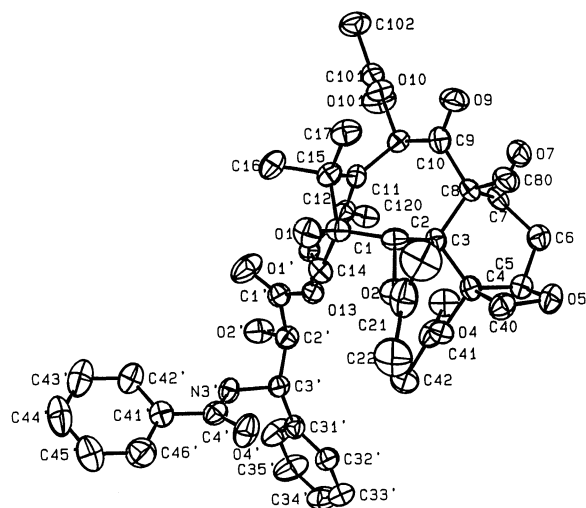


Fig. 1. ORTEP drawing of 2-debenzoyl, 2-acetoxy paclitaxel showing the atomic labeling scheme. The thermal ellipsoids were drawn at 50% probability level.

began with baccatin 4, which was in turn derived from paclitaxel 1 *via* a reductive side chain cleavage reaction (17). Prolonged treatment of baccatin 4 with chlorotriethylsilane and imidazole in DMF thus afforded 7,13-bisTES baccatin 5. Selective removal of the C2-benzoate moiety from 5 (Red-A1/THF), followed by C2-reacylation (DCC/DMAP/AcOH/Toluene) (13) thus afforded 7 in overall 71% yield. Desilylation (Pyridine/48%HF/CH<sub>3</sub>CN) and selective C7 resilylation (TESCl/imidazole/DMF) afforded 9 in overall yield of 57%. Final side chain attachment onto 9 *via* Holton's protocol (18,19) followed by desilylation of 11 thus afforded the C2-acetate of paclitaxel 2. All of these compounds (5, 6, 7, 8, 9, 11, and 2) were characterized by their <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra as well as HRMS.

2-debenzoyl, 2-acetoxy paclitaxel 2 was found to be inactive in a tubulin polymerization assay and a cytotoxicity assay against the HCT116 human colon cancer cell line. This again suggests that the C2 benzoate is indeed involved in intimate tubulin binding (13). However, the availability of crystals of the compound suitable for X-ray crystallographic studies made it possible to investigate the conformation of an inactive paclitaxel analog and the differences in the conformation when compared to docetaxel, an active paclitaxel analog.

## X-Ray Diffraction Experimental

Recrystallization of the synthesized 2-debenzoyl, 2-acetoxy paclitaxel from a mixture of isopropyl alcohol and methanol gave colorless plates. A fragment of approximate size 0.12 × 0.35 × 0.50 mm cut from a large crystal was mounted on a quartz fiber with epoxy adhesive and was used for preliminary examination and diffraction intensity data collection. Since crystals were unstable in air, the crystal used for experiments was coated with a thin layer of epoxy adhesive to prevent the crystal from quick decomposition. Diffraction experiments were carried out at room temperature on an Enraf-Nonius CAD4 diffractometer using graphite monochromated Cu K $\alpha$  radiation ( $\lambda = 1.5418$  Å). Cell constants were obtained from a least-squares fit to data for 25 well centered reflections in the range  $13.12^\circ \leq \theta \leq 22.04^\circ$ . Unit cell constants were  $a = 9.058(3)$ ,  $b = 18.306(5)$ ,  $c = 15.043(1)$  Å,  $\beta = 97.09(1)^\circ$  and  $V = 2475.1(9)$  Å<sup>3</sup>. From the systematic absence, the space group was determined to be  $P2_1$ . Intensity data were collected with  $-10 \leq h \leq 0$ ,  $0 \leq k \leq 20$ ,  $-16 \leq l \leq 16$  to  $\theta = 60^\circ$ . As a check of crystal stability, three reflections were remeasured every 2 hours during data collection and showed significant crystal decay indicated by an average loss, 23%, in intensities of standards. A total of 3801 unique reflections was measured using an  $\omega/2\theta$  scan mode. The Lorentz and polarization effects were corrected. The crystal decay was approximately linear and the reflection data was adjusted by using the slope of the least-squares line derived from a plot of intensity *versus* time. After data reduction, the unique data set contained 3496 observed reflections with  $I \geq 3\sigma(I)$ .

