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Theoretical Calculations of β -Lactam Antibiotics. III. AM1, MNDO, and MINDO/3 Calculations of Hydrolysis of β -Lactam Compound (Azetidin-2-One Ring)

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Semiempirical AM1, MINDO/3, and MNDO methods have been used in the study of the alkaline hydrolysis of β -lactam antibiotics through a base-catalyzed, acyl-cleavage, bimolecular mechanism. In this work, the hydroxyl ion has been chosen as nucleophilic agent and the azetidin-2-one ring like a model of β -lactam antibiotic. The MINDO/3 method does not predict correctly the energies of small rings. This, together with the fact that, like MNDO, it cannot detect the occurrence of hydrogen bonds, gives rise to uncertain estimates of energy barriers. The AM1 method can be considered the most suitable for studying the hydrolysis of β -lactam compounds.

INTRODUCTION

One of the major roots of bacterial resistance to β -lactam antibiotics (penicillins, cephalosporins, and their analogs) is the presence of β -lactamases in cells, which hydrolyse β -lactams, thereby canceling their bactericidal action.

Many authors have suggested that the mechanism of enzyme hydrolysis is similar to that of alkaline hydrolysis.¹ In fact, this has been the subject of much experimental work on the acid, basic, and enzymatic hydrolysis of β -lactam antibiotics.²

On the other hand, theoretical studies on β -lactams have so far focused on conformational analyses aimed at correlating such molecular parameters as the pyramidal character of the β -lactam nitrogen, the C—N distance, or the polarity of the double bond in the dihydrothiazine ring of cephalosporins with their chemical (basic hydrolysis rate constant) and biological reactivity (MIC).³ Few reports, however, have so far been published on the hydrolysis of β -lactams.⁴

In this work, we performed a thorough analysis of the alkaline hydrolysis of β -lactams by using the semiempirical AM1, MINDO/3, and MNDO methods. Because of the high complexity of penicillin and cephalosporin molecules, in a first step we studied the β -lactam (azetidin-2-one) ring using hydroxyl ion as nucleophilic agent. The mechanism involved is of base-catalyzed, acyl cleavage,

bimolecular (B_{AC2}) type and includes a nucleophilic attack on the carbonyl group followed by cleavage of the C—N bond.

METHODOLOGY

All computations were carried out using the semiempirical theoretical calculation MINDO/3,⁵ MNDO,⁶ and AM1 methods,⁷ which were implemented in the form of a locally modified version⁸ of the package MOPAC.⁹ The software was run on VAX 8820 and 9000 computers. The reaction mechanism was found to be of B_{AC2} type (i.e., base-catalyzed, acyl-cleavage, bimolecular).

The initial geometry of the β -lactam model was the most stable conformation obtained with each semiempirical method. Hydroxyl ion was initially assumed to be in its singlet state and placed at a distance of 3 Å on the upper or lower side and perpendicular to the plane containing the β -lactam ring.

All calculations throughout the reaction development were derived from a single-determinant wave function (RHF) with no configuration interaction, and were based on the Davidon-Fletcher-Powell (DFP) optimization algorithm.¹⁰

As a further control test for diradical character, single-point calculations were performed with the UHF formalism¹¹ on selected RHF-calculated transition states, essentially zero expectation values for the $\langle S^2 \rangle$ operator and enthalpies of formation

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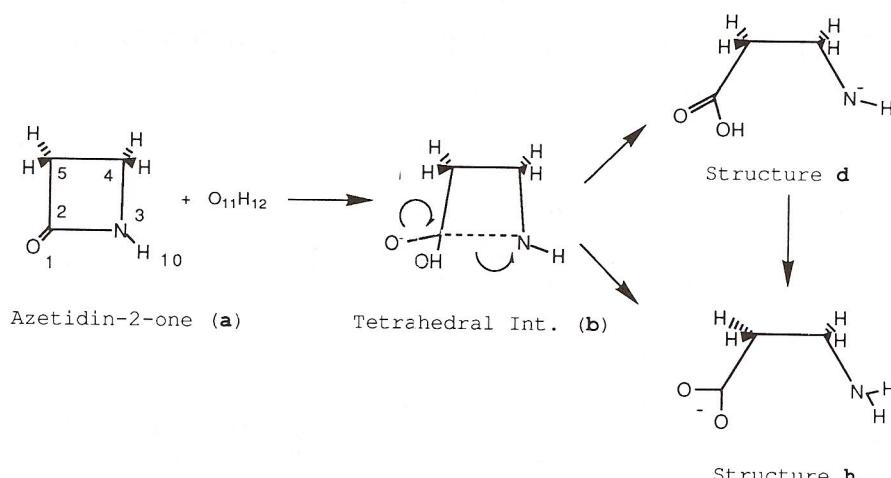


Figure 1. β -lactam (azetidin-2-one) + OH^- reaction. $\text{B}_{\text{AC}2}$ mechanism. Numeration of the β -lactam ring.

essentially equal to the RHF enthalpies recorded in every case.

The geometries for stationary points were redetermined by minimizing the energy with respect to all geometric parameters using the DFP algorithm with the keyword PRECISE to diminish the convergence criterion by a factor of 100.

The geometry and energy of the transition states detected along the reaction coordinate were refined by minimizing the gradient norm using the NLLSQ algorithm.¹²

Transition states were characterized by the fact that the matrix of the second derivative of the energy with respect to the position (i.e., the Hessian matrix) has one and only one negative eigenvalue. This test was applied to every case.

