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A Theoretical Proposal for the Synthesis of Carbapenems from 4-(2-Propynyl)azetidinones Promoted by $[W(CO)_5]$ as an Alternative to the Ag^+-Assisted Process

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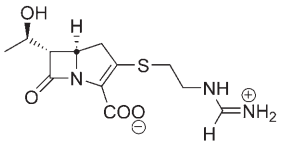
Abstract: The synthesis of carbapenems from 4-(2-propynyl)azetidinones assisted by both Ag^+ and $[W(CO)_5]$ was theoretically investigated by using the B3LYP/6-31+G(d)-LANL2DZ level, taking into account the effect of solvent by the PB-SCRF model implemented in Jaguar. According to our results, the silver-assisted cyclization is a concerted process for which the low yield experimentally observed could mainly stem from the alkaline hydrolysis of the β-lactam ring. This process is very efficiently catalyzed by Ag^+, making it competitive with the formation of the carbapenem. The cycloisomerization of 4-(2-propynyl)azetidinone promoted by $[W(CO)_5]$ is proposed as an alternative synthetic strategy to obtain the carbapenem. The *endo* cycloisomerization is by far the most favorable one. When the process is assisted by $[(thf)W(CO)_5]$, although the main product is the carbapenem, the formation of a carbene complex represents a certain competition. The presence of a Me_3N molecule from the very start of the reaction causes an important catalytic effect considerably reducing the energy barriers corresponding to the H atom transfers and rendering a very efficient process. Moreover, this catalytic action determines the evolution of the system through only one mechanistic route which produces the carbapenem, hindering the formation of the carbene. Therefore, the cycloisomerization of 4-(2-propynyl)azetidinone promoted by $[(Me_3N)W(CO)_5]$ constitutes an interesting alternative to the silver-assisted cyclization.

Keywords: carbapenems · density functional calculations · reaction mechanisms · silver · tungsten

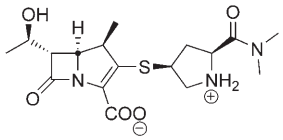
Introduction

β-Lactam antimicrobials have been widely used to treat serious infections for nearly 60 years, owing to their excellent efficacy, safety, and tolerability profiles. Among the many different structurally distinct classes of β-lactams, carbapenems are considered as the class that is the most potent and has the widest spectrum of antimicrobial activity. Imipenem, meropenem, and ertapenem are the three members of this class of antibiotics currently available for clinical use.[1,2]

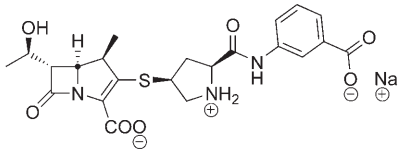
Therefore, the basic skeleton of carbapenems has attracted and continues to attract the attention of synthetic chemists. The synthetic strategies developed for the stereoselective synthesis of bicyclic β-lactam antibiotics usually relies on the previous construction of a monocyclic β-lactam adequate for subsequent annulation of the second ring.[3] An organotransition-metal approach to the carbapenem ring system from 4-(2-propynyl)azetidinones has been proposed in which the alkynyl-substituted azetidinones underwent



imipenem



meropenem



ertapenem

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Supporting information for this article (includes Tables 1S–4S, Figures 1S–4S and a detailed drawing of all structures) is available on the WWW under http://www.chemeurj.org/ or from the author.

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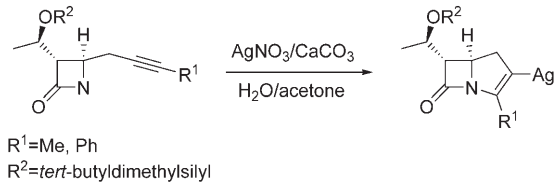
slow cyclization to carbapenems in the presence of silver nitrate (Scheme 1).[4] This silver-mediated ring closure through N−C3 bond formation, however, presents low yields, and

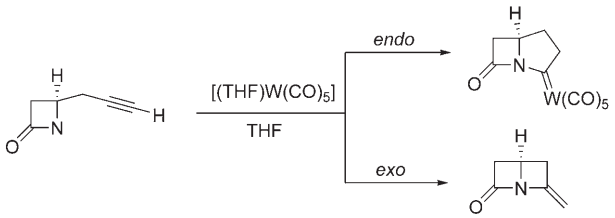


R^1=Me, Ph
R^2=*tert*-butyldimethylsilyl

Scheme 1.

therefore it is desirable that new synthetic strategies are developed to carry out this process in a more efficient way.

