Importance of a Synperiplanar Stepwise Mechanism through Neutral Intermediates in the Aminolysis of Monocyclic β-Lactams: A Theoretical Analysis

Natalia Díaz, Dimas Suárez, and Tomás L. Sordo*

Departamento de Química Física y Analítica, Universidad de Oviedo, Julián Clavería 8, 33006 Oviedo, Spain

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The ring opening of 2-azetidinone via a neutral CH_3NH_2-assisted aminolysis process is studied using different quantum chemical methods (MP2/6-31G**, B3LYP/6-31G**, and G2(MP2,SVP) levels of theory) as a further step to the theoretical investigation of the aminolysis reaction of β-lactam antibiotics. The exploration of the corresponding potential energy surface (PES) renders a concerted pathway and two different stepwise routes through several neutral tetrahedral intermediates. A nonconcerted route involving an N inversion of a tetrahedral intermediate is the most favored mechanism, the formation of a first antiperiplanar intermediate constituting the rate-determining step with an activation energy in solution of 42.2 kcal/mol. The N-inversion process leads to a synperiplanar intermediate whose ring opening requires 40.9 kcal/mol as Gibbs energy barrier. This stepwise mechanism is favored by 5.2 and 6.0 kcal/mol with respect to the concerted mechanism and the alternative antiperiplanar stepwise process, respectively. Reaction coordinate calculations indicate that *zwitterionic* structures in solution would be extremely unstable intermediates to play a significant kinetic role in the process. The experimental linear Brønsted plots on the pK_a of monoamines for the aminolysis of both monocyclic and bicyclic β-lactams are well rationalized in terms of an ionic formal partitioning that describes the main transition structures as composed of a methylammonium cation and a 1,1-amino alcoholate anion. According to our analyses, the methyl-induced stabilization of the TSs stems mainly from the intrinsic stabilization achieved by the corresponding ionic moieties, especially the catalytic one. From the above results, it is inferred that monocyclic β-lactams would react preferentially along a stepwise mechanism. For bicyclic β-lactams in which the N-inversion is impeded, the concerted route could be slightly favored although other factors not considered in this work could have an important kinetic role.

Introduction

The major antigenic determinant of penicillin allergy detected by the inmunological system is the penicilloyl group bound by an amide linkage to ϵ-amino groups of lysine residues in plasmid proteins as a result of an aminolysis reaction of the β-lactamic ring.[1] Recent experimental studies[2] of the binding of benzylpenicillin to human serum albumin (HSA) have identified benzylpenicilloyl-containing peptides in different binding regions of HSA that involve several lysine residues.

The aminolysis of the β-lactam antibiotics is a nucleophilic substitution reaction at the carbonyl of β-lactams in which an acyl group is transferred from one amino group to another involving the C−N bond fission of the β-lactam.[3] For a series of primary monoamines, it has been found that the importance of the different terms contributing to the observed pseudo-first-order rate constant for the disappearance of the β-lactamic compounds **1**−**3** in Scheme 1 depends on the basicity and concentration of the amine and the pH.[3b] Thus, at high pH the aminolysis reaction of β-lactams **1**−**3** proceeds predominantly via the specific hydroxide-catalyzed pathway while the kinetic constants on $[RNH_2]$ and $[RNH_2]^2$ corresponding to the uncatalyzed and the amine-catalyzed aminolysis, respectively, are the predominant terms when weakly basic amines react with β-lactams in the biologically relevant pH range 6−8.

Kinetic experiments have provided some mechanistic insight into the aminolysis processes of β-lactams.[4−7] Thus, the nonlinear dependence of the rate of hydroxide-catalyzed aminolysis of benzylpenicillin **1** and 6-β-aminopenicillanic acid **2** upon hydroxide ion concentration has been interpreted in terms of formation of a *zwitterionic* tetrahedral intermediate involved in a stepwise mechanism.[4] The nonlinear Brønsted plot for general base catalysis of the reaction of hydrizine and benzylpenicillin **1**, with limiting slopes of $\beta \leq 0.2$ and $\beta \geq 0.8$ for strong and weak bases, respectively, may be also an indication of a change in the rate-limiting step of a

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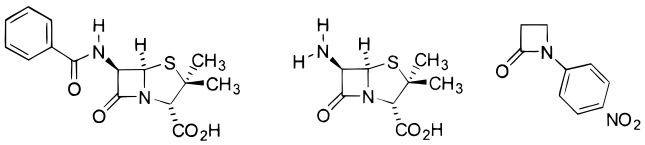
Scheme 1



1 2 3

stepwise process.[5] In contrast, it has been shown that for a series of amines the kinetic pattern of their reactivity toward the monocyclic β-lactam **3** does not involve a change in the rate-determining step.[6] On the other hand, the Brønsted β values on the pK_a of amines for the amine-catalyzed aminolysis of **1**−**3** have all values close to unity,[4,6,7] thus indicating that an amine molecule carries a unit positive charge at the corresponding rate-determining transition structures. These Brønsted β values for the thermal and amine-catalyzed reactions are apparently consistent with a stepwise mechanism through *zwitterionic* intermediates proposed for the general-base-catalyzed aminolysis of β-lactams.[3a,4]

Previous theoretical works have focused on thermal and H_2O-assisted hydrolysis processes[8] as well as alkaline hydrolysis[9] of azetidinones. The investigation of the mechanistic role of key residues in enzymes to hydrolyze peptidic bonds has also been approached by ab initio methods.[10] Very recently, the noncatalyzed ammonolysis and aminolysis of 2-azetidinone via neutral mechanisms have been studied by us.[11] For these thermal reactions, the most favored mechanism is a stepwise route involving a syn tetrahedral intermediate for both the ammonolysis and aminolysis processes. We have also investigated the ring opening of 2-azetidinone via a neutral NH_3-assisted ammonolysis process, rendering again a concerted pathway and a stepwise one through a neutral tetrahedral intermediate.[12] According to these calculations, the most favored mechanism is the stepwise one whose rate-determining step implies the cleavage of the intermediate with a simultaneous NH_3-assisted H-transfer from a hydroxyl group to the forming amino group, with both groups having an antiperiplanar orientation. Interestingly, the catalytic moiety resembles an ammonium cation in the main transition states involved in the NH_3-catalyzed reaction of 2-azetidinone in accordance with the experimental interpretation of Brønsted plots for the aminolysis reaction of benzylpenicillin.

As a further step in the investigation of the aminolysis of β-lactams, we report in this work a quantum chemical study of the methylamine-catalyzed reaction between methylamine and 2-azetidinone, which is the structural unit common to all the β-lactamic antibiotics. An additional stepwise mechanism is presented that is more favorable than the previously reported one.[12] To gain some theoretical insight into the kinetic influence produced by substitution on amines, the effect of the methyl groups on the catalyst and the nucleophile will be thoroughly analyzed. In addition, the kinetic role of zwitterionic intermediates will be also compared with that of the neutral tetrahedral intermediates. From these results, a more detailed interpretation of the experimentally reported kinetic data on the aminolysis of β-lactams will be offered.