The structure was solved by direct methods using program *SHELXS-86* (20) and was refined by full-matrix least-squares techniques using computer software *MolEN* (21). The solution showed that the crystal is an isopropanol and methanol solvate of 2-debenzoyl, 2-acetoxy paclitaxel of a molecular formula  $C_{42}H_{49}NO_{14} \cdot 2C_3H_8O \cdot CH_4O$  in each asymmetric unit. The final refinements included 605 parameters, a scale factor and atomic coordinates and anisotropic temperature factors for non-hydrogen atoms. Although all hydrogen atoms were clearly shown in difference Fourier maps, only hydroxyl hydrogens, including those of solvent molecules, were located in difference Fourier maps and the positions of all the other hydrogen atoms were calculated from an idealized geometry with standard bond lengths and angles. All hydrogen atoms had isotropic temperature factors and were included in structure factor calculations with

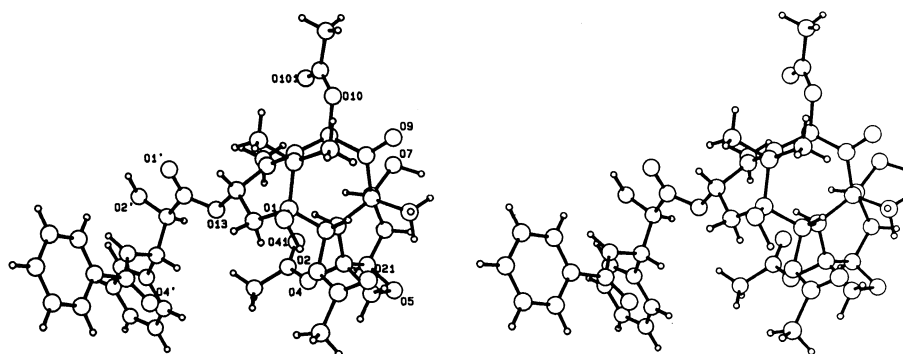


Fig. 2. Stereoscopic view of X-ray structure of 2-debenzoyl, 2-acetoxy paclitaxel.

fixed parameters. The refinement converged at  $R(F) = 0.054$  and  $wR(F) = 0.057$ ,  $S = 1.288$  for 3496 reflections with unit weights. The final difference Fourier map showed no recognizable residual features ( $-0.093 \geq \Delta\rho \geq 0.226 \text{ e}\text{\AA}^{-3}$ ). The atomic coordinates were deposited in the Cambridge Crystallographic Data Center.

## RESULTS AND DISCUSSION

An *ORTEP* representation of the molecular structure generated from the final coordinates (22) with the atom-numbering scheme is given in Figure 1. For a better view, Figure 2 is a stereo drawing of the molecule. The derived bond lengths and angles are given in Table I and Table II, respectively. A comparison to the crystal structure of docetaxel indicates that the conformation of tetracyclic ring systems, the core, in 2-debenzoyl, 2-acetoxy paclitaxel is essentially identical to docetaxel. Figure 3 is a stereoscopic view of 2-debenzoyl, 2-acetoxy paclitaxel and docetaxel (16) superimposed over the tetracyclic ring system obtained by using Chem3D. The deviations of the least-square fit of the two tetracyclic cores are small, in the range of 0.019 to 0.119 Å. Only slight differences in the conformations of substitute groups at C2, C4 and C10 are observed between the two molecules. In particular, although 2-debenzoyl, 2-acetoxy paclitaxel has an acetyl group at C2 instead of a benzoyl group in docetaxel, the conformation of the common part remains. The largest shift is seen at the carbonyl oxygen