The design and development of efficient, clean, and fast methods to get cyclic compounds is an important challenge in modern synthetic and pharmaceutical chemistry.[5] The alkynol cycloisomerization promoted by Group 6 metallic complexes is one of these interesting transformations widely used in recent years for the synthesis of compounds of biological interest with high yields.[6] In principle, this same synthetic strategy could be useful for obtaining carbapenems through the cycloisomerization of 4-(2-propynyl)azetidinones promoted by Group 6 metal-carbonyl complexes in THF. This reaction may proceed through two different reaction pathways leading to *endo* or *exo*-cycloisomerization products (Scheme 2). The *endo* product, which a priori



Scheme 2.

could be expected to be the major product, would correspond to a carbapenem structure. As in the chemistry of ω-alkynols, the presence of a tertiary amine could play an important catalytic role in the present case.[6a]

In this work, we present a theoretical investigation of the mechanism of the silver-mediated cyclization of 4-(2-propynyl)azetidinone in water trying to uncover the reason for the low yield experimentally found for this process. We also investigated the viability of the cycloisomerization of 4-(2-propynyl)azetidinone promoted by $[W(CO)_5]$ as a convenient alternative to the silver-assisted process.

Computational Methods

Full geometry optimizations were performed with the B3LYP DFT method[7] by using the relativistic effective core pseudopotential LANL2DZ[8] for Ag and W. In the case of Ag, one set of *f* polarization functions ($\zeta_f = 0.473$) was added. For the remaining atoms the 6-31+G(d) basis set was employed. This theory level has been shown to be adequate[9] to the kind of study undertaken in the present work. The Gaussian 03 series of programs was used.[10] The nature of the stationary points was further checked and zero point vibrational energies (ZPVEs) were evaluated by analytical computations of harmonic vibrational frequencies at the same theory level. Intrinsic reaction coordinate (IRC) calculations were also carried out to check the connection between the transition states (TSs) and the minimum-energy structures by using the Gonzalez and Schlegel method[11] implemented in Gaussian 03. ΔG values were also calculated within the ideal gas, rigid rotor, and harmonic oscillator approximations.[12] A pressure of 1 atm and a temperature of 298.15 K were assumed in the calculations.

To take into account condensed-phase effects, we performed single-point calculations on the gas-phase-optimized geometries by using Jaguar's Poisson–Boltzmann self-consistent reaction field model (PB-SCRF) at the same theory level as that used in the gas-phase calculations.[13] This model supplies a better solvation energy for Ag^+ than the PCM[14] method implemented in Gaussian 03. According to our PB-SCRF Jaguar calculations in water solution, $\Delta G_{solvation}(OH^-) = -106.7$ kcal mol^{-1} and $\Delta G_{solvation}(Ag^+) = -110.1$ kcal mol^{-1} are in reasonable agreement with the experimental values of -102.9 ± 1.9 and -117.6 ± 2.3 kcal mol^{-1}.[15] Addition to $\Delta G_{gas\ phase}$ of the relative solvation Gibbs energy gives $\Delta G_{solution}$. Relative permittivities 7.58 and 78.39 and probe radii 2.52 and 1.40 Å were assumed in the calculations to simulate THF and water, respectively, as the solvents used in experimental work.

Results and Discussion

We will present first an analysis of the silver-assisted cyclization of 4-(2-propynyl)azetidinone. Table 1 presents the relative electronic energies and Gibbs energies in solution, and Figure 1 displays the corresponding Gibbs energy profile in water solution. Figure 1S and Table 1S of the Supporting Information collects the optimized geometries of all the critical structures located along the reaction coordinate and their energies. Tables 2 and 2S and Figures 2 and 2S display the corresponding results for the analysis of the hydrolysis of a 4-(2-propynyl)azetidinone-Ag^+ complex. Next, we will

Table 1. Relative electronic energies and relative Gibbs energies in water solution (kcal mol^{-1}) corresponding to all the critical structures located along the reaction coordinate for the silver-assisted cyclization of 4-(2-propynyl)azetidinone.