Methods

Ab initio calculations were carried out with the G94 system of programs[13] in which extra links for the solvent effect treatment have been added.[14] Stable structures were fully optimized and transition structures (TSs) located at the MP2/6-31G**, and B3LYP/6-31G** levels.[15,16] All the critical points were further characterized by analytic computation of harmonic frequencies at the B3LYP/6-31G** level. Thermodynamic data (298 K, 1 bar) were computed using B3LYP/6-31G** frequencies within the ideal gas, rigid rotor, and harmonic oscillator approximations.[17]

To estimate the effect of larger basis sets and more elaborated *N*-electron treatments on the relative energies, electronic energies were also computed for all the MP2/6-31G** optimized structures using a modified version of the G2(MP2,-SVP) scheme,[18] which approximates the QCISD(T)/6-311+G-(3df,2p) level in an additive fashion as follows:

$$E_{[\mathrm{QCISD(T)/6\text{-}311+G(3df,2p)}]} \approx E_{[\mathrm{G2(MP2,SVP)}]} = E_{[\mathrm{QCISD(T)/6\text{-}31G^*}]} + E_{[\mathrm{MP2/6\text{-}311+G(3df,2p)}]} - E_{[\mathrm{MP2/6\text{-}31G^*}]}$$

However, since the single-point QCISD(T)/6-31G* calculations on the systems under study in this work were very demanding computationally, we assumed a formal reaction scheme to estimate the QCISD(T)/6-31G* energies for all the methyl-substituted critical structures along the reaction profile. Scheme 2 illustrates this point in more detail for a particular case.

The QCISD(T)/6-31G* energy for the aminolysis reaction ($\Delta E_{\mathrm{QCISD(T)/6-31G^*}}$(**III**)) is approximated by two terms corresponding to $\Delta E_{\mathrm{QCISD(T)/6-31G^*}}$(**I**) for step **I** in Scheme 2 and a $\Delta E_{\mathrm{MP2/6-31G^*}}$(**II**) term for an isodesmic reaction step **II** which is reasonably estimated at the MP2/6-31G* level. The asterisk mark in Scheme 2 means that the MP2/6-31G** geometry of the methyl substituted structure was used to perform the corresponding QCISD(T)/6-31G* calculations after having

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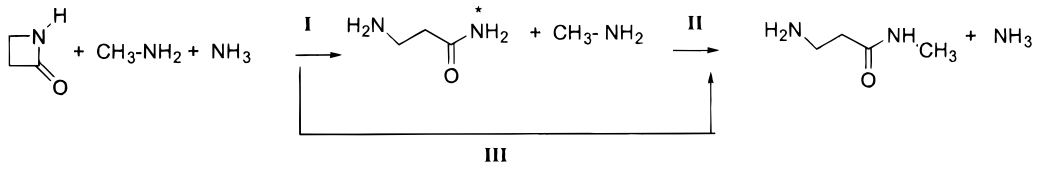
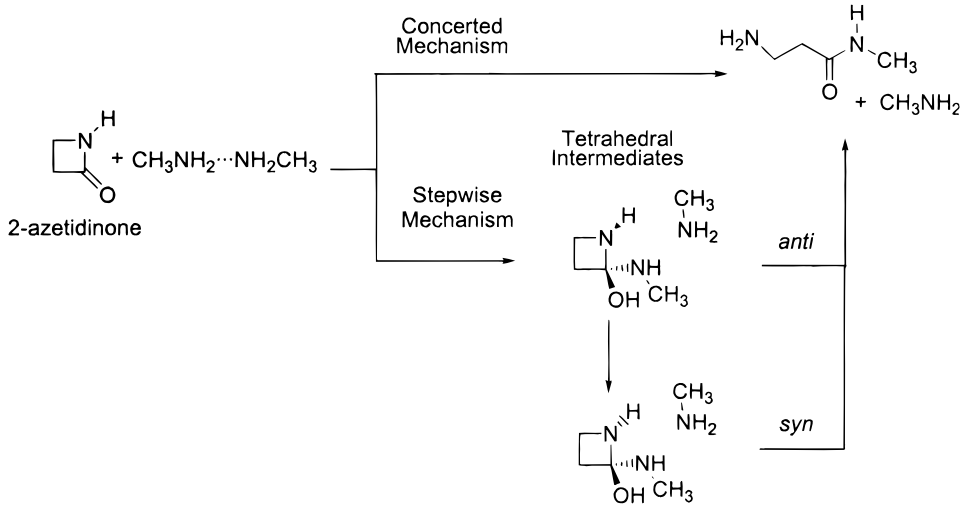
Scheme 2



$$\Delta E_{\mathrm{QCISD(T)/6\text{-}31G^*}}\ (\mathbf{III}) \approx \Delta E_{\mathrm{QCISD(T)/6\text{-}31G^*}}\ (\mathbf{I}) + \Delta E_{\mathrm{MP2/6\text{-}31G^*}}\ (\mathbf{II})$$

Scheme 3



replaced the methyl group by one H atom using a standard N−H bond length of 1.01 Å.

To test this modified G2(MP2,SVP) method, the energy barrier for the concerted thermal aminolysis reaction between 2-azetidinone and methylamine was calculated using the normal G2(MP2,SVP) procedure as well as the modified G2-(MP2,SVP) method presented above. The corresponding barriers are 38.5 and 38.1 kcal/mol at the standard and modified G2(MP2,SVP) levels, respectively, thus differing in only 0.4 kcal/mol. This energetic difference is substantially lower than 1.63 kcal/mol corresponding to the average absolute deviation of the G2(MP2,SVP) method.[18] The modified G2(MP2,SVP) method, which considerably reduces the computational cost of the QCISD(T)/6-31G* calculations by reducing in 38 the number of basis functions, was therefore employed to calculate the energy profile for the methylamine-assisted aminolysis reaction of 2-azetidinone.

Quantum chemical computations on solvated structures were carried out by means of a general self-consistent-reaction field (SCRF) model.[19] The solvent is represented by a continuum characterized by its relative static dielectric permittivity, ϵ. The solute, which is placed in a cavity created in the continuum after spending some cavitation energy, polarizes the continuum, which in turn creates an electric field inside the cavity. Once the equilibrium is reached, the electrostatic part of the free energy corresponding to the solvation process is obtained using a monocentric multipolar expansion of the molecular charge distribution.[20] The SCRF continuum model employed assumes a general cavity shape that is obtained using van der Waals solute atomic spheres with modified radii ($1.3084r_{\mathrm{vdW}}$),[19a] necessary to fulfill the volume condition. A relative permittivity of 78.30 was used to simulate water as the solvent used in the experimental work.

