Making Easier the β-Lactam Fragmentation via Metal-Assistance: Mechanistic Insight


Abstract: The OsH$_6$(P$_3$Pr$_3$)$_2$-mediated fragmentation of a 4-(2-pyridyl)-2-azetidinone has been achieved and its mechanism has been investigated by DFT calculations. The addition of the C4-H bond of the substrate to OsH$_6$(P$_3$Pr$_3$)$_2$ allows the active participation of an osmium lone pair in the B-type β-lactam fragmentation process. This new mechanism makes the N1-C4/C2-C3 fragmentation of the lactamic core thermally accessible through a stepwise process.

The β-lactam ring is part of the core structure of several antibiotic families. The enzymatic hydrolysis of the N1-C2 bond results in their irreversible inactivation as a consequence of the acylation of the active sites. Additionally, the N1-C2 rupture has been used in the preparation of β-amino acids. Cleavages of the less polar N1-C4, C4-C3, and C3-C2 bonds are also known and have important applications in organic synthesis as part of the so-called β-lactam synthon method.

The concerted or sequential breakage of parallel N-C and C-C bonds is less usual. The rupture of N1-C2 and C3-C4 (A in Scheme 1) is the inverse process to the Staudinger reaction and gives rise to a ketene and an imine, whereas the breakage of N1-C2 and C3-C4 (B in Scheme 1) leads to an olefin and an isocyanate. Both types of fragmentation have been observed by EI-Mass spectrometry. The A-type fragmentation occurs under irradiation. However, although the B-type fragmentation of N-(arylidenamino)- and N-(alkylidenamino)-2-azetidinones occurs at room temperature, under ozonolysis, the thermal B-type fragmentation of the β-lactam ring is generally a difficult reaction, which should entail a high energy barrier. Previous calculations have reported activation energies of more than 40 kcal mol$^{-1}$ for such process. It appears to be a concerted asynchronous [2+2] cycloreversion, since it takes place with complete retention of the stereochemistry. Metal-promoted degradation of β-lactams remains unknown. Here, we report a much easier osmium-mediated fragmentation which shows a different reaction mechanism rather than the concerted [2+2] cycloreversion.

The hexahydride complex OsH$_6$(P$_3$Pr$_3$)$_2$ (1) has proven to activate σ-bonds of a wide range of organic molecules, including the N-H bond of 4-(2-pyridyl)-2-azetidinones. The replacement of the hydrogen atom of this group by aryl protects the nitrogen atom against the metal center, which is directed towards the C3-H bond of the four-membered ring. The addition of this bond to the osmium atom activates the rupture of the N1-C4 and C2-C3 bonds. Thus, the treatment of toluene solutions of 1 with 1.0 equiv of cis-1-(4-methoxyphenyl)-3-methoxy-4-(pyridin-2-yl)azetidin-2-one (I), for 6 h, under reflux affords the trihydride-osmium(IV) derivative OsH$_3$[κ$^2$-C,N-[py-2-CH=COMe]{(P$_3$Pr$_3$)$_2$}] (2) which was isolated as a yellow solid in 60% yield (eq 1).

Complex 2 was characterized by X-ray diffraction analysis. The structure (Figure 1) proves the N1-C4 and C2-C3 bond cleavage of the β-lactam ring. The geometry around the osmium atom can be rationalized as a distorted pentagonal bipyramid with the phosphine ligands occupying axial positions (P(1)-Os-P(1A) = 167.32(5)º). The metal coordination sphere is completed by the chelated group, which acts with a N(1)-Os-C(7) bite angle of 75.98(18)º and the hydrides. The metallacycle is planar and shows a significant electron delocalization which is translated into bond lengths between those expected for single and double bonds. This is clearly evident in the C(7)-C(6) and C(6)-C(5) distances of 1.401(7) and 1.434(7) Å, which are similar. As expected for three inequivalent hydride ligands, the $^1$H NMR spectrum, in toluene-$d_6$, at 203 K shows three hydride signals at -6.16, -10.82, and -11.55 ppm. In the $^{13}$C($^1$H) NMR spectrum, the most noticeable feature is the resonance...
due to C(7), which appears at 236.1 ppm as a triplet (J_C-H = 6.4 Hz). This unusually low field, the planarity of the bicycle, and the electron delocalization point out that complex 2 is better described as a 3-osmaindolizine species, resulting from the formal replacement of the CH-group at 3-position of the five-membered ring of a 10-π-electron indolizine derivative by the OsH4(PiPr3)2 metal fragment. In agreement with equivalent phosphines, the 31P{1H} NMR spectrum contains at 22.5 ppm a singlet.