RESULTS

As noted earlier, the basic hydrolysis of β -lactam compounds takes place via a $\text{B}_{\text{AC}2}$ mechanism that involves a nucleophilic attack on the amide carbon of the β -lactam ring. This mechanism is quite commonplace for amides¹³ and, as can be seen in Figure 1, the nucleophilic attack gives rise to a tetrahedral intermediate that is cleft at the C_2-N_3 bond to two potential products in which the hydrogen is bound to oxygen (d) or nitrogen (h).

The reaction mechanism was studied by using three semiempirical methods. Thus, the MINDO/3 method is the most suitable for the determination of geometric parameters (both of penicillins¹⁴ and of cephalosporins¹⁵); hence, the bond distances and angles and dihedral angle of the β -lactam ring (the central core of penicillins and cephalosporins) provided by the MINDO/3 method are also those fitting the experimental and *ab initio* results best.

On the other hand, the MNDO and AM1 methods predict a C_2-N_3 bond distance that is slightly longer than the experimental values.^{14,15} The length of this bond is related to the pyramidal character of the β -lactam nitrogen: The longer it is (as predicted by the MNDO and AM1 methods 1.43 vs. 1.372 Å for the MINDO/3 method), the higher the pyramidal character of the nitrogen and the lower the conjugation of the $\text{O}=\text{C}-\text{N}$ system. In addition, the differences in the energies provided by the three methods are occasionally quite large as a result of the different approximations used for optimization. Reportedly, the MINDO/3 method overestimates the energies of cyclic compounds, particularly of small rings. On the other hand, the AM1 method is the only of the three that is capable of detecting the occurrence of hydrogen bonding.

MINDO/3

Figure 2 shows the three different reaction profiles provided by the MINDO/3, MNDO, and AM1 methods, while Table I lists the major geometric and energy parameters of the different transition states and energy minima obtained by the three semiempirical methods. Figure 3 depicts the structures corresponding to the different intermediate and final states of the reaction pathway.

This method cannot predict the pyramidal character of the nitrogen atom in the four-member ring, so the initial structure (a) has its H_{10} atom in a planar arrangement with respect to the β -lactam ring. This conformation is consistent with that reported by Sedano et al.,¹⁶ who used *ab initio* calculations at the STO-3G, 3-21G, and 6-31G level and arrived at the conclusion that the conformation in which nitrogen occurred in a planar arrangement was more stable than that in which the

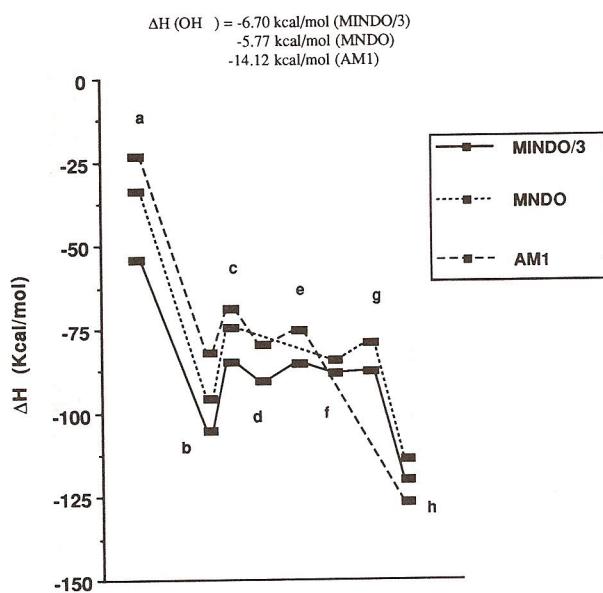


Figure 2. Schematic representation of the reaction profile provided by the MINDO/3, MNDO, and AM1 methods. See also Table I.

hydrogen lay above the β -lactam plane, with an inversion barrier of 1.66 kcal/mol with respect to the planar conformer. The geometric values obtained for structure **a** are fully coincident with those reported by Sedano et al.¹⁶ and Petrongolo et al.⁴ from SCF-MO-LCAO *ab initio* calculations at the 6-31G and STO-3G levels, respectively. The planarity of the azetidin-2-one ring is maintained even in the presence of bulky substituents, as confirmed by the X-ray analysis of 1-(*p*-chlorophenyl)-3-isopropyl-4-phenyl-azetidin-2-one.¹⁷ Accordingly, the nucleophilic attack by the hydroxyl ion yields the same result whether it takes place on the upper (β) or lower (α) side.

Initially, the hydroxyl ion approaches the C₂ atom from an infinite distance perpendicularly to the plane of the β -lactam ring. According to theoretical and X-ray studies,¹⁸⁻²⁴ the nucleophile must approach the carbon atom along a line perpendicular to the amide plane. However, the initial position of the nucleophile is not critical since, as noted by Lipscomb et al.^{22,24} there is a fairly wide conical well on the potential energy surface inviting nucleophilic attack from a direction more or less perpendicular to the amide plane of the carbonyl carbon. The approach is hindered by no energy barrier, as in gas-phase nucleophile attacks,²⁵ and the energy always decreases up to the formation of the tetrahedral intermediate (**b**), which is much more stable (51.2 kcal/mol) than the initial structure. According to Dewar and Storch,²⁶ the lack of an activation energy is a result of the occurrence of no hydration or dehydration process in the gas phase.

The formation of the C₂—O₁₁ bond endows the

carbon with tetrahedral character and consequently displaces the carbonyl oxygen to the β side of the ring. This structure preserves the planarity of the β -lactam ring (see the value of the C₂N₃—C₄C₅ dihedral angle in Table I), whereas the C₂—N₃ bond length is 0.1 Å longer. The tetrahedral intermediate is structurally similar to that reported by Alagona et al.²⁰ for the basic hydrolysis of formamide and by Petrongolo et al.⁴ for that of the β -lactam ring. However, the C₂—N₃ bond distance is somewhat shorter than those obtained by them.