Structures	ΔE_{elec}	$\Delta G_{solution}$
Reactants	0.0	0.0
C1Ag	−36.1	3.6
TSAg	−30.4	19.2
PAg	−49.7	17.1

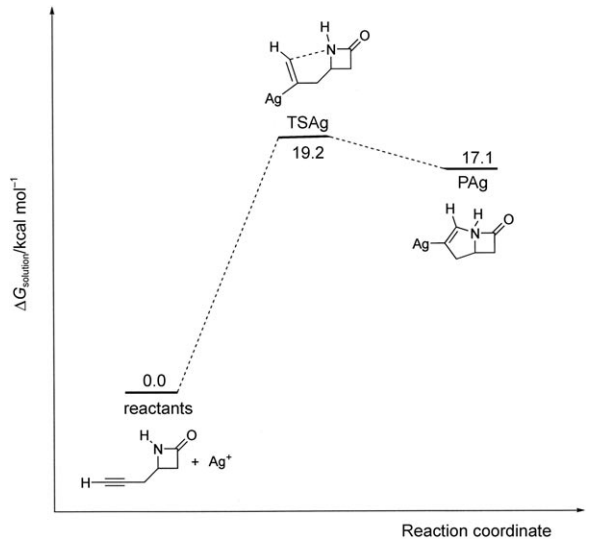


Figure 1. Gibbs energy profile in solution for the silver-assisted cyclization of 4-(2-propynyl)azetidinone.

Table 2. Relative electronic energies and relative Gibbs energies in solution (kcal mol^{-1}) corresponding to all the critical structures located along the reaction coordinate for the alkaline hydrolysis of the 4-(2-propynyl)azetidinone assisted by Ag^+.

Structures	ΔE_{elec}	$\Delta G_{solution}$
Reactants (C2Ag+OH$^-$)	0.0	0.0
CH	−145.9	13.9
TSCIH	−142.3	20.3
IH	−168.9	−6.1
TSIPH	−167.2	−15.8
PH	−168.2	−25.2

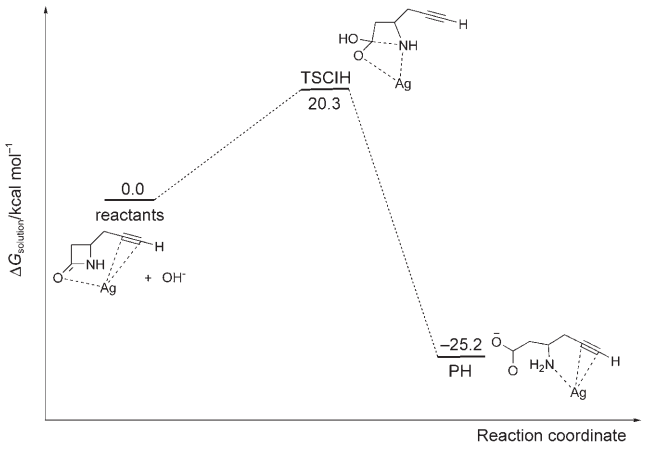


Figure 2. Gibbs energy profile in solution for the alkaline hydrolysis of the 4-(2-propynyl)azetidinone assisted by Ag^+.

present the study of the cycloisomerization of 4-(2-propynyl)-azetidinone promoted by [(thf)W(CO)$_5$]. Table 3 presents the corresponding relative electronic energies and Gibbs energies in solution, Figure 3 shows the Gibbs energy profiles in THF solution, and Figure 3S and Table 3S of the Supporting Information display the optimized geometries of all the critical structures located along the reaction coordinate and their corresponding energies. Finally, Tables 4 and 4S and Figures 4 and 4S report the corresponding results for the cycloisomerization of 4-(2-propynyl)azetidinone assisted by [(Me$_3$N)W(CO)$_5$]. Unless otherwise stated we will discuss in the text the relative Gibbs energies in solution.