Table I. Bond Lengths (Å)

| Bond      | Distance | Bond      | Distance |
|-----------|----------|-----------|----------|
| O1–C1     | 1.429(7) | C1–C2     | 1.533(8) |
| O1'–C1'   | 1.186(8) | C1–C14    | 1.544(8) |
| O2'–C2'   | 1.404(7) | C1–C15    | 1.595(9) |
| O2–C2     | 1.462(7) | C2–C3     | 1.561(8) |
| O2–C21    | 1.364(8) | C2'–C3'   | 1.543(9) |
| O4–C4     | 1.459(7) | C3–C4     | 1.537(8) |
| O4–C41    | 1.355(6) | C3–C8     | 1.600(8) |
| O4'–C4'   | 1.244(7) | C3'–C31'  | 1.536(8) |
| O5–C5     | 1.454(7) | C4–C5     | 1.526(8) |
| O5–C40    | 1.449(8) | C4–C40    | 1.516(8) |
| O7–C7     | 1.453(7) | C4'–C41'  | 1.480(9) |
| O9–C9     | 1.201(7) | C5–C6     | 1.542(9) |
| O10–C10   | 1.456(7) | C6–C7     | 1.513(9) |
| O10–C101  | 1.351(7) | C7–C8     | 1.559(8) |
| O13–C1'   | 1.315(6) | C8–C9     | 1.567(8) |
| O13–C13   | 1.466(7) | C8–C80    | 1.512(8) |
| O21–C21   | 1.196(8) | C9–C10    | 1.500(7) |
| O41–C41   | 1.191(8) | C10–C11   | 1.502(8) |
| O101–C101 | 1.196(8) | C11–C12   | 1.340(7) |
| N3'–C3'   | 1.451(7) | C11–C15   | 1.536(8) |
| N3'–C4'   | 1.356(8) | C12–C13   | 1.529(8) |
| C1'–C2'   | 1.546(8) | C12–C120  | 1.502(8) |
| C13–C14   | 1.521(8) | C42'–C43' | 1.38(1)  |
| C15–C16   | 1.552(9) | C43'–C44' | 1.38(1)  |
| C15–C17   | 1.520(8) | C44'–C45' | 1.36(1)  |
| C21–C22   | 1.49(1)  | C45'–C46' | 1.37(1)  |
| C31'–C32' | 1.371(9) | C101–C102 | 1.49(1)  |
| C31'–C36' | 1.374(8) | C32'–C33' | 1.39(1)  |
| C33'–C34' | 1.381(9) | C34'–C35' | 1.35(1)  |
| C35'–C36' | 1.39(1)  | C41–C42   | 1.502(9) |
| C41'–C42' | 1.361(9) | C41'–C46' | 1.40(1)  |

Table II. Bond Angles (°)

