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An Unprecedented Side Chain Conformation of Paclitaxel (Taxol®): Crystal Structure of 7-Mesylpaclitaxel

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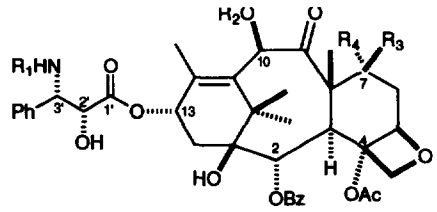
Abstract: The single-crystal X-ray diffraction study of 7-Mesylpaclitaxel, a bioactive paclitaxel analog, has revealed a novel paclitaxel side chain conformation which differs from any other known conformations, including the hydrophobic collapse and the apolar conformation, as found in solid state and in solution. This conformation appears to be induced by specific interactions of the side chain with solvent. Copyright © 1996 Elsevier Science Ltd

The structural complexity, novel mechanism of action, and effectiveness of paclitaxel (**1**) for the treatment of advanced ovarian and breast cancer have generated enormous interest in both chemical and biological research.[2-10] An important aspect of the paclitaxel research is the possible correlation of conformation and activity. Combined NMR and molecular modeling studies of paclitaxel and docetaxel (Taxotere®) (**2**) in solutions have showed two predominant conformations.[11] One occurs in non-polar organic solvents and the other in polar solutions, called 'apolar' and 'hydrophobic collapse' conformation, respectively. They differ in which part of the side-chain, N3'-benzoyl or 3'-phenyl group, forms hydrophobic interactions with the 2-benzoyl and 4-acetyl groups. Experiments have demonstrated that water induces a transition from the apolar to the hydrophobic collapse conformation.[12] Recently, the hydrophobic collapse conformation was found to be the only conformation in a 2D-NMR study on a water-soluble and bioactive derivative of paclitaxel in water.[13] Interestingly, the two conformations have also been observed in crystal structures of paclitaxel and two active analogs, docetaxel and 10-deacetyl-7-epitaxol (**4**).[14-16] Of particular significance, the crystal structure of 10-deacetyl-7-epitaxol provided the first evidence that the "hydrophobic collapse" conformation of paclitaxel could exist in a non-aqueous environment.[16]

As our studies on the paclitaxel conformation continued, a new side chain conformation, which is distinguished from the two well known conformations, has been recently discovered within the crystal of a bioactive analog, 7-mesylpaclitaxel (**3**). Including one of the two conformers found in the crystal of paclitaxel that differs from the hydrophobic collapse model,[15] a total of four solid state conformations has been observed in single crystals of bioactive molecules. In this paper, we report the crystal structure of 7-mesylpaclitaxel[17] and provide a detailed comparison of this conformation to the others.



1 R_1=Bz, R_2=Ac, R_3=OH, R_4=H **Paclitaxel**
2 R_1=Boc, R_2=H, R_3=OH, R_4=H **Docetaxel**
3 R_1=Bz, R_2=Ac, R_3=OMs, R_4=H **7-Mesylpaclitaxel**
4 R_1=Bz, R_2=H, R_3=H, R_4=OH **10-Deacetyl-7-epitaxol**

Consistent with previous observations, the core tetracyclic ring system has a rigid structure. The conformation of the core in 7-mesylpaclitaxel (**3**) is essentially identical to this portion of crystal structures of **1**, **2** and **4**. As shown in Figure 1, slight differences in conformation occur within the substituent group at C2, correspondent to rotations of the phenyl ring as one expects. No significant changes in the conformation of the core are observed as a consequence of the change from an *axial* (**1**, **2** and **3**) to an *equatorial* (**4**) O7 group. The largest shift at the benzoyl group at C2 is only 0.88, 0.40 and 0.54 Å away from the same atom in **1**, **2** and **4**, respectively.

Table 1. Selected Torsion Angles (°) for the Side-chain of Conformer A of 10-Deacetyl-7-epitaxol, 7-Mesylpaclitaxel, Docetaxel and Conformer A of Paclitaxel

	10-deacetyl-7-epitaxol	7-mesylpaclitaxel	Docetaxel	Paclitaxel
C13-O13-C1'-O1'	11.8	12.3	-6.6	2
C13-O13-C1'-C2'	-166.6	-166.4	168.0	180
O13-C1'-C2'-O2'	-134.0	-159.5	-176.7	-84
O13-C1'-C2'-C3'	108.3	77.0	60.2	159
O1'-C1'-C2'-O2'	47.5	21.8	-2.2	93
O1'-C1'-C2'-C3'	-70.0	-101.6	-125.3	-24
C1'-C2'-C3'-C31'	-66.4	-174.4	-179.4	-64
C1'-C2'-C3'-N3'	168.8	61.3	56.4	176
H2'-C2'-C3'-H3'	173.2	64.2	57.3	-174
O2'-C2'-C3'-N3'	51.7	-60.2	-64.7	60
O2'-C2'-C3'-C31'	176.4	64.2	59.5	180
C2'-C3'- N3'-C4'	-143.0	-98.6	-141.3	-118
H3'-C3'-N3'-H'(N3')	153.6	-163.0	159.4	158
C31'-C3'-N3'-C4'	92.4	134.6	97.3	120
C3'-N3'-C4'-O4'	-3.0	1.4	12.8	1
C3'-N3'-C4'-C41'[a]	177.0	179.7	-172.4	-178
N3'-C3'-C31'-C32'	-130.5	-117.6	-154.6	-73
C2'-C3'-C31'-C32'	106.8	118.0	83.6	-166

[a] In docetaxel, the corresponding torsion angle is C3'-N3'-C4'-O5'.