The main TSs were also analyzed carrying out a configurational analysis (CA).[21] This interpretative tool rewrites a TS monodeterminantal wave function (built in this work from the B3LYP/6-31G** MOs[22]) as a combination of the electronic configurations of the interacting fragments, obtaining thus a more chemically graspable picture. This analysis was performed using a revised version of the ANACAL program.[23] In addition, the electrostatically derived B3LYP/6-31G** atomic charges were also computed for the main TSs according to the Merz−Kollman−Singh scheme.[24]

Results and Discussion

The exploration of the PES for the reaction between 2-azetidinone and the methylamine dimer[25] rendered three possible pathways for this process starting with prereactive complexes (see Scheme 3). The concerted and the anti stepwise processes are readily comparable to those previously described for the NH_3-assisted ammonolysis reaction.[12] In addition, as mentioned in the Introduction, a new stepwise mechanism is now examined in this work. This pathway proceeds through the ring opening of the intermediate with a syn H-transfer assisted by the catalytic CH_3NH_2 molecule.

The concerted mechanism consists of the attack to the amide C atom by the nucleophilic methylamine. The

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(25) MP2/6-31G** and B3LYP/6-31G** levels of theory render a similar structure (N···N distance ≈ 3.1−3.2 Å) and interaction energies for the *trans*-methylamine dimer (−5.2 and −4.4 kcal/mol, respectively).

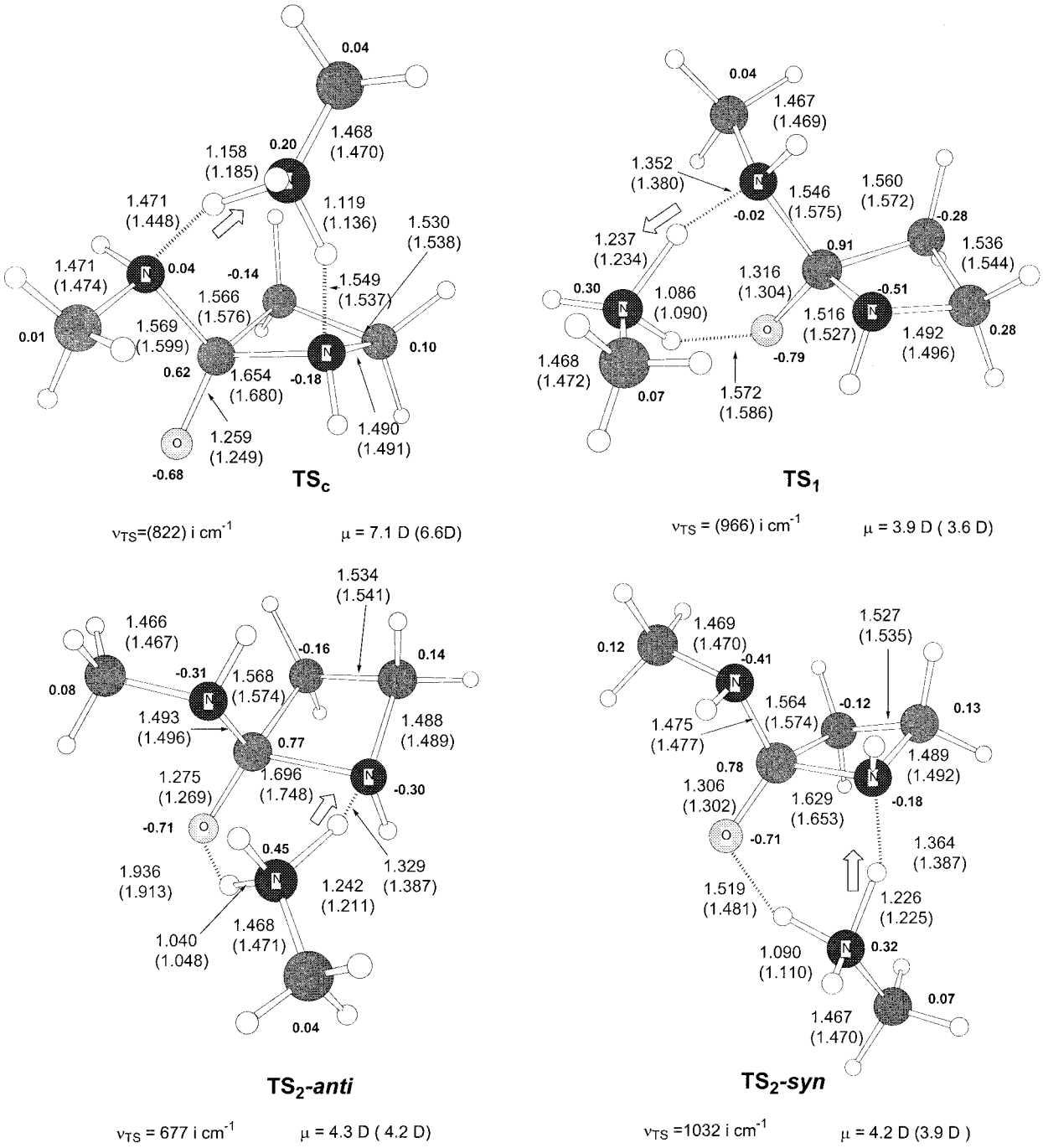


Figure 1. MP2/6-31G**-optimized structures for the main TSs corresponding to the CH_3NH_2-assisted aminolysis reaction of 2-azetidinone. Distances are in Å. B3LYP/6-31G** values are in parentheses. B3LYP/6-31G** MKS atomic charges with hydrogen atoms are summed into heavy atoms in bold characters. Hollow arrows sketch the main components of the corresponding transition vectors.

catalytic CH_3NH_2 removes an H atom from the nucleophilic amine and gives another one to the leaving amine group with the simultaneous rupture of the β-lactam ring.

The first step of the nonconcerted routes proceeds through the CH_3NH_2-assisted addition of the H−NHCH$_3$ bond across the carbonyl double bond to give an amino alcohol tetrahedral intermediate. This intermediate can evolve through two different pathways, anti and syn in Scheme 3, for ring opening assisted by the catalytic methylamine to give the final product *N*-methyl-3-aminopropanamide.