Table 3. Relative electronic energies and relative Gibbs energies in solution (kcal mol^{-1}) corresponding to the critical structures located along the reaction coordinate for the cycloisomerization of 4-(2-propynyl)azetidinone promoted by [(thf)W(CO)$_5$].

Structures	ΔE_{elec}	$\Delta G_{solution}$
endo pathway		
CW	0.0	0.0
TSWN1	22.8	13.2
MWN1	−0.4	−0.3
TSWN2	5.1	8.8
MWN2	−1.9	2.0
TSWN3	27.2	24.0
PW	−17.1	−8.8
TSWN4	26.8	25.1
MWN4	−18.7	−13.6
TSWN5	22.0	21.1
exo pathway		
CW	0.0	0.0
TSWX1	30.6	28.3
MWX1	25.6	25.2

Silver-assisted cyclization of 4-(2-propynyl)azetidinone: Initially the interaction of Ag^+ with the triple bond of 4-(2-propynyl)azetidinone gives rise to a complex C1Ag (Table 1), which is a minimum structure on the electronic energy surface, but not on the Gibbs energy surface in solution owing to the effect of solvent. Therefore, in solution separate reactants evolve through a TS, TSAg, (19.2 kcal mol^{-1}) for the five-membered ring closure through the N−C bond formation to yield the carbapenem product PAg (17.1 kcal mol^{-1}). At TSAg, the Ag atom originally bridging the triple bond is coordinated to the middle carbon atom of the propynyl chain leaving the terminal carbon atom exposed to the attack of the lone pair of the nitrogen atom, the N−C distance being 2.424 Å. The Gibbs energy barrier in solution for this process is 19.2 kcal mol^{-1}.

To investigate the origin of the low yield experimentally found for the silver-assisted cyclization of 4-(2-propynyl)azetidinone[4] we have considered as a likely competitive process the hydrolysis of the 4-(2-propynyl)azetidinone-Ag^+ complex by the OH^- ions generated by the addition of $CaCO_3$.

Hydrolysis of the 4-(2-propynyl)azetidinone-Ag^+ complex: The interaction of Ag^+ with 4-(2-propynyl)azetidinone also gives rise to a complex, C2Ag, in which the silver cation interacts with the triple bond of the side chain and with the oxygen atom of the carbonyl group. We found that this complex is the starting point for the hydrolysis process by OH^-. The electronic energy profile for this hydrolysis proceeds far under the energy level corresponding to C2Ag+OH$^-$