The intermediate can evolve in two different ways:

1. With cleavage of the C—N bond and opening of the β -lactam ring to yield product **d** and subsequent transfer of hydrogen to the β -lactam nitrogen (**h**).
2. With opening of the β -lactam ring and simultaneous transfer of the hydrogen to yield product **h**.

The former pathway involves a transition state (**c**) characterized by the opening of the β -lactam ring, which is reflected both, in an increased C₂—N₃ length and in widened N₃C₄C₅ and C₄C₅C₂ angles, despite which the planarity of the β -lactam ring is preserved (C₂N₃—C₄C₅ dihedral angle = -1.86°). This transition state evolves to a ground state (**d**) characterized by the upper opening of the ring and a decreased ring planarity (C₂N₃—C₄C₅ dihedral angle = -20.8°). This product is less stable in a gas state than is the tetrahedral intermediate.

Compound **d** evolves with transfer of the hydrogen to the nitrogen atom to yield product **h**. However, a direct transfer gives rise to a reaction profile as a function of the H₁₂—N₃ with a discontinuity at ca. 2.6 Å. An analysis of structure **d** reveals that the hydrogen to be transferred is rather distant from the nitrogen atom (4.086 Å) and in an inappropriate orientation, so the transfer process must take place in two steps involving a turn and the transfer proper. We investigated two possible turns, namely, that of the acid group (about the C₂—C₅ bond) and that of the hydrogen in this group (about the C₂—O₁₁ bond).

The variation of the energy as a function of the H₁₂O₁₁—C₂O₁ dihedral angle shows a global minimum (**d**), a local minimum (**f**), and two maxima (**e** and **e'**). These structures were optimized according to their nature of maximum and minimum, and yielded the geometric parameters and energy values listed in Table I. The dihedral angle changes from -7.49° (**d**) through a maximum (**e**) to a minimum (**f**) of about 180°. Structure **f**, with an H₁₂—N₃ bond distance of 2.812 Å, transfers the hydrogen to the β -lactam nitrogen via a maximum (**g**) to the final product (**h**).

Table I. Optimized energetic and geometric parameters (bond distance, bond angle, and dihedral angle) for the different structures of the pathway reaction by the MNDO/3, MNDO, and AM1 methods.

MNDO/3	Structure						ϵ'	\mathbf{d}'
	a	b	c	d	e	f		
$d(C_2-N_3)$	1.372	1.482	2.137	3.004	2.987	3.094	3.086	2.133
$d(O_{11}-C_2)$	—	1.413	1.355	1.346	1.367	1.350	1.340	1.360
$d(H_{12}-N_3)$	—	2.971	3.263	4.086	2.992	2.812	2.039	1.029
$C_4C_5C_2$	87.3	90.1	105.8	120.7	120.4	122.5	123.1	90.2
$C_2N_3-C_4C_6$	0.0	0.1	-1.9	-20.8	-20.0	-21.7	-27.1	1.0
ΔH (kcal/mol)	-47.37	-105.33	-85.06	-90.81	-85.44	-88.24	-87.88	-2.9
						-120.16	-101.82	-81.79
							-82.37	-90.65

MNDO	Structure						\mathbf{m}_1	\mathbf{c}_1
	a	b	c	d	e	f		
$d(C_2-N_3)$	1.435	1.555	2.223	2.898	2.780	3.042	2.831	3.207
$d(O_{11}-C_2)$	—	1.554	2.188	2.884	—	—	—	1.559
$d(H_{12}-N_3)$	—	1.416	1.374	1.365	1.376	1.374	1.320	1.262
—	—	1.427	1.378	1.366	—	—	—	1.417
$C_4C_5C_2$	87.3	—	—	3.895	3.088	2.268	1.004	1.009
$C_2N_3-C_4C_6$	-6.2	88.2	102.6	113.7	112.6	116.3	114.6	115.3
		88.3	102.5	115.2	-24.2	-19.6	-27.1	-35.6
ΔH (kcal/mol)	-28.15	4.7	7.2	21.5	-79.11	-78.24	-84.45	-79.30
		-96.08	-74.73	-79.11	-78.91	-78.77	-	-113.83

AM1	Structure						\mathbf{m}_1	\mathbf{c}_1
	a	b	c	d	e	f		
$d(C_2-N_3)$	1.411	1.555	2.112	3.232	2.952	3.046	1.560	2.067
$d(O_{11}-C_2)$	—	1.551	2.097	3.144	—	—	—	—
$d(H_{12}-N_3)$	—	1.433	1.386	1.376	1.391	1.268	1.431	1.392
—	—	1.450	1.393	1.375	—	4.282	2.879	1.005
$C_4C_5C_2$	86.0	—	—	4.156	4.156	107.9	112.3	2.495
$C_2N_3-C_4C_6$	-4.4	87.9	97.9	110.5	110.5	107.9	88.0	97.8
		-4.1	-1.2	-33.8	-33.8	-26.4	-28.1	-4.6
ΔH (kcal/mol)	-9.06	-2.7	2.0	31.2	31.2	-75.69	-126.58	-1.3
		-82.04	-68.85	-79.87	-79.87	-79.52	-78.17	-66.92

Numbering and nominating is consistent with the text. Bond distance are in Å and bond and dihedral angles in °. Energy in kcal/mol. In MNDO and AM1 methods, the upper value corresponds to the intermediate α and the lower to the intermediate β .