Another ring-opening process of the tetrahedral intermediates consisting of the catalyzed H-shift from the amino group to the amidic N atom to yield an open-chain hydroxyimine product is not considered in this work given that this process has resulted clearly disfavored both kinetically and thermodynamically for the NH_3-assisted ammonolysis process.[12]

The optimized geometries of the main TSs located along the concerted and stepwise reaction paths are shown in Figure 1 (the rest of geometries are available as Supporting Information). Table 1 collects the relative energies along the reaction profiles obtained at the different theory levels including the ZPVE correction from the B3LYP/6-31G** unscaled frequencies and the corresponding relative Gibbs energy values, both in the

Table 1. Relative Energies[a] (kcal/mol) with Respect to Reactants of the Structures Considered in the Aminolysis Reaction of 2-Azetidinone Assisted by Methylamine (Δ*G* Values in Parentheses Correspond to the NH_3-Assisted Ammonolysis of 2-Azetidinone)

structures	MP2/6-31G**	B3LYP/6-31G**	G2(MP2,SVP)[b]	$\Delta G_{gas-phase}$[c]	$\Delta G_{solution}$[d]
reactants	0.0	0.0	0.0	0.0 (0.0)	0.0 (0.0)
C_C	−10.4	−7.6	−7.4	12.0 (11.7)	16.1 (5.8)
TS_C	19.2	26.0	23.9	47.0 (56.6)	47.4 (57.4)
P_C	−31.0	−26.1	−28.4	−8.9 (−2.6)	−5.4 (1.4)
C_S	−12.8	−10.2	−10.0	7.4 (8.5)	15.1 (16.1)
TS_1	12.0	19.3	15.8	39.2 (49.0)	42.2 (52.2)
I_1-*anti*	−7.7	0.8	−5.3	16.6 (22.3)	23.3 (29.6)
TS_2-*anti*	17.7	25.9	21.2	44.6 (52.0)	48.2 (55.9)
P_S	−32.4	−27.7	−32.4	−9.8 (−3.3)	−5.6 (3.0)
TS_I	−0.3	6.2	1.0	22.8 (28.3)	28.9 (35.1)
I_2-*syn*	−5.1	3.1	−3.8	18.6 (24.3)	23.7 (29.4)
TS_H	−3.8	4.1	−2.2	20.2 (24.2)	25.7 (27.8)
I_3-*syn*	−4.0	3.5	−2.2	19.5 (24.1)	25.5 (30.4)
TS_2-*syn*	10.1	17.5	13.8	37.1 (44.1)	40.9 (48.9)

[a] Including ZPVE correction from B3LYP/6-31G** frequencies. [b] Single-point calculations on MP2/6-31G** geometries. [c] Thermal corrections at the B3LYP/6-31G** level and electronic energies at G2(MP2,SVP). [d] Including MP2/6-31G** SCRF solvation energies.

gas phase and in solution. The $\Delta G_{gas-phase}$ values combine the G2(MP2,SVP) electronic energies and the thermal corrections from the B3LYP/6-31G** analytical frequencies. MP2/6-31G** SCRF ($\epsilon = 78.3$) solvation energies were calculated for all the structures using their MP2/6-31G** gas-phase geometries. Addition of solvation energies to the $\Delta G_{gas-phase}$ values gives the $\Delta G_{solution}$ values in Table 1. Figures 2−4 show the calculated Gibbs energy profiles for the three mechanisms found in this work.

Concerted Mechanism. The methylamine dimer and 2-azetidinone form a prereactive complex $\mathbf{C_C}$ in which the main intermolecular contacts holding it together are the H bonds between the catalytic CH_3NH_2 molecule and the amidic N center of 2-azetidinone (NH···N ≈ 2.3−2.5 Å) and the nucleophilic methylamine with one of the methylene groups of 2-azetidinone (CH···N ≈ 2.3 Å). In addition, the nucleophilic CH_3NH_2 molecule establishes a weak CH···O contact with the carbonylic O of 2-azetidinone with an equilibrium distance of ∼2.7 Å. The G2(MP2,SVP) level predicts a binding energy of −7.4 kcal/mol for the $\mathbf{C_C}$ structure.

$\mathbf{C_C}$ evolves through a TS for the concerted aminolysis cleavage of 2-azetidinone ($\mathbf{TS_C}$ in Figure 1). As in the case of the ammonolysis reaction, $\mathbf{TS_C}$ presents a very tight structure with a single C−N bond practically formed (∼1.6 Å) whereas the endocyclic C−N bond is barely cleaved (∼1.7 Å). The corresponding transition vector is clearly dominated by a hydrogen shift (see Figure 1). The Δ*G* of $\mathbf{TS_C}$ with respect to separate reactants is 47.0 and 47.4 kcal/mol in the gas phase and in solution, respectively. Comparing these values with those corresponding to the noncatalyzed aminolysis reaction (49.7 and 51.3 kcal/mol),[11] we see that the Δ*G* barrier decreases in about 3−4 kcal/mol due to catalysis by the second methylamine molecule.

Completion of the hydrogen shift and the ring opening of β-lactam through the elongation of the breaking C−N bond leads to a product complex $\mathbf{P_C}$ that is 8.9 kcal/mol ($\Delta G_{gas-phase}$) and 5.4 kcal/mol ($\Delta G_{solution}$) more stable than separate reactants (see Figure 2). The G2(MP2,SVP) reaction energy, which amounts to −28.4 kcal/mol, predicts an important thermodynamic driving force for the aminolysis reaction which stems from the release of the strain energy of the four-membered ring at the latter stages of the reaction coordinate.[11]

Stepwise Mechanisms. The prereactive complex $\mathbf{C_S}$ presents a weak H-bonding interaction between the nucleophilic methylamine molecule and a methylene group in 2-azetidinone (CH···N ≈ 2.5−2.7 Å) while the catalytic CH_3NH_2 molecule forms a typical H-bond with the carbonylic O atom (NH···O ≈ 2.1 Å). $\mathbf{C_S}$ is about 10.0 kcal/mol more stable than separate reactants in terms of G2(MP2,SVP) energies, thus being 2.6 kcal/mol more stable than $\mathbf{C_C}$.

The approach of CH_3NH_2 to the carbonylic C atom in 2-azetidinone takes place in a synperiplanar orientation with respect to the N lone pair in 2-azetidinone with simultaneous H-transfer to the carbonylic O atom assisted by the catalytic CH_3NH_2 molecule (see $\mathbf{TS_1}$ in Figure 1). The forming C−N bond is quite advanced at $\mathbf{TS_1}$ (C−N ≈ 1.55 Å), while the transition vector results clearly dominated by a hydrogen shift. The calculated Δ*G* values for $\mathbf{TS_1}$ with respect to separate reactants are 39.2 and 42.2 kcal/mol in the gas phase and in solution, respectively.

$\mathbf{TS_1}$ is connected with an amino alcohol intermediate $\mathbf{I_1}$-***anti*** in which the hydroxyl group and the lone pair of the endocyclic N atom present an antiperiplanar orientation (see Figure 3). The catalytic CH_3NH_2 molecule interacts with the amino alcohol moiety in $\mathbf{I_1}$-***anti*** through OH···N and N···HN interactions with equilibrium distances of around 1.9 and 2.2 Å, respectively. In terms of $\Delta G_{gas-phase}$ values, $\mathbf{I_1}$-***anti*** is less stable by 9.2 and 16.6 kcal/mol than $\mathbf{C_S}$ and separate reactants, respectively.