Figure 1. Molecular diagram of the complex 2 (50% probability ellipsoids).

One could at first glance think that the reaction shown in eq 1 is a consequence of a thermal B-type fragmentation of the β-lactam, which occurs without the participation of 1. Thus, the subsequent pyridyl-assisted C(sp2)-H bond activation of the olefin should afford 2. However, this possibility must be totally rejected, since the treatment of toluene solutions of olefin should afford the transition state takes place via a concerted asynchronous mechanism through the activation in toluene, under reflux, to afford the OsH 4(PiPr3)2 undergoes thermal activation in toluene, under reflux, for 6 h leads to OsH4(cis-C,N- [py-2-CH=CH])[PP3].14 (3) and methanol, instead of 2. The reaction involves the C-OMe bond activation of the substrate (eq 2).

In an effort to gain insight into the mechanistic details of the unprecedented osmium-mediated fragmentation, we carried out DFT calculations (B3LYP-D3, see Supporting Information). The changes in Gibbs energy (ΔG) were computed in toluene, at 384 K, and P = 1 atm. Initially, for comparative reasons, we have computed the fragmentation of 1 by cleavage of its N1-C4 and C2-C3 bonds without the participation of the osmium complex. In agreement with previous studies of this process,7,15 the reaction takes place via a concerted asynchronous mechanism through the transition state TS-0, in which the rupture of the N1-C4 bond (2.46 Å) is much more advanced than that of the C2-C3 bond (1.62 Å) (Figure 2). As expected, this process demands a high activation barrier of 41.8 kcal mol−1, consistent with a thermally inaccessible reaction. Then, we have theoretically studied the reaction in presence of the osmium complex. Figure 3 shows the Gibbs energy profile for the formation of the complex 2, whereas Scheme 2 summarizes the steps of the process.

Figure 2. Transition state structures for the fragmentation of 1 without (TS-0) and with the osmium complex (TS-C and TS-D), with their relative Gibbs energies in toluene. In parenthesis, geometrical parameters in I (TS-0) and intermediates C and D (TS-C and TS-D).

The saturated hexahydride complex 1 undergoes thermal activation in toluene, under reflux, to afford the OsH4(PiPr3)2 species, which has been previously trapped with pyridines and characterized as the corresponding tetrahydride derivatives OsH4(pyridine-R)(PiPr3).16 It is reasonable to think that in the presence of I, coordination of the pyridine nitrogen to OsH4(PiPr3)2 occurs to form species A. Its formation, which is exergonic by 1.8 kcal mol−1, is the first step for the chelate-assisted activation of the lactamic C4-H bond. Since A is saturated, the C4-H activation requires the previous dissociation of a hydrogen molecule to give the dihydride B, which cancels the unsaturated character of the metal center by means of a strong agostic interaction between the C4-H bond (C-H = 1.100 Å) and the metal center (Os-C = 3.281 Å, Os-H = 2.700 Å). The oxidative addition of the coordinated C-H bond to the osmium atom leads to C, with a barrier of 22.7 kcal mol−1 (TS-B). The trihydride C exists as two conformers (denoted as C1 and C2) associated to the rotation of the methoxy substituent of the four-membered ring.

The oxidative addition of the C4-H bond weakens the N1-C4 bond, which is elongated by 0.053 Å in C1 or 0.043 Å in C2 compared to B. As a result, its rupture takes place with a low barrier of 8.3 kcal mol−1 from C1 (TS-C, Figure 2), to give the alkylidene D (Os-C = 1.999 Å). This intermediate exists as five rotamers, which can be interconverted with a maximum energy of 9.3 kcal mol−1 (see supporting information). The lactam ring opening produces the elongation of the C2-C3 bond from 1.531 Å in C1 to 1.614 Å in D2. The stretching of the bond facilitates its cleavage, which occurs with activation energy of only 5.6 kcal mol−1 (TS-D, Figure 2).
Figure 3. Gibbs energy profile, in toluene, for the β-lactam fragmentation leading to 2.