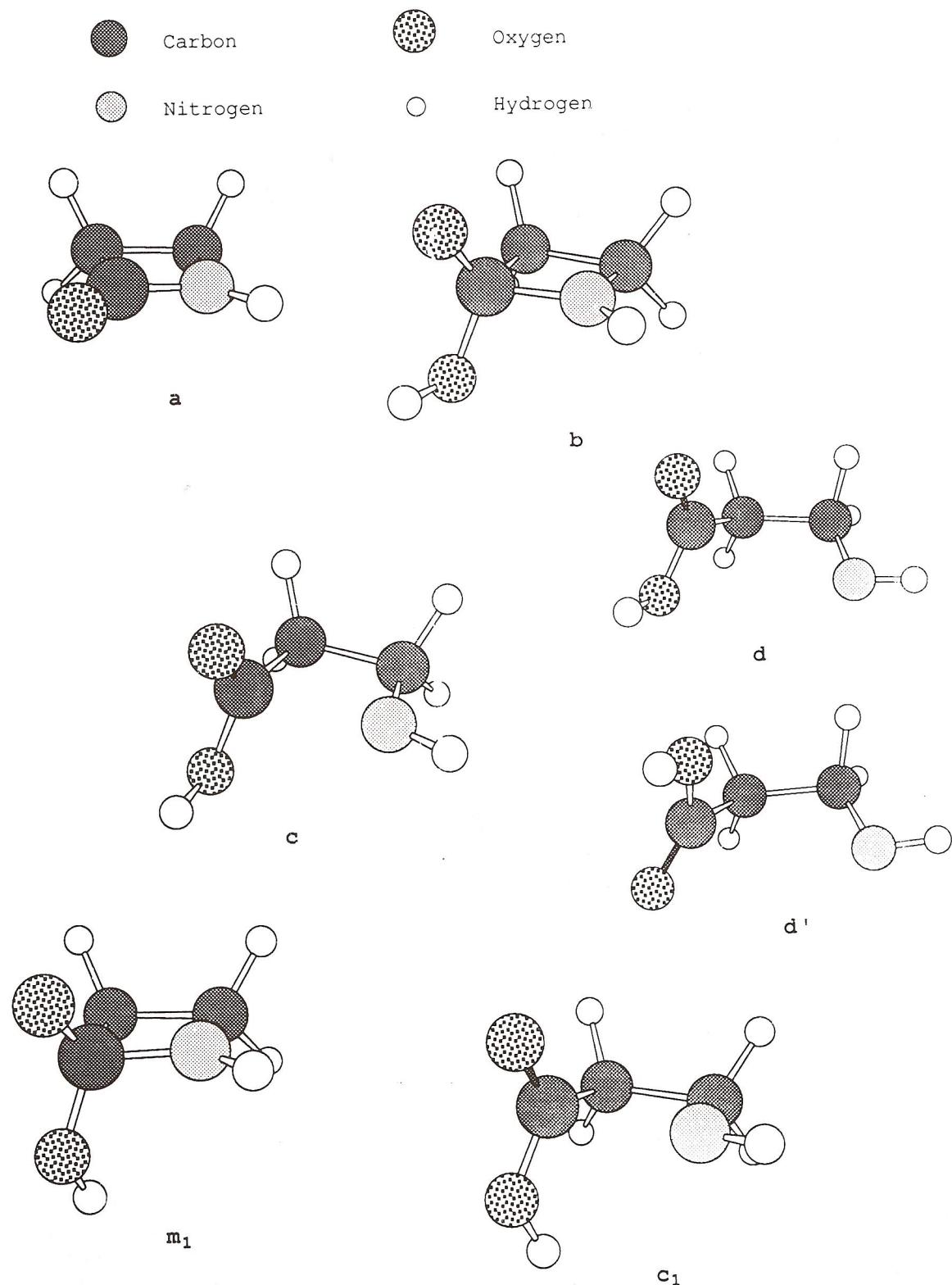
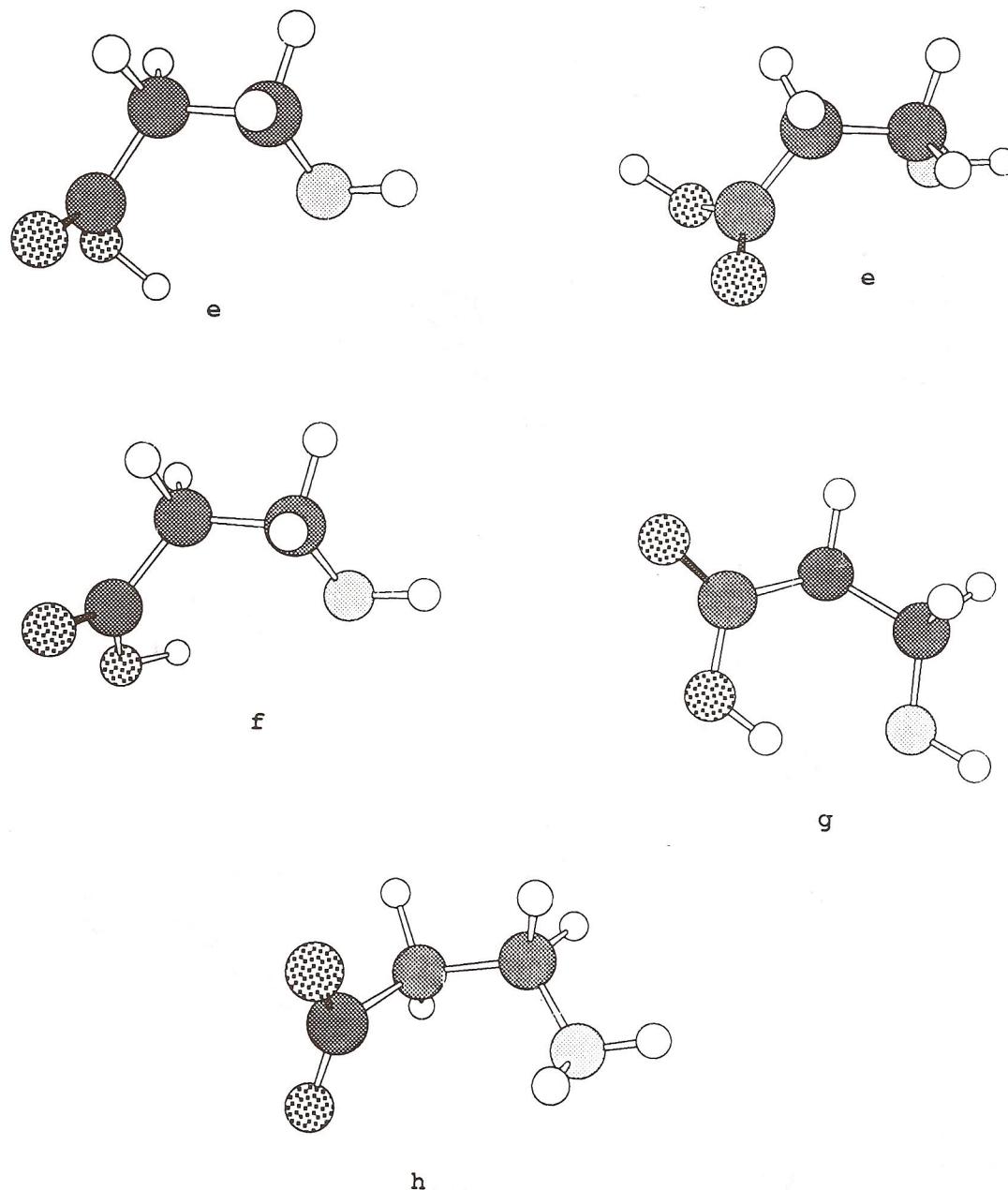