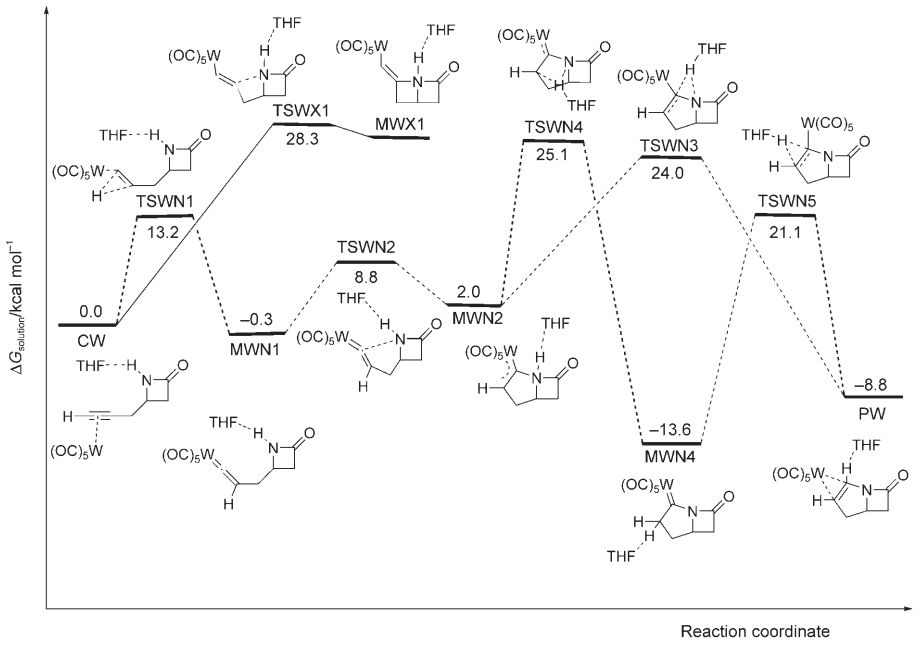


Figure 3. Gibbs energy profile in THF solution for the cycloisomerization of 4-(2-propynyl)azetidinone promoted by $[(thf)W(CO)_5]$.

Table 4. Relative electronic energies and relative Gibbs energies in solution (kcal mol^{-1}) corresponding to the critical structures located along the reaction coordinate for the cycloisomerization of 4-(2-propynyl)azetidinone assisted by $[(Me_3N)W(CO)_5]$.

Structures	ΔE_{elec}	$\Delta G_{solution}$
CWA	0.0	0.0
TSWNA1	23.1	13.6
MWNA1	−0.6	−0.1
TSWNA2	6.2	9.7
MWNA2	−0.3	2.2
TSWNA3	3.4	1.2
MWNA3	1.2	−3.6
TSWNA4	3.8	1.7
MWNA4	2.9	0.1
TSWNA5	11.3	6.5
PWA	−16.4	−9.3

(Table 2). Initially an adduct is formed, CH, corresponding to the attack of OH^- on the carbonyl carbon atom, which evolves through a TS, TSCIH, for ring opening through breakage of the amidic bond to form an intermediate, IH. This intermediate proceeds through a TS, TSIPH, for the hydroxyl H transfer to the nitrogen atom leading, finally, to the product of the hydrolysis, PH.

In solution, this two-stage mechanism transforms into a concerted one characterized by the TS TSCIH with an energy barrier of 20.3 kcal mol^{-1}, the hydrogen transfer taking place along the evolution of this TS into the final product. The process is exergonic by 25.2 kcal mol^{-1} (Table 2 and Figure 2).[16]

We also investigated the alkaline hydrolysis of 4-(2-propynyl)azetidinone in the absence of Ag^+. In solution, we found a concerted mechanism with an energy barrier of 40.8 kcal mol^{-1}. Therefore, the presence of Ag^+ produces a very important catalytic effect of 20.5 kcal mol^{-1}, which makes the ring-opening process competitive with the formation of a bicyclic species. This competition could be one of the reasons for the low yield experimentally found for the Ag^+-assisted synthesis of carbapenems from 4-(2-propynyl)azetidinones.

Cycloisomerization of 4-(2-propynyl)azetidinone promoted by $[(thf)W(CO)_5]$: The starting point for this reaction is the complex, CW, in which the W atom of $[(thf)W(CO)_5]$ is coordinated to the triple bond in 4-(2-propynyl)azetidinone and the THF molecule, which has been previously found to play an important role in these kinds of processes, is coordinated to the amidic hydrogen atom (Figure 3).[9a] We present first the results corresponding to the *endo* cycloisomerization. Along this *endo* reaction coordinate CW evolves through a TS, TSWN1, (13.2 kcal mol^{-1}) for H migration from C_α to C_β to yield a vinylidene intermediate MWN1 (−0.3 kcal mol^{-1}). From MWN1 the nucleophilic attack of the lone pair of the N atom on the C_α atom gives rise to the bicyclic intermediate, MWN2, (2.0 kcal mol^{-1}) through the TS TSWN2 (8.8 kcal mol^{-1}) in which the C–N distance is 2.132 Å. MWN2 can evolve in two different ways for the migration of the amidic H atom assisted by the THF molecule. Along the first route the amidic H atom migrates up to C_α through a TS, TSWN3, (24.0 kcal mol^{-1}) rendering the final carbapenem product, PW, (−8.8 kcal mol^{-1}) in which the W atom of the $W(CO)_5$ moiety is coordinated to the C–C double bond, while the THF molecule solvates the five-membered ring. The second migration route for the amidic H goes through the TS TSWN4 (25.1 kcal mol^{-1}) leading to the formation of a carbene complex, MWN4, (−13.6 kcal mol^{-1}) in which the migrating H atom is bonded to C_β. MWN4 is connected with the product PW through a Gibbs energy barrier of 34.7 kcal mol^{-1} corresponding to the TS TSWN5 for the migration of one of the β-H atoms of the carbene to the α-carbon atom. Thus, the present theoretical results indicate that although the major product of this process is the carbapenem, the formation of a carbene complex represents a certain competition.