| Atoms          | Angle    | Atoms          | Angle    |
|----------------|----------|----------------|----------|
| C2–O2–C21      | 119.1(5) | C2–C3–C8       | 115.2(4) |
| C4–O4–C41      | 116.9(5) | C4–C3–C8       | 110.0(4) |
| C5–O5–C40      | 90.4(4)  | N3'–C3'–C2'    | 109.9(5) |
| C10–O10–C101   | 116.9(4) | N3'–C3'–C31'   | 112.0(5) |
| C1'–O13–C13    | 115.3(4) | C2'–C3'–C31'   | 111.9(5) |
| C3'–N3'–C4'    | 120.4(4) | O4–C4–C3       | 108.6(4) |
| O1'–C1'–O13    | 126.8(6) | O4–C4–C5       | 111.0(5) |
| O1'–C1'–C2'    | 121.8(5) | O4–C4–C40      | 107.5(5) |
| O13–C1'–C2     | 111.4(5) | C3–C4–C5       | 120.5(5) |
| O1–C1–C2       | 106.6(4) | C3–C4–C40      | 122.0(5) |
| O1–C1–C14      | 110.3(5) | C5–C4–C40      | 85.3(4)  |
| O1–C1–C15      | 105.6(4) | O4'–C4'–N3'    | 121.8(6) |
| C2–C1–C14      | 111.5(5) | O4'–C4'–C41'   | 122.2(5) |
| C2–C1–C15      | 112.1(5) | N3'–C4'–C41'   | 115.9(5) |
| C14–C1–C15     | 110.5(4) | O5–C5–C4       | 91.6(4)  |
| O2–C2–C1       | 103.2(4) | O5–C5–C6       | 112.6(5) |
| O2–C2–C3       | 108.1(4) | C4–C5–C6       | 119.9(5) |
| C1–C2–C3       | 119.5(4) | C5–C6–C7       | 112.6(5) |
| O2'–C2'–C1'    | 108.7(5) | O7–C7–C6       | 109.2(5) |
| O2'–C2'–C3'    | 113.2(5) | O7–C7–C8       | 111.1(5) |
| C1'–C2'–C3'    | 110.6(5) | C6–C7–C8       | 113.1(5) |
| C2–C3–C4       | 113.5(5) | C3–C8–C7       | 104.2(4) |
| C3–C8–C9       | 115.8(4) | C1–C15–C16     | 110.9(5) |
| C3–C8–C80      | 113.1(5) | C1–C15–C17     | 109.5(4) |
| C7–C8–C9       | 102.7(4) | C11–C15–C16    | 109.9(4) |
| C7–C8–C80      | 113.1(5) | C11–C15–C17    | 117.1(5) |
| C9–C8–C80      | 107.7(5) | C16–C15–C17    | 105.2(5) |
| O9–C9–C8       | 118.6(5) | O2–C21–O21     | 122.7(7) |
| O9–C9–C10      | 120.9(5) | O2–C21–C22     | 110.1(6) |
| C8–C9–C10      | 120.1(5) | O21–C21–C22    | 127.1(7) |
| O10–C10–C9     | 106.9(4) | C3'–C31'–C32'  | 119.1(5) |
| O10–C10–C11    | 110.4(4) | C3'–C31'–C36'  | 121.7(5) |
| C9–C10–C11     | 115.3(5) | C32'–C31'–C36' | 119.2(6) |
| C10–C11–C12    | 121.6(5) | C31'–C32'–C33' | 120.7(5) |
| C10–C11–C15    | 118.7(4) | C32'–C33'–C34' | 119.5(6) |
| C12–C11–C15    | 119.3(5) | C33'–C34'–C35' | 119.8(7) |
| C11–C12–C13    | 116.7(5) | C34'–C35'–C36' | 120.9(6) |
| C11–C12–C120   | 126.7(5) | C31'–C36'–C35' | 119.8(7) |
| C13–C12–C120   | 116.5(5) | O5–C40–C4      | 92.1(4)  |
| O13–C13–C12    | 110.4(4) | O4–C41–O41     | 124.2(6) |
| O13–C13–C14    | 106.4(5) | O4–C41–C42     | 110.3(6) |
| C12–C13–C14    | 111.2(4) | O41–C41–C42    | 125.5(5) |
| C1–C14–C13     | 115.6(5) | C4'–C41'–C42'  | 123.2(6) |
| C1–C15–C11     | 104.4(4) | C4'–C41'–C46'  | 118.5(6) |
| C42'–C41'–C46' | 118.1(6) | O101–C101–C102 | 125.3(6) |
| C41'–C42'–C43' | 121.8(7) | C42'–C43'–C44' | 119.1(7) |
| C43'–C44'–C45' | 119.6(8) | C44'–C45'–C46' | 121.4(8) |
| C41'–C46'–C45' | 120.0(7) | O10–C101–O101  | 123.9(6) |
| O10–C101–C102  | 110.8(5) |                |          |

of acetyl group at C2, which is only 0.567 Å away from the same atom of benzoyl group at C2 in docetaxel.

The overall conformation of the side-chain at C13 in 2-debenzoyl, 2-acetoxy paclitaxel has great similarity to that in docetaxel although its chemical structure at the end of the chain is different from docetaxel. The orientation of the side chain, relative to the core, is also similar. Table III lists selected torsional angles for the side-chain in docetaxel and 2-debenzoyl, 2-acetoxy paclitaxel. The differences in corresponding angles are small and no significant conformation changes have been indicated. The large differences seen in

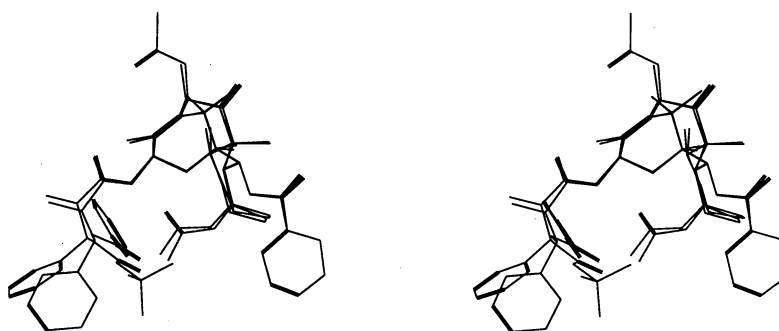


Fig. 3. Stereoscopic view of 2-debenzoyl, 2-acetoxy paclitaxel and docetaxel (16) superimposed over the tetracyclic ring system.