The side-chain at C13 is flexible and adopts a different conformation. Table 1 lists the torsion angles of the C-13 side chain for each conformation that has been observed so far. 7-Mesylpaclitaxel assumes a similar geometry about the O13-C1' bond as 10-deacetyl-7-epitaxol and about C2'-C3' as docetaxel. The most dramatic differences between 7-mesylpaclitaxel and the others occurs in the geometry about two bonds, C1'-

C2' and C3'-N3'. The torsion angles about C1'-C2' are in between the values observed with 10-deacetyl-7-epitaxol and docetaxel, i.e., the hydrophobic and the apolar conformation. On the other hand, the values about C3'-N3' bond are different from either of the two conformations, which happen to be essentially the same. While all the four conformations have a similar geometry about the N3'-C4' bond, the difference about the C3'-C31' bond is small and reflects free rotation of the 3'-phenyl ring around the C-C single bond. In the crystal, 7-mesylpaclitaxel exists as a 1:1 complex with ethyl acetate, the solvent from which the crystal was grown. The molecule has a kinked C-13 side chain, which is apparently caused by interactions with the solvent. The carbonyl oxygen of the solvent molecule forms three-center hydrogen bonds, as the acceptor, with O2' (O2'-H···O = 121.2°, O···O = 3.118 Å, H···O = 2.470 Å) and N3' (N3'-H···O = 121.2°, N···O = 2.965 Å, H···O = 2.119 Å) and thus cross-links the two functional groups. As a result, the closest distance between the side chain and the taxane core is found to be O4'···C14, 3.320 Å. The 3'-phenyl is closer to the 4-acetyl group (4.147 Å for the shortest C···C distance) than to the 2-benzoyl group (> 6.6 Å) while the N3'-benzoyl is pointing out and far away from the core (>8.4 Å between the two phenyl groups).

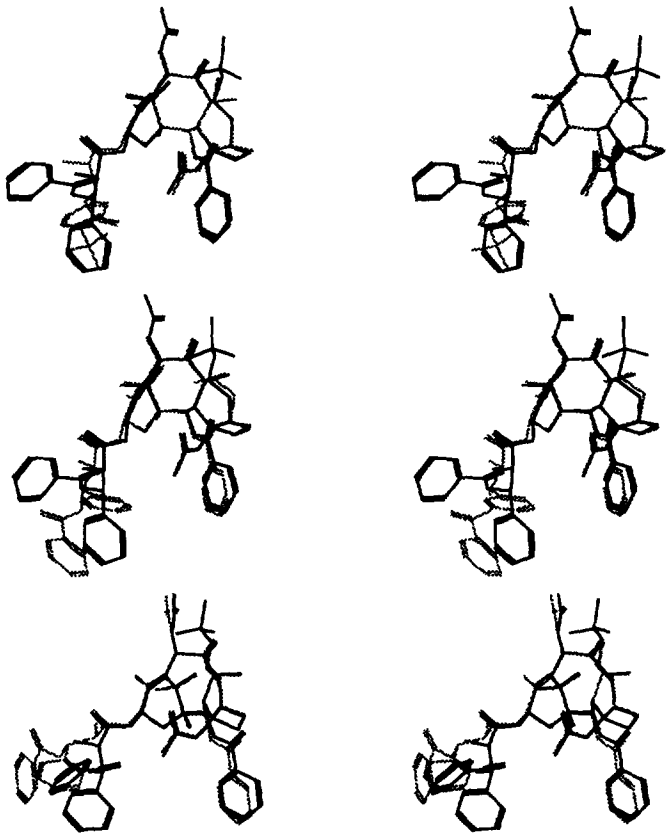


Figure 1. Stereoscopic view of molecules of **3** (black) superimposed with **2** (top), conformer A of **4** (middle) and conformer A of **1** (bottom) over the tetracyclic ring system.

Solvation is a common feature for crystals of **1**, **2**, **3** and **4**. In the crystal of 7-mesylpaclitaxel, solvent molecules are found in layers that are of a zig-zag shape along the crystallographic *b*-axis and are infinitely extended in the direction of the *a*-axis. The northern portion of the side chain and the A-ring of the core are exposed to the solvent. The other common observation in these crystal structures is that the side chain is always involved in solvent interactions. In particular, the 2'-hydroxyl and the 4'-carbonyl groups form hydrogen bonds with either solvent or neighboring molecules. In the case of 7-mesylpaclitaxel, as mentioned earlier, the 4'-carbonyl oxygen is in short contact with C14 within the same molecule (3.320 Å), suggesting a weak intramolecular C-H···O hydrogen bond. Hydrogen bonding is also observed in the crystal of **3** between the 1-OH and the carbonyl oxygen of the 4-acetyl group (O-H···O = 142.2°, O···O = 2.943 Å, H···O = 2.165 Å), which connects the molecules in adjacent unit cells to form infinite long chains along the *b*-axis.

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17. X-ray Crystallography: Final atomic coordinates have been deposited in the Cambridge Crystallographic Database. Colorless crystals grown from ethyl acetate are Monoclinic, space group *P21*, a = 8.5953(7), b = 12.257(1), c = 24.388(2) Å, β = 90.29(1)° and V = 2569.3(4) Å^3, d_x = 1.250 g cm^{-3}. Full-matrix least-squares refinements gave $R(F)$ = 0.042, $wR(F)$ = 0.043 for 649 parameters and 4473 reflections with $I \geq 3\sigma(I)$.

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