Figure 3. Structures corresponding to the different intermediate and final states of the reaction pathway by MINDO/3 method.

The other possible turn involved in the hydrogen transfer is started with the rotation of the acid group (C_2-C_5) to product d. There are two possible nearly isoenergetic structures with a $O_1C_2-C_5C_4$

dihedral angle of 80° (d) and -120° (d'), respectively. In this latter structure, the hydrogen atom is still at too long a distance (4.193 Å) and inappropriately oriented with respect to the nitrogen

**Figure 3.** (continued)

atom, so it cannot be taken as the starting point for the direct transfer of hydrogen either. The reaction pathway followed in passing from structure **d** to **f** was a turn about the $O_1C_2-C_5C_4$ angle followed by another about the $H_{12}O_{11}-C_2O_1$ angle from ca. 0–100°. This pathway leads to a maximum with an energy of 82.10 kcal/mol, which coincides with the highest-energy maximum of the rotation about the $O_{11}-C_2$ bond in compound **d** (**e**). In summary, the evolution of compound **d** by rotation about the C_2-O_{11} bond takes place via one of two possible maxima (**e** and **e'**) to point **f** and then to the final product (**h**). These processes involve an energy barrier close to 5.3 kcal/mol in the former

case and 8.4 kcal/mol in the latter, which is thus less likely to occur than the former.

The other possible evolution of the tetrahedral intermediate calls for a conformational change. As noted earlier, the H_{12} atom is at a long distance from the nitrogen and inappropriately oriented for the transfer, so a rotation about the $H_{12}O_{11}-C_2O_1$ dihedral angle from –17 to 173.3° (**m₁**) is required; the energy barrier and difference between the two conformations are 4 and 3.5 kcal/mol, respectively. On the basis of this structure (**m₁**), we studied the hydrogen transfer and the cleavage of the C–N bond simultaneously. Figure 4 (a and b) shows the potential surface obtained as a function