C2'-C3'-C31'-C32' and, of course, in C32'-C31'-C3'-N3' are expected and correspond to rotations of the phenyl group around C3'-C31' single bond. The very well determined structure of 2-debenzoyl, 2-acetoxy paclitaxel allows examination of possible intramolecular hydrogen bonding engaging with the 1' ester carbonyl, the 2' hydroxyl and the 3' NH within the side-chain, which are believed to structure the side chain in a specific orientation relative to the core in docetaxel (23). An examination of the geometry of these hydrogen bonds, [O1'  $\cdots$  H(O2') = 2.225 Å, O1'  $\cdots$  H-O2' = 102.8° and O2'  $\cdots$  H(N3') = 2.611 Å, O2'  $\cdots$  H-N3' = 96.7°], suggests that they are weak interactions. They are the minor components of three center hydrogen bonds involving the solvent molecules which will be further discussed later. These interactions should be regarded as an intrinsic component of the molecular structure. They occur because other intra- and intermolecular forces confer a favorable conformation to which these weak interactions add a small energetic advantage (24).

In the crystal of 2-debenzoyl, 2-acetoxy paclitaxel, each asymmetric unit contains one methanol and two iso-

propyl alcohol molecules together with the molecule of 2-debenzoyl, 2-acetoxy paclitaxel. These solvent molecules are ordered and were well defined during structure refinements. Our results show that they have played an essential role in crystallization of the compound and stabilization of the crystal lattice. All three solvent molecules form hydrogen bonds with each other or with 2-debenzoyl, 2-acetoxy paclitaxel molecules. Among the six observed intermolecular hydrogen bonds (Table IV), five involve solvent molecules. As shown in Figure 4, interactions between 2-debenzoyl, 2-acetoxy paclitaxel molecules are realized *via* solvent-mediated hydrogen bonding. For instance, O5 interacts with O2' *via* Me and Iso1 and with N3' *via* Me, Iso1 and Iso2.

It is of particular interest that the pattern of hydrogen bonding in crystal structure of 2-debenzoyl, 2-acetoxy paclitaxel shows great similarity to that of docetaxel. In both structures, O1' interacts with a solvent molecule, a methanol in docetaxel but an isopropyl alcohol (Oiso1  $\cdots$  O2' = 2.983 Å) and has a short contact with the other isopropyl alcohol (Oiso2  $\cdots$  O2' = 3.308 Å) rather than a hydrogen bond with the methanol and a short contact with the water in docetaxel. In 2-debenzoyl, 2-acetoxy paclitaxel, the O4' atom makes a hydrogen bond with O7 (O7  $\cdots$  O4' = 2.836 Å), instead of O5 in docetaxel, of the core as an acceptor. There is a hydrogen bond (Oiso2  $\cdots$  N3' = 2.932 Å) formed between N3' and the second isopropyl alcohol molecule. However, the same atom in docetaxel does not form any intermolecular hydrogen bonding. The absence of this hydrogen bond might explain to

Table III. Torsional Angles (°) of the Side-Chain for 2-Debenzoyl, 2-Acetoxy Paclitaxel and Docetaxel

|                               | 2-debenzoyl,<br>2-acetoxy<br>Paclitaxel | Docetaxel |
|-------------------------------|-----------------------------------------|-----------|
| C13-O13-C1'-O1'               | -0.7                                    | -6.6      |
| C13-O13-C1'-C2'               | 178.8                                   | 168.0     |
| O13-C1'-C2'-O2'               | -166.0                                  | -176.7    |
| O13-C1'-C2'-C3'               | 69.1                                    | 60.2      |
| C1'-C2'-C3'-C31'              | -169.8                                  | -179.4    |
| C1'-C2'-C3'-N3'               | 65.1                                    | 56.4      |
| H2'-C2'-C3'-H3'               | 67.0                                    | 57.3      |
| O1'-C1'-C2'-O2'               | 13.6                                    | -2.2      |
| O1'-C1'-C2'-C3'               | -111.3                                  | -125.3    |
| C2'-C3'-N3'-C4'               | -141.7                                  | -141.3    |
| C2'-C3'-C31'-C32'             | 123.1                                   | 83.6      |
| O2'-C2'-C3'-N3'               | -57.2                                   | -64.7     |
| O2'-C2'-C3'-C31'              | 67.9                                    | 59.5      |
| C3'-N3'-C4'-O4'               | 0.5                                     | 12.8      |
| C3'-N3'-C4'-C41' <sup>a</sup> | 177.5                                   | -172.4    |
| C31'-C3'-N3'-C4'              | 93.4                                    | 97.3      |
| C32'-C31'-C3'-N3'             | -113.1                                  | -154.6    |
| H3'-C3'-N3'-H'(N3')           | 159.5                                   | 159.4     |