The rupture of the C2-C3 bond of D5 leads to the alkenyl derivative E (Os-C4 = 2.174 Å, C4-C3 = 1.342 Å), which is 24.8 kcal mol⁻¹ more stable than its precursor. Intermediate E is an isomer of 2, containing a four-membered heterometallacycle. The expansion of the ring to afford 2 involves the regeneration of the C4-H bond by means of the reductive elimination of olefin, the rotation of the latter around the pyridine-olefin bond, and the oxidative addition of the C3-H bond. The reductive elimination step entails a quite high barrier of 32.0 kcal mol⁻¹ (TS-E). This value is consistent with the stability of the OsH₃(C-L)(PPr₃)₂ species of osmium(IV), which is consequence of the reductor character of osmium and the marked tendency of this element to form saturated species. The reductive elimination leads to F, which exists as two conformers associated to the rotation of the methoxy substituent of the generated olefin. The rotation of the olefin around the pyridine-olefin bond takes place in several stages (see Supporting Information), with a maximum activation energy of 8.1 kcal mol⁻¹ above F₁, and places the C3-H bond in front of the osmium atom. The intramolecular oxidative addition in G to give 2 is almost a barrierless reaction (TS-G).

The retro-[2+2]-cycloaddition nature of the reaction without metal is apparent from the movement of the orbital centroids. Two electron pairs are involved in the reaction (Scheme 3). The electron pair describing the N1-C4 bond is moving toward the N1-C2 region, to form the N=C double bond of the isocyanate. At the same time, the C2-C3 electron pair is moving toward the C3-C4 region to form the alkene double bond. As N1-C4 and C2-C3 are σ bonds, the displacement of their related electron pairs implies the cleavage of the ring.
The metal promoted C4-H activation step (TS-B) anchors the β-lactam ring to the osmium, allowing in this way that an osmium lone pair can participate in the process (Scheme 4). The displacements of the orbital centroids underscore the key role played for this osmium lone pair in the β-lactam fragmentation. In the first bond-breaking step, where the N1-C4 bond is cleaved, this lone pair is moving to form a double bond with C4, yielding a zwitterionic alkylidene intermediate.19 The concomitant formation of this lone pair is moving to form a double bond with C4, yielding a zwitterionic alkylidene intermediate.19 The concomitant formation of this lone pair is moving to form a double bond with C4, yielding a zwitterionic alkylidene intermediate.19 The concomitant formation of this lone pair is moving to form a double bond with C4, yielding a zwitterionic alkylidene intermediate.19 The concomitant formation of this lone pair is moving to form a double bond with C4, yielding a zwitterionic alkylidene intermediate.19 The concomitant formation of this lone pair is moving to form a double bond with C4, yielding a zwitterionic alkylidene intermediate.19 The concomitant formation of this lone pair is moving to form a double bond with C4, yielding a zwitterionic alkylidene intermediate.19

In conclusion the addition of the C4-H bond of the four-membered ring of 4-(2-pyridyl)-2-azetidinones to the OsH2(PiPr3)2 metal fragment allows the active participation of an osmium lone pair in the B-type β-lactam fragmentation process. This new mechanism makes the N1-C4/C2-C3 bond breaking steps.

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Keywords: azetidinone • β-lactam fragmentation • osmium • hexahydride • DFT calculations

References


[12] CCDC 1415339 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.


An NBO analysis of TS-C displays a strong interaction between an osmium $d_{π}$ orbital, described as Os lone pair, and the antibonding (N1-C4)$^{*}$ natural bond orbital (see Supporting Information).
The complex OsH$_6$(PPr$_3$)$_2$ breaks the lactamic core of the 4-(2-pyridyl)-2-azetidinones previous addition of the C4-H bond to the metal center by means of a new mechanism entailing the active participation of an osmium lone pair.

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