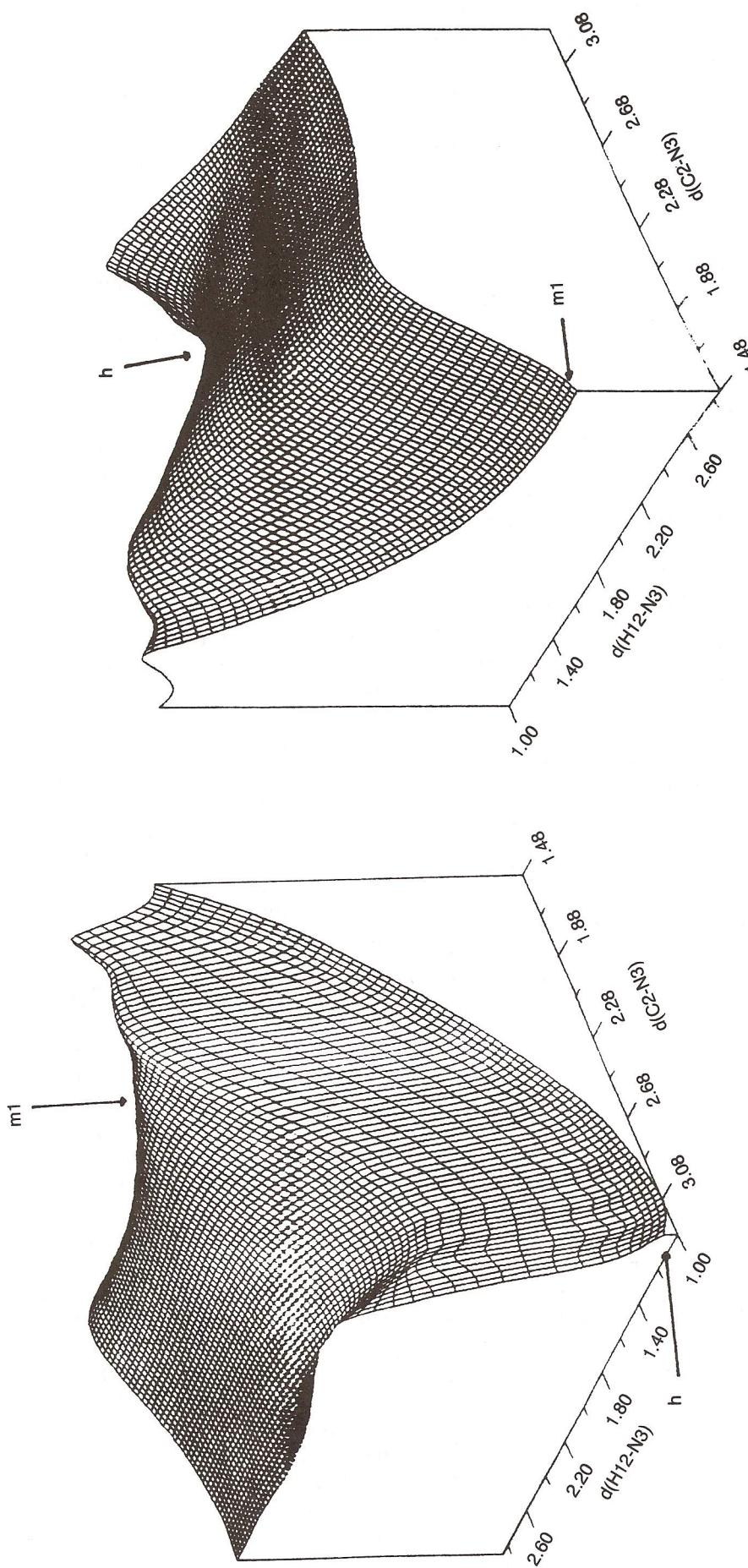


Figure 4. Potential energy surface MINDO/3 method. Transfer of the hydrogen atom from oxygen (m_1) to nitrogen (h).

of the two most significant distances, viz. those of the C_2-N_3 and $H_{12}-N_3$ bonds. The procedure used for this purpose involves creating a series of intermediate structures by changing the distance of the C_2-N_3 bond between 1.48 and 3.25 Å and that of the $H_{12}-N_3$ bond from 2.85 to 1.00 Å, and optimizing all other geometric parameters. As can be clearly seen, structure **m₁** evolves to product **h** via a maximum (**c₁**). An analysis of the structure corresponding to this point reveals that the C—N distance has increased substantially with respect to the minimum distance in the tetrahedral intermediate, while the H_{12} — N_3 distance is still rather long, so the transfer has not yet started at this point. The distance of the O_{11} — H_{12} bond remains constant at ca. 0.95 Å, so the variation in the N_3 — H_{12} bond distance can only be ascribed to a turn of ca. 15° about the acid group, accompanied by cleavage of the C—N bond. In addition, this maximum is structurally analogous, except for the conformation of H_{12} , with that obtained for pathway (1), **c**, and is similar to that reported by Alagona et al. for the hydrolysis of formamide.²⁰ These results, together with the fact that structure **c₁** is more energetic than **c** (see Table I), indicate that the tetrahedral intermediate tends to evolve with cleavage of the C—N bond and subsequent transfer of hydrogen.

The product with the hydrogen bound to the nitrogen atom (**h**) is much more stable than the other reaction products. This structure is characterized by a slight pyramidal character of the nitrogen resulting from cleavage of the C—N bond. The distances of the O_1 and O_{11} atoms to the hydrogens bound to nitrogen range between 3.44–4.70 Å, which excludes the occurrence of hydrogen bonds, consistent with the fact that MINDO/3 cannot detect this type of bond.

MNDO

Unlike MINDO/3, MNDO predicts some pyramidal character for the β-lactam nitrogen, so the nucleophilic attack on the α side (lower side, facing H_{10}) is not equivalent to the attack on the β side (upper side) of the β-lactam ring, which thus yield two different tetrahedral intermediates (**b_α** and **b_β**), both of which are highly stabilized (about 60 kcal/mol) with respect to the initial product (**a**). As can be seen in Table I, intermediate α is 2.5 kcal/mol more stable than intermediate β.

This tetrahedral intermediate features a C—N bond length of 1.555 Å, which is virtually coincident with those reported by Alagona et al.²⁰ and Petrongolo et al.⁴ for this structure. On the other hand, the pyramidal character of the nitrogen

atom is more marked than in the starting compound. The increase arises from decreased conjugation of the lone electron pair of nitrogen with the π molecular orbital of the carbonyl group.

As with the MINDO/3 method, the tetrahedral intermediate may evolve via two different pathways.