A direct pathway for the ring-opening of $\mathbf{I_1}$-***anti*** occurs through the H-transfer from the hydroxyl group to the catalytic amine rendering a methylammonium group that, in turn, moves along an out-of-plane bending motion with respect to the β-lactamic ring.[12] In this way, $\mathbf{TS_2}$-***anti*** is reached where an H atom is being transferred to the leaving amino group with simultaneous partial breaking of the endocyclic C−N bond (see Figure 1). The transition vector is clearly dominated by the hydrogen shift. $\mathbf{TS_2}$-***anti*** is 44.6 kcal/mol ($\Delta G_{gas-phase}$) and 48.2 kcal/mol ($\Delta G_{solution}$) above separate reactants, while the corresponding product complex, $\mathbf{P_S}$ is 9.8 ($\Delta G_{gas-phase}$) and 5.6 kcal/mol ($\Delta G_{solution}$) more stable than reactants.

The intermediate $\mathbf{I_1}$-***anti*** may also evolve through a TS for the inversion of the endocyclic N atom ($\mathbf{TS_I}$ in Figure 4), thus leading to a second conformer $\mathbf{I_2}$-***syn*** 2.0

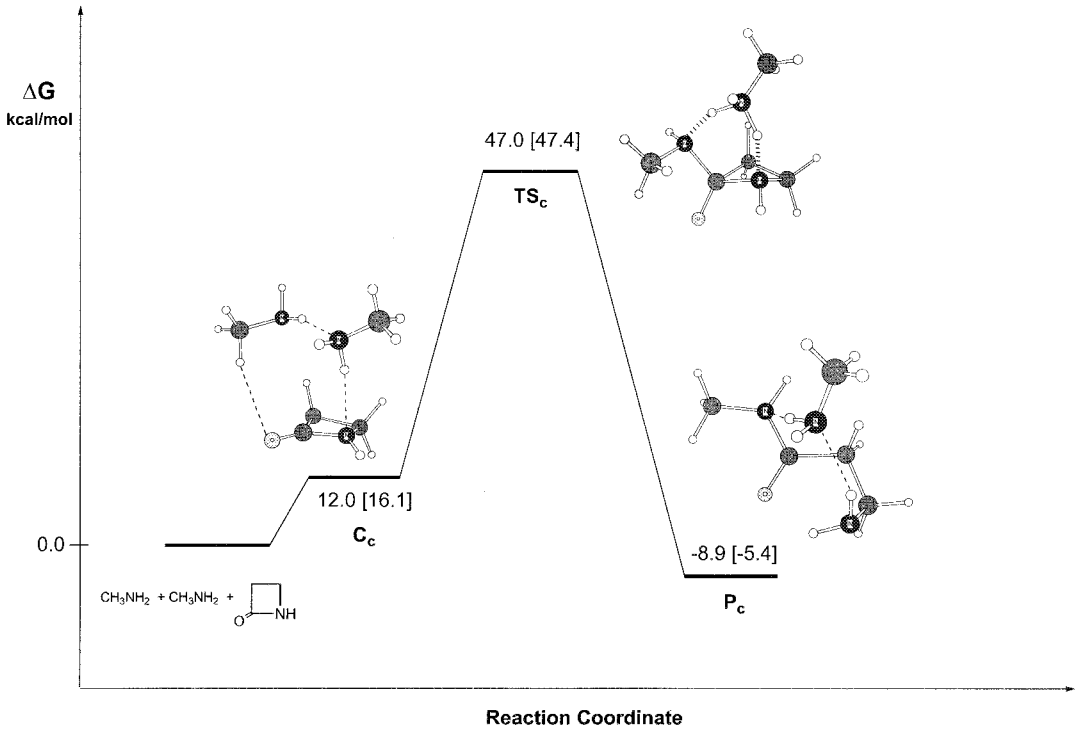


Figure 2. Gibbs energy profiles (kcal/mol) both in the gas-phase and in solution (in brackets) for the concerted reaction channel corresponding to the CH_3NH_2-assisted aminolysis reaction of 2-azetidinone.

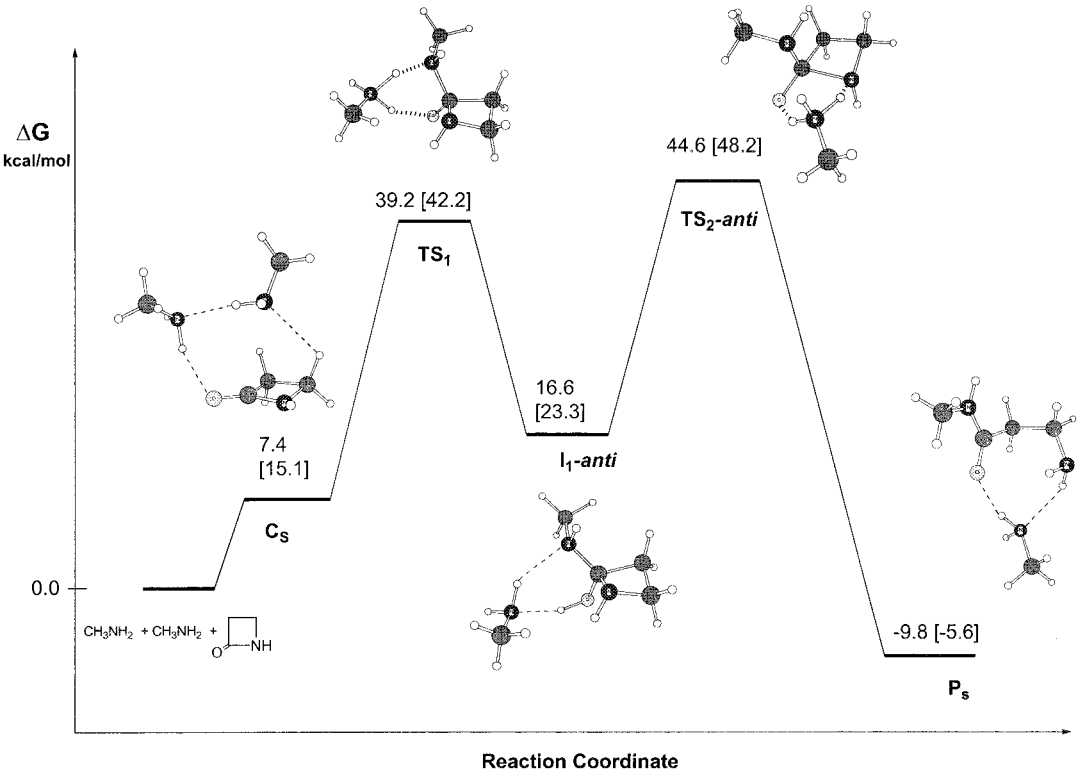


Figure 3. Gibbs energy profiles (kcal/mol) both in the gas phase and in solution (in brackets) for the antiperiplanar stepwise reaction channel corresponding to the CH_3NH_2-assisted aminolysis reaction of 2-azetidinone.

kcal/mol less stable than **I$_1$-*anti***. From **I$_2$-*syn***, a TS for the rearrangement of the intermolecular H-bonds between the catalytic methylamine molecule and the intermediate can be reached (**TS$_H$** in Figure 4). **TS$_H$** is connected with a third conformer **I$_3$-*syn*** that is 2.9 kcal/mol less stable than **I$_1$-*anti***. Thus, we see in Table 1 that the conversion **I$_1$-*anti*** → **I$_2$-*syn*** → **I$_3$-*syn*** occurs via two TSs with low energy barriers of 6.2 and 3.6 kcal/mol with respect to **I$_1$-*anti***, respectively.[26] The greater stability of **I$_1$-*anti*** is most likely due to the stereoelectronic repul-

(26) For the ammonolysis reaction profile, inclusion of thermal corrections results in a barrierless **I$_2$-*syn*** → **I$_3$-*syn*** conversion since the corresponding **TS$_H$** structure becomes more stable than **I$_2$-*syn*** by 0.1 and 1.6 kcal/mol in the gas phase and in solution, respectively.