According to our computational results, the *exo*-cycloisomerization process yields a highly strained bicyclic species MWX1 (25.2 kcal mol^{-1}) through a TS, TSWX1, for the nucleophilic attack of the lone pair of the N atom on C_β with an energy barrier of 28.3 kcal mol^{-1} (Figure 3). Consequent-

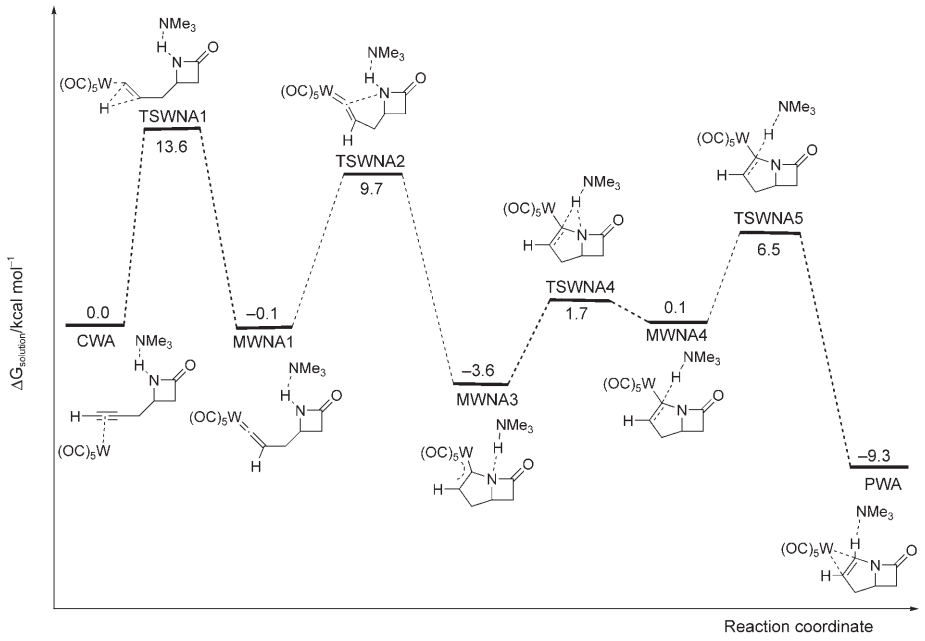


Figure 4. Gibbs energy profile in THF solution for the cycloisomerization of 4-(2-propynyl)azetidinone assisted by $[(Me_3N)W(CO)_5]$.

ly, this process cannot compete with the formation of the bicyclic species MWN2 through the *endo* cycloisomerization.