<sup>a</sup> In docetaxel, this torsional angle is C3'-N3'-C4'-O5'.

Table IV. Distances (Å) and Angles (°) of Hydrogen Bonds

|                                     | D $\cdots$ A | H $\cdots$ A | D-H $\cdots$ A |
|-------------------------------------|--------------|--------------|----------------|
| O1'-H $\cdots$ O2' <sup>i</sup>     | 2.656        | 2.225        | 102.8          |
| N3'-H $\cdots$ O2' <sup>i</sup>     | 2.888        | 2.661        | 96.7           |
| Oiso1 $\cdots$ H-Oiso2 <sup>i</sup> | 2.834        | 2.245        | 118.2          |
| Oiso1 $\cdots$ H-O2' <sup>i</sup>   | 2.983        | 2.023        | 152.4          |
| Oiso2 $\cdots$ H-N3' <sup>i</sup>   | 2.932        | 2.064        | 149.6          |
| OMe $\cdots$ H-Oiso1 <sup>ii</sup>  | 2.894        | 2.079        | 155.3          |
| OMe-H $\cdots$ O5 <sup>iii</sup>    | 2.832        | 1.667        | 168.5          |
| O7-H $\cdots$ O4' <sup>iv</sup>     | 2.836        | 1.767        | 179.4          |

Symmetry codes:

- (i)  $x, y, z$
- (ii)  $-1 + x, y, z$
- (iii)  $-1 + x, y, -1 + z$
- (iv)  $2 - x, -0.5 + y, 1 - z$

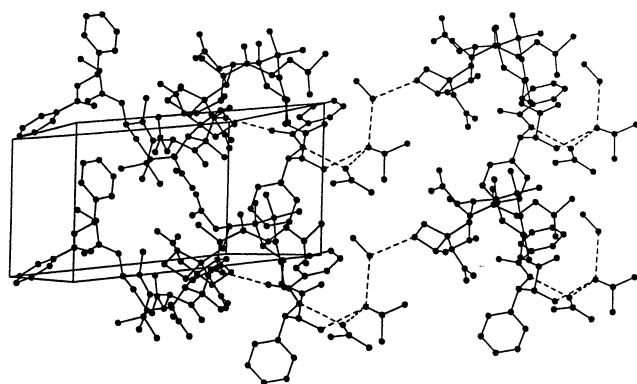


Fig. 4. Molecular packing in the crystal structure of 2-debenzoyl, 2-acetoxy paclitaxel showing hydrogen bonding scheme.

some degree the relatively larger deviation on the conformation of 2-debenzoyl, 2-acetoxy paclitaxel from docetaxel at the end of the side chain. There are two three center hydrogen bonds involving intra- and intermolecular interactions. They are also bifurcated. One is formed between O2', O1' and Oiso1 with O2' as the proton donor. The second one is between N3', O2' and Oiso2 with N3' as the proton donor.

So far, most of important features of paclitaxel, such as its binding to receptors and its bound-state conformation, have been proposed based on the crystal structure of docetaxel, the only crystal structure reported among paclitaxel analogs. The influence of solvents on the conformation of the side chain has already been shown and emphasized in solution (23); however, the contribution of solvation to the structure and conformation of docetaxel in the crystal is more or less underestimated. According to our results, the great similarity of the conformation of 2-debenzoyl, 2-acetoxy paclitaxel to docetaxel seems mainly due to the similarity of the arrangement of solvent molecules around the side chain. The hydrogen bonds between solvent molecules and the side chain appear to be dominant interactions and give rise to the specific orientation of the side chain at C-13. In other word, the conformation of 2-debenzoyl, 2-acetoxy paclitaxel observed in crystals might arise primarily as the result of solvation and molecular packing in the lattice.

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