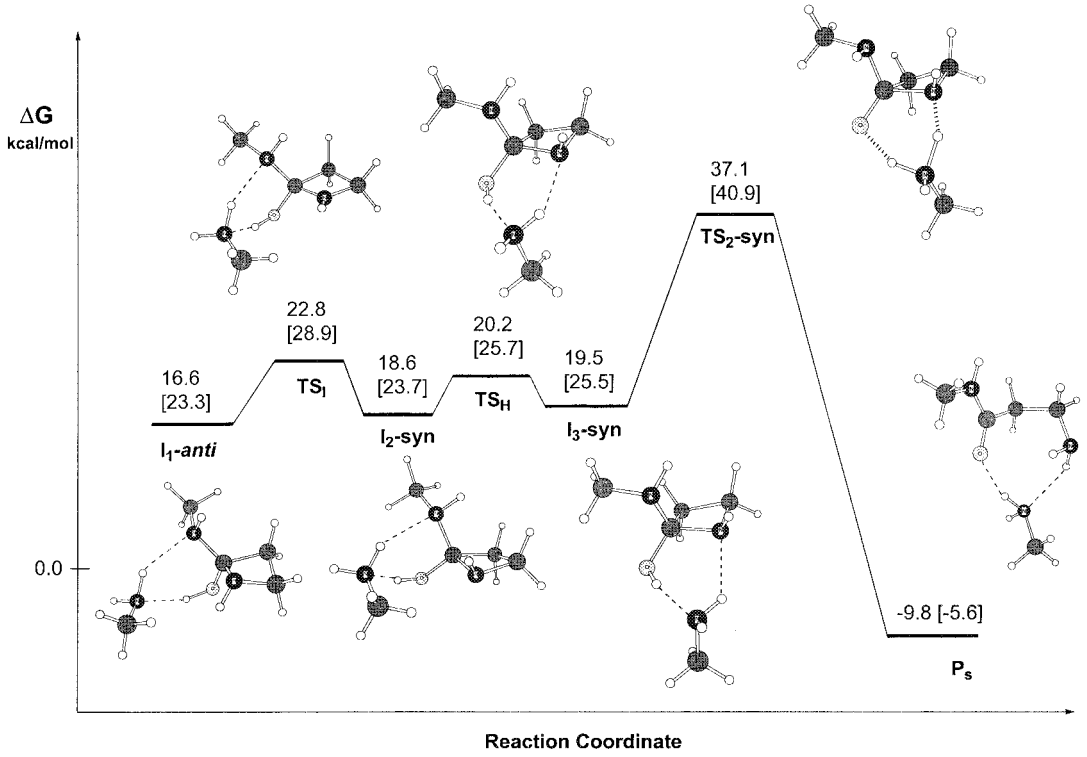


Figure 4. Gibbs energy profiles (kcal/mol) both in the gas phase and in solution (in brackets) for the evolution of the antiperiplanar intermediate through the synperiplanar stepwise reaction channel corresponding to the CH_3NH_2-assisted aminolysis reaction of 2-azetidinone.

sion[27] associated with the synperiplanar orientation between the hydroxyl group and the lone pair of the endocyclic N atom in **I_2-*syn*** and **I_3-*syn***.

The CH_3NH_2 molecule in **I_3-*syn*** establishes OH···N and NH···N contacts that are particularly appropriated for catalyzing the cession of a H atom from the hydroxyl group to the amino group in the tetrahedral intermediate, thus facilitating the ring opening of **I_3-*syn*** through a synperiplanar TS (**TS_2-*syn*** in Figure 1). The geometry and transition vector of **TS_2-*syn*** are very similar to those of **TS_1** because both are TSs for the amine nucleophilic attack to an amide group with synperiplanar amine assisted H-shift (see Figure 1). The $\Delta G_{gas-phase}$ value of **TS_2-*syn*** amounts to 37.1 kcal/mol above reactants, i.e., 2.1 and 7.5 kcal/mol under **TS_1** and **TS_2-*anti*** (see Table 1). Comparing **TS_2-*syn*** with its counterpart TS in the thermal aminolysis process,[11] the presence of the catalyst is seen to reduce the energy barrier by 9.0 kcal/mol.

Comparison between the Concerted and Stepwise Gibbs Energy Profiles. The gas-phase Gibbs energy profiles shown in Figures 2−4 correspond to the three different mechanisms found in this work for the CH_3NH_2-assisted aminolysis of 2-azetidinones. The less favored mechanism is the concerted one. The two stepwise mechanisms have in common the first step (**C_s** → **TS_1** → **I_1-*anti***). The rate-determining step for the antiperiplanar stepwise mechanism is the cleavage of the β-lactamic ring (**TS_2-*anti***). The most favored mechanism is the synperiplanar stepwise one in which the rate-determining step is the formation of the **I_1-*anti*** intermediate (**TS_1**) with a Gibbs energy barrier of 39.2 kcal/mol.

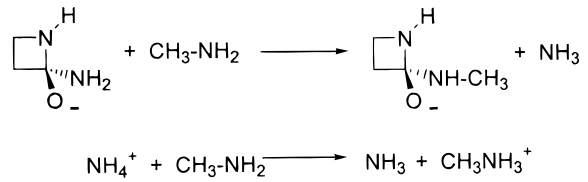
Inclusion of MP2/6-31G** SCRF solvation energies stabilizes preferentially the separate reactants, and therefore the energy barriers become greater in solution (see Figures 2−4). The electrostatic influence of solvent stabilizes the TS for the concerted mechanism only slightly less than the separate reactants given that, in contrast with the rest of the critical structures, **TS_C** presents a bare accumulation of charge in the O atom, capable of polarizing the solvent continuum to a larger extent (see the atomic charges and dipole moments in Figure 1). So in solution **TS_C** is 2.1 kcal/mol more stable than **TS_2-*anti***, and, consequently, the concerted mechanism is now more favorable than the antiperiplanar stepwise one. The rest of kinetic preferences are much less affected: **TS_1** remains more stable than **TS_C** by 5.2 and 1.2 kcal/mol above **TS_2-*syn***.