Contrary to MINDO/3 results, in the first pathway the system evolves to product **f** via a maximum (**c_α**, **c_β**) characterized by significant opening of the β-lactam ring. Structure **c_β**, resulting from the nucleophilic attack on the same side as H_{10} , features a higher energy than structure **c_α**, so the attack via the side opposite to H_{10} is more favorable.²⁷

Unlike MINDO/3, the MNDO method detects no intermediate structure with a lower energy than **f**. Energy calculations for structure **d** revealed it to be 5.3 kcal/mol less stable than **f**.

Once the hydrogen is oriented toward the β-lactam nitrogen [**f**, $d(H_{12}-N_3) = 2.268$ Å], the transfer takes place directly via a maximum of –79.30 kcal/mol (**g**) to the final product (**h**), which is much more stable than the tetrahedral intermediate. The structure **h** obtained by the MNDO method differs from that provided by MINDO/3 essentially in a greater planarity loss in the β-lactam ring (the $C_2N_3-C_4C_5$ dihedral angle varies from –60 to –25°, respectively) and in the pyramidal character of the β-lactam nitrogen. The turn about the C_4-C_5 bond leads to an extended conformation with an energy of –112.16 kcal/mol, i.e., slightly higher than that of product **h**, which is thus the most stable.

The second pathway involves a prior conformational change whereby the H_{12} atom takes a much more appropriate arrangement for the transfer. The turn about the C_2-O_{11} bond in the tetrahedral intermediate leads to a maximum with an energy barrier of ca. 3 kcal/mol to a minimum (**m₁**) with an $H_{12}O_{11}-C_2O_1$ dihedral angle of –151.4°. This structure is 2.9 kcal/mol less stable than the tetrahedral intermediate, yet it is the starting point for the hydrogen transfer.

By using the same procedure described in the former method, we obtained the potential surface as a function of the C_2-N_3 and $H_{12}-N_3$ bonds. This surface has a similar shape to that obtained by the MINDO/3 method. The surface maximum (**c₁**) corresponds to a structure with a C—N and an H—N distance of 2.167 and 2.463 Å, respectively, so the hydrogen transfer has not yet started at this point [$d(O_{11}-H_{12}) = 0.946$ Å], but the C—N bond has been cleaved to a substantial extent. The geometry and energy of this maximum are very similar to those of the maximum obtained via the other pathway (**c**).

AM1

The AM1 method optimizes a starting compound in which the H₁₀ atom is not in a planar arrangement with respect to the β -lactam ring. The nitrogen atom has a more marked pyramidal character than that provided by the MNDO method. As with MNDO, the nucleophilic attack varies depending on whether it takes place on side α or β . As can also be seen from Table I, again, structures **b**, **c**, and **d**, obtained by the nucleophilic attack of hydroxyl ion on the side opposite to H₁₀ (α), are more stable than those obtained by attack on side β . Figure 5 depicts the structures corresponding to the different intermediate and final states of the reaction pathway.

Structure **d** was analyzed in various respects including the rotation about the C₅—C₄ bond. As can be seen in Figure 6, there exists a conformer with a C₂C₅—C₄N₃ dihedral angle of ca. 180° with a lower energy than point **d**. In this structure, which is characterized by a zigzag C₂C₅—C₄N₃ chain, the hydrogen atom is at a long distance from the nitrogen, so direct evolution to product **h** is virtually impossible.

As with MINDO/3, the reaction profile for the direct transfer of the H₁₂ atom from the acid group to the nitrogen shows a discontinuity at an H₁₂—N₃ distance of 2.82 Å. The conversion of structure **d** into **h** requires the hydrogen atom to be transferred (H₁₂) to take the appropriate orientation, which can be achieved by two different turns: about the C₂—O₁₁ bond or about the acid group (rotation about the C₂—C₅ bond).

Compound **d** evolves by a turn about the C₂—O₁₁ via a maximum (**e**) to the final product **h** with an intervening transfer of the hydrogen to the β -lactam nitrogen. This is the only method that predicts the transfer directly for a given value of the H₁₂O₁₁—C₂O₁ dihedral angle, which must be related to the capability of AM1 to detect and even overestimate the occurrence of hydrogen bonds.

The other turn, a rotation about the acid group, leads to two minima with O₁C₂—C₅C₄ dihedral angles of 77.62 and -100°, respectively, and two maxima at ca. 180 and 0°. As with MINDO/3, the rotation about the acid group and subsequent transfer take place via a complex mechanism involving a maximum with an energy barrier of 6.5 kcal/mol, which is thus greater than the 4.2 kcal/mol obtained for the conversion of **d** into **e**.

Therefore, the turn about the C—O bond from structure **d**, followed by the hydrogen transfer, is again the more favorable pathway in terms of energy.

We also carried out a parallel study of the simultaneous transfer of the hydrogen atom, cleavage of the C—N bond, and opening of the β -lactam ring

from the tetrahedral intermediate (**b**). Again, such an intermediate much undergo a conformational change. The rotation about the C₂—O₁₁ bond in structure **b** evolved via a maximum at ca. -125°, with an energy barrier of 4.5 kcal/mol, to a minimum (**m**₁) that was 3.9 kcal/mol less stable than the intermediate itself.

From this structure, we determined the simultaneous evolution of the hydrogen transfer and the opening of the C—N bond. The potential surface as it happened in the MINDO/3 and MNDO shows that the system evolves via a maximum (**c**₁) with a C₂—N₃ and H₁₂—N₃ distance of 2.067 and 2.568 Å, respectively, to the final product **h**.

As with the corresponding structures obtained with MINDO/3 and MNDO, this maximum (**c**₁) is characterized by the fact that the hydrogen transfer has not yet started and by its structural similarity, except for the orientation of H₁₂, to the maximum obtained by following the other pathway, (**c**), but 1.9 kcal/mol less stable.