Cycloisomerization of 4-(2-propynyl)azetidinone promoted by $[(Me_3N)W(CO)_5]$: In view of the role played by a tertiary amine molecule in the cycloisomerization of ω-alkynols,[6a,18] we thought that the assistance by Me_3N from the very start of the cycloisomerization of 4-(2-propynyl)azetidinone could determine the development of a more favorable synthetic route. To model this evolution we used a molecule of Me_3N coordinated to the migrating H atom instead of the THF molecule. We will report only the *endo* route, which is the most favorable one. The results obtained for this process are collected in Table 4 and the corresponding Gibbs energy profile in solution is displayed in Figure 4. As in the previous case the initial complex, CWA, in which the W atom of $[(Me_3N)W(CO)_5]$ is coordinated to the triple bond in 4-(2-propynyl)azetidinone, evolves through the TS TSWNA1 (13.6 kcal mol^{-1}) for the formation of the vinylidene intermediate MWNA1 (−0.1 kcal mol^{-1}). Next, MWNA1 undertakes an intramolecular cyclization by attack of the amidic nitrogen atom on the C_α to form the bicyclic intermediate MWNA3 (−3.6 kcal mol^{-1}) through the TS TSWNA2 (9.7 kcal mol^{-1}). It is interesting to remark that in solution this cyclization takes place with simultaneous transfer of the amidic H atom to the amine N, whereas in the gas phase both processes take place in two steps. Finally, MWNA3 evolves into the carbapenem product PWA (−9.3 kcal mol^{-1}[41]) through migration of the H atom from the Me_3N to the C_α. This process takes place in two separate steps. First, the protonated amine moves to locate the H atom in front of the C_α through the TS TSWNA4 (1.7 kcal mol^{-1}) to yield the intermediate MWNA4 (0.1 kcal mol^{-1}) and then the H atom is transferred from the amine to the C_α through the TS TSWNA5 (6.5 kcal mol^{-1}). It must be remarked that no reaction path yielding a carbene product from MWNA3 was located after an extensive search.

According to our theoretical results, the tertiary amine Me_3N plays a crucial catalytic role in the cycloisomerization of 4-(2-propynyl)azetidinone to yield a carbapenem considerably reducing the energy barriers corresponding to the H-atom transfers so that the rate-determining step is now the formation of the vinylidene (13.6 kcal mol^{-1}). Moreover, this catalytic action determines the evolution of the system through only one mechanistic route which produces the carbapenem, hindering the formation of the carbene complex.

In summary, the silver-assisted cyclization of 4-(2-propynyl)azetidinone is a concerted process with a Gibbs energy barrier in solution of 19.2 kcal mol^{-1}. The low yield experimentally observed for this reaction could mainly stem from the alkaline hydrolysis of the β-lactam ring which is very efficiently catalyzed by the presence of Ag^+, making it competitive with the formation of the carbapenem product. We also investigated the cycloisomerization of 4-(2-propynyl)azetidinone promoted by $[W(CO)_5]$ as an alternative synthetic strategy to obtain the carbapenem. The *endo* cycloisomerization is by far the most favorable one and the *exo* mechanism, which produces a second four-membered ring cannot compete with it. When the process is assisted by $[(thf)W(CO)_5]$, although the main product is the carbapenem, the formation of a carbene complex represents a certain competition. The presence of a Me_3N molecule from the very start of the reaction causes an important catalytic effect considerably reducing the energy barriers corresponding to the H-atom transfers so that the rate-determining step is now the formation of the vinylidene with an energy barrier of 13.6 kcal mol^{-1}. Moreover, this catalytic action determines the evolution of the system through only one mechanistic route which produces the carbapenem, hindering the formation of the carbene. Therefore, the present theoretical results clearly indicate that the cycloisomerization of 4-(2-propynyl)azetidinone promoted by $[(Me_3N)W(CO)_5]$ constitutes an interesting alternative to the silver-assisted cyclization in which high yields are expected in the absence of competitive hydrolysis processes.

Acknowledgements

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[16] To check the effect of geometry optimization in solution we optimized in solution the electronic energy profile corresponding to the hydrolysis of 4-(2-propynyl)azetidinone catalyzed by Ag^+. This task could only be accomplished with the Onsager method[17] as implemented in Gaussian 03, because PCM (Gaussian03) and PB-SCRF (Jaguar) failed in the calculation. The effect of solvent for the Onsager-optimized structures was finally evaluated by means of single point calculations using the PB-SCRF method (Jaguar) on the Onsager optimized structures. The Onsager optimized geometries are quite similar to the gas-phase-optimized ones, the largest difference appearing in TSCIH in which Ag^+ is now slightly more separated from the carbonyl O atom and a little closer to the N atom (Figure 2S). On the other hand, the resulting Gibbs energy profile is quite similar to the gas-phase-optimized one with a Gibbs energy barrier of 19.9 kcal mol^{-1} (Table 2S).
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