Analysis of the Transition Structures. As in the NH_3-assisted ammonolysis previously studied,[12] all the TSs resemble a $CH_3NH_3^+$ moiety interacting with 1,1-methylamino alcoholate anions. In effect, **TS_c, TS_1, TS_2-*anti***, and **TS_2-*syn*** present C−N single bonds between the nucleophilic amine molecule and the carbonylic C atom in 2-azetidinone practically formed, endocyclic C−N bonds barely opened, and the two H atoms involved in the proton transfer preferentially bonded to the catalytic N atom.

B3LYP/6-31G** configurational analyses were carried out assuming two different fragment partitions. The coefficient of the zero configuration *AB*, in both **TS_c** and **TS_1**, has a much greater value ($C_{AB} \approx 0.64$) when A = $CH_3NH_3^+$ and B = 1,1-methylaminoalcohoxy anion than in the case of assuming an A = $(CH_3NH_2)_2$ and B = 2-azetidinone neutral partition ($C_{AB} \approx 0.39$). Similarly, the electronic structures of **TS_2-*anti*** and **TS_2-*syn*** are

(27) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983.

Scheme 4



dominated by the corresponding ionic partitions with zero configuration values of 0.67 and 0.64, respectively.

Effects of the Methyl Groups. A detailed comparison of the theoretical results obtained for the NH_3-assisted ammonolysis and CH_3NH_2-assisted aminolysis of 2-azetidinones may be useful to further understand the effects of substitution on a series of monoamines reacting with β-lactams.

At both MP2/6-31G** and B3LYP/6-31G** levels of theory, inspection of geometrical parameters for the aminolysis of 2-azetidinone and those corresponding to the ammonolysis process reveals a slight structural effect of methyl substitution in the TSs whereas practically nonsignificant differences are observed in the case of the prereactive complexes, intermediates, and products. With respect to their counterpart TSs for the ammonolysis process, the TSs in Figure 1 manifest slight changes of the reactive bonds (±0.01 Å) as a consequence of the enhanced nucleophilicity and basicity of methylamine with respect to those of ammonia.

Concerning the thermodynamic effects, we note that the gas-phase Gibbs reaction energies for the $(CH_3NH_2)_2$ + 2-azetidinone aminolysis process are stabilized with respect to those for ammonolysis. Thus, the product complexes $\mathbf{P_C}$ and $\mathbf{P_S}$ are 6.3 and 6.5 kcal/mol more stable than the corresponding product complexes between 3-aminopropanamide and ammonia while the tetrahedral intermediates are stabilized by around 5 kcal/mol (see Table 1).

Interestingly, our calculations predict that the transition states achieve an important energetic stabilization upon methyl substitution. The $\Delta G_{gas-phase}$ values for $\mathbf{TS_C}$ and $\mathbf{TS_1}$ are 9.6 and 9.8 kcal/mol below their respective analogues in the ammonolysis reaction while $\mathbf{TS_2}$-***anti*** and $\mathbf{TS_2}$-***syn*** are stabilized to a lesser extent by 7.4 and 7.0 kcal/mol, respectively (see Table 1).

The ionic picture of the TSs accounts well for the kinetic effects of the methyl groups. On one hand, we calculated the B3LYP/6-31G** interaction energies between the ionic moieties at the main TSs for both the ammonolysis and aminolysis processes. Since the methyl group partially delocalizes the positive charge in the catalyst, the interaction energies between ionic moieties at $\mathbf{TS_c}$, $\mathbf{TS_1}$, $\mathbf{TS_2}$-***anti***, and $\mathbf{TS_2}$-***syn*** for the aminolysis process are, respectively, 13.8, 18.5, 9.9, and 17.3 kcal/mol lower in absolute value than those for the ammonolysis. On the other hand, we calculated the isodesmic B3LYP/6-31G** reaction energies for the processes in Scheme 4 using the B3LYP/6-31G** molecular geometry each charged moiety has in the corresponding TSs for the aminolysis and ammonolysis reactions.

According to the isodesmic energies, the 1,1-aminoalcoholate moieties are stabilized upon methyl substitution by 4.4, 5.6, 3.6, and 3.8 kcal/mol at $\mathbf{TS_c}$, $\mathbf{TS_1}$, $\mathbf{TS_2}$-***anti***, and $\mathbf{TS_2}$-***syn***, respectively**.** Similarly, the stabilization achieved by the catalytic $CH_3NH_3^+$ fragments at $\mathbf{TS_c}$, $\mathbf{TS_1}$, $\mathbf{TS_2}$-***anti***, and $\mathbf{TS_2}$-***syn*** amounts to 11.6, 16.9, 9.0, and 14.8 kcal/mol. These figures clearly show that the methyl kinetic effects stem from the intrinsic stabilization of the 1,1-aminoalcoholate moiety and, especially, the catalytic $CH_3NH_3^+$ one. This effect of the methyl groups compensates the lowering of the interaction between the ionic moieties. Ongoing from weak to strong basic monoamines, the preferential stabilization of $\mathbf{TS_C}$ and $\mathbf{TS_1}$ would be reinforced.

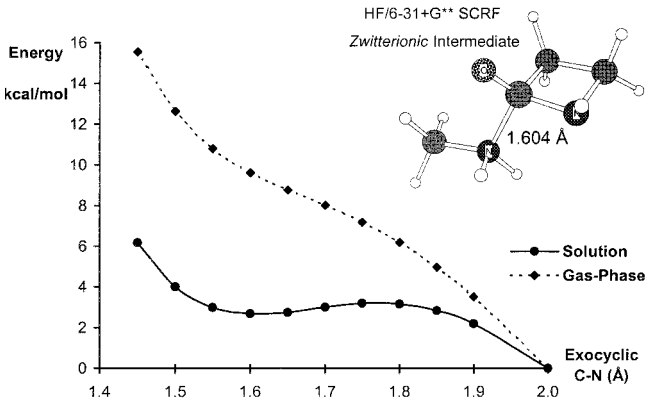


Figure 5. HF/6-31+G**energy profiles (kcal/mol) both in the gas phase and in solution for the formation of *zwitterionic* structures in the reaction between 2-azetidinone and methylamine.

Zwitterionic vs Neutral Tetrahedral Intermediates. The Gibbs energy profiles in Figures 3 and 4 describe stepwise reaction mechanisms for the aminolysis of 2-azetidinone assisted by one CH_3NH_2 molecule, which acts as a bifunctional catalyst.[21b] This catalytic action of amines leads to the formation of neutral tetrahedral intermediates during aminolysis or ammonolysis of 2-azetidinone. This is in contrast with previous assumptions of a stepwise mechanism involving the formation of zwitterionic tetrahedral intermediates.[3a−b] The nonlinear dependence on hydroxide concentration of the rate of the hydroxide-catalyzed aminolysis of benzylpenicillin is the main experimental evidence in favor of a stepwise mechanism.[4] However, the hydroxide-catalyzed process may well pertain to other reaction mechanisms not comparable with those discussed in this work.

To investigate the relative stability of zwitterionic intermediates in the reaction between methylamine and 2-azetidinone, we carried out HF/6-31+G** reaction coordinate calculations both in the gas phase and in solution by varying the corresponding C−N distance between the 2-azetidinone and methylamine reactants. Figure 5 represents the resultant energy profiles as well as the structure of a zwitterionic intermediate located on the HF/6-31+G** PES in solution. From data in Figure 5, we see clearly that, as expected, solvent induces the appearance of a well in the energy profile corresponding to a zwitterionic intermediate, whereas no critical structure is found in the gas-phase reaction coordinate. However, the solvent stabilization of the zwitterionic structure seems insufficient to support a mechanistic role of these intermediates in the aminolysis of β-lactams. According to HF/6-31+G** calculations, only 0.5 kcal/mol are required to dissociate the zwitterionic intermediate into separate reactants through a TS with a C−N distance of 1.772 Å. When including ZPVE corrections, this TS for fragmentation disappears, becoming 0.4 kcal/mol more stable than the zwitterionic intermediate. We conclude that, even in strongly polar media, 1,1-methy-

lammonium alcoholate zwitterions, like that shown in Figure 5, would be very unstable intermediate species with a very short mean life before fragmentation into reactants. Therefore, the formation of an encounter complex between the zwitterionic intermediate and a basic catalyst and its subsequent rupture to products would be very unlikely events.

Comparison with Experiment. For the uncatalyzed and amine-catalyzed reaction of monoamines with benzylpenicillin and other β-lactams in aqueous solutions, the structure of the rate-determining TS has been experimentally characterized from the corresponding Brønsted β values close to unity,[4,6−7] thus indicating the presence of a positively charged amine molecule at the TS. Indeed, these are the experimental facts with which our theoretical results on the amine-assisted aminolysis of 2-azetidinone should be compared. The formal partitioning of all the TSs into two interacting ionic moieties ($CH_3NH_3^+$···amino alcoholate anion) is in full agreement with the experimental Brønsted linear plots. Moreover, our calculations give more information showing that these Brønsted linear plots are compatible with both the concerted and nonconcerted routes for the aminolysis of β-lactams, the positive charge being located on the conjugate-acid of the catalytic amine molecule. Of course, theory could be useful to further determine the concerted or stepwise character of the most favored mechanism, complementing thus experimental studies.

For monocyclic β-lactams, such as 1-*p*-nitrophenylazetidin-2-one **3** studied experimentally,[6] predictions based on the Gibbs energy profiles corresponding to the aminolysis of 2-azetidinone should be quite reliable. From Figures 2−4, it is clear that the synperiplanar stepwise mechanism through the N-inversion of tetrahedral intermediates is the most favored one. Along this pathway, the TSs for the formation and rupture of the intermediates, $\mathbf{TS_1}$ and $\mathbf{TS_2}$-***syn***, have a similar geometry and an activation energy. These TSs are interconnected through several tetrahedral intermediates 16−19 kcal/mol less stable than reactants in terms of ΔG, which can be in rapid interconversion through H-bond rearrangement and N-inversion processes with low energy barriers of around 4−6 kcal/mol. From the magnitude of the resultant ΔG difference between $\mathbf{TS_1}$ and $\mathbf{TS_C}$, 7.8 and 5.2 kcal/mol in the gas phase and in solution, respectively, it is reasonable to expect that for compounds such as 1-*p*-nitrophenylazetidin-2-one the kinetic preference for the stepwise mechanism observed for 2-azetidinone would hold. Similarly, more basic amines would increase in general the rate of the process without changing the kinetic preference for the stepwise mechanism.

Experimental results have shown that the initial nucleophilic attack occurs toward the less hindered face of bicyclic β-lactams.[3a,b] Therefore, the formation of tetrahedral intermediates would lead to an antiperiplanar orientation between the hydroxyl group and the lone pair of the pyramidalized N-atom in the β-lactam ring. Clearly, the N-inversion process would be largely impeded in such bicyclic systems, discarding thus the synperiplanar rupture of the β-lactam ring. According to our calculations for the aminolysis of 2-azetidinone, the concerted reaction is slightly favored in solution with respect to the antiperiplanar rupture of the tetrahedral intermediate. These results may suggest that a concerted mechanism could be the most favorable one for the aminolysis of bicyclic β-lactams. Nevertheless, the difference between the energy barriers of the rate-limiting steps for the concerted and stepwise mechanisms is small and the preference for one or the other reaction channel could be determined by substituent effects, molecular environment, or other factors.

Conclusions

High-level theoretical calculations including the electrostatic effect of solvent on the reaction of 2-azetidinone with the methylamine dimer via neutral mechanisms predict that the reaction proceeds more favorably in a stepwise manner through several tetrahedral intermediates that are less stable than reactants and the prereactive complex. The formation of a first antiperiplanar intermediate constitutes the rate-determining step of the process with an activation energy in solution of 42.2 kcal/mol. Through a low energy barrier inversion process, this intermediate isomerizes to a synperiplanar one that, in turn, connects with a TS for the ring-opening and syn H-transfer process with an activation energy of 40.9 kcal/mol in solution. The Gibbs reaction energy to give *N*-methyl-3-aminopropanamide is around −5 kcal/mol with respect to separate reactants. Other possible reaction pathways, i.e., the concerted mechanism and the direct cleavage of the antiperiplanar intermediate, present larger activation $\Delta G_{solution}$ barriers of 47.4 and 48.2 kcal/mol, respectively. Interestingly, reaction coordinate calculations indicate that zwitterionic structures in solution would be extremely unstable intermediates to play a significant kinetic role in the process.

As in the case of the ammonolysis process, a formal molecular partitioning of all the TSs distinguishes a CH_3-NH_3^+ moiety interacting with 1,1-methylamino alcoholate anions. This fact is useful to rationalize the experimental linear Brønsted plots on the pK_a of monoamines for the aminolysis of both monocyclic and bicyclic β-lactams. A comparative analysis between the aminolysis and ammonolysis processes of 2-azetidinone renders insight into the kinetic influence of substitution in monoamines. Thus, the methyl-induced stabilization of about 7−10 kcal/mol is well explained in terms of the intrinsic stabilization achieved by the corresponding 1,1-amino alcoholate and $CH_3NH_3^+$ moieties at the TSs due to inductive effect of the methyl groups, especially at the catalytic moiety.

For monocyclic β-lactams, a clear kinetic preference for the stepwise route can be expected from the Gibbs energy profile obtained for 2-azetidinone. For more rigid systems, as benzylpenicillin, the N-inversion process is largely impeded and the kinetic preference for the concerted or the nonconcerted antiperiplanar mechanism is not so accentuated. In this case, the effect of environment and substitution in β-lactams could be decisive.

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Supporting Information Available: Figures showing the molecular geometries for all the structures except TSs in Figure 1. Figures representing the critical structures located along the synperiplanar stepwise reaction profile for the NH_3-assisted ammonolysis reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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