We finally studied the turns about the C—O and C₅—C₄ bonds in the final product (**h**), which provided a minimal-energy structure (**h**') with an energy of -122.94 kcal/mol for an O₁C₂—C₅C₄ dihedral angle of 127°. This energy difference with respect to point **h** can be ascribed to the occurrence of a hydrogen bond in structure **h** [d(O₁₁—H₁₀) = 2.23 Å], which cannot be formed by the other structure (**h**') and is only predicted by the AM1 method.

CONCLUSIONS

The reaction profiles provided by the three semiempirical methods (AM1, MNDO, and MINDO/3) used to study the alkaline hydrolysis of the azetidin-2-one ring via a B_{AC2} mechanism led to different results in relation both to the intermediates and to the energies involved in the process.

The MINDO/3 method maintains the *sp*² character of the β -lactam nitrogen throughout the reaction profile, particularly for the tetrahedral intermediate, which results in an underestimated C—N distance compared to those provided by MNDO and AM1.

The nucleophilic attack on side α (opposite H₁₀) is slightly favored over that on side β , thereby supporting the results reported by Boyd for the bicyclic system of penicillins.²⁷

As regards the hydrolysis of these compounds, all three methods predict that the transfer of hydrogen to the nitrogen atom to yield product **h** takes place only after the C—N bond has been cleaved to a substantial extent, which is consistent with the findings of Maraver et al. for the hydrolysis of esters.²⁸

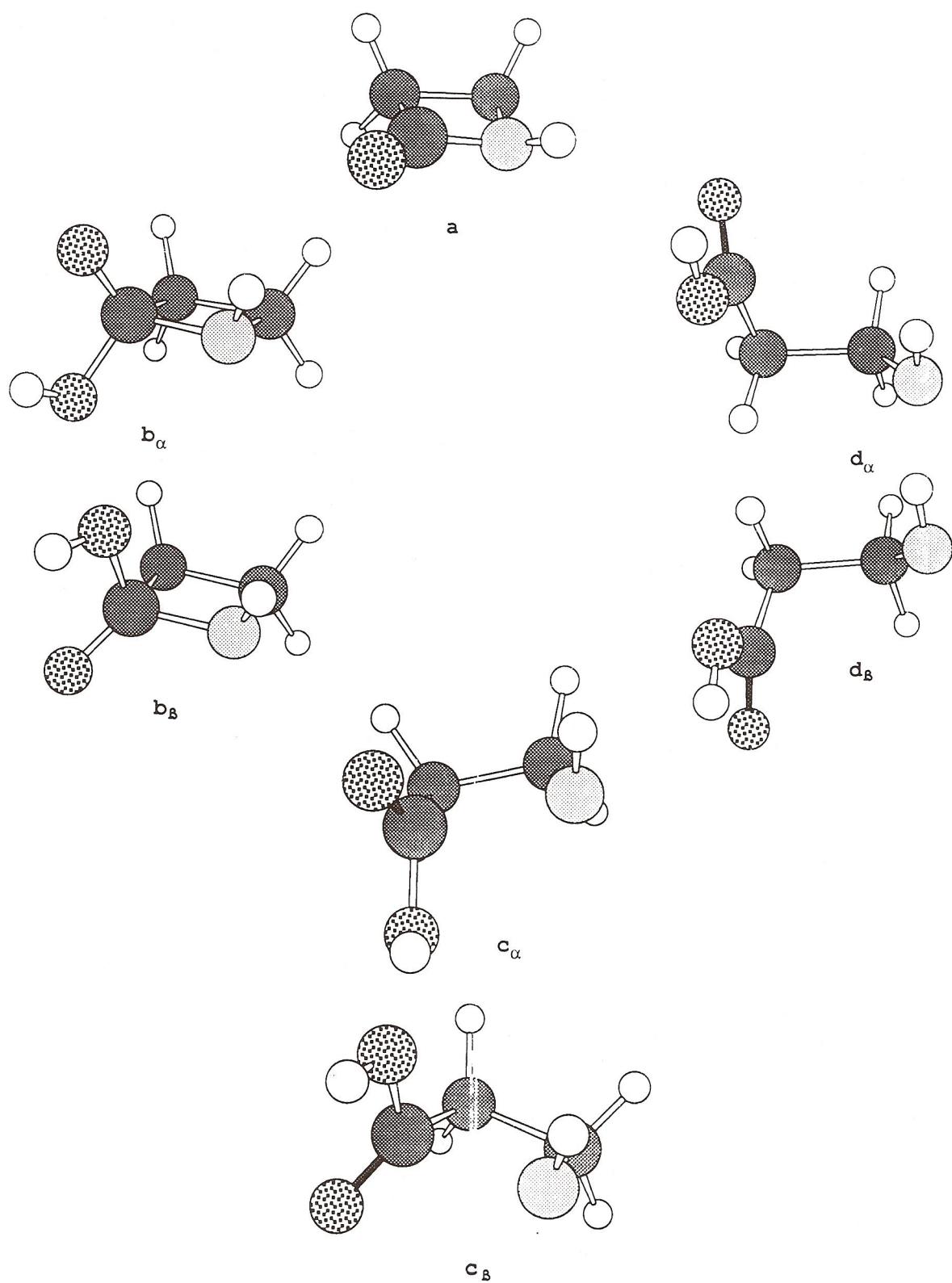


Figure 5. Structures corresponding to the different intermediate and final states of the reaction pathway by AM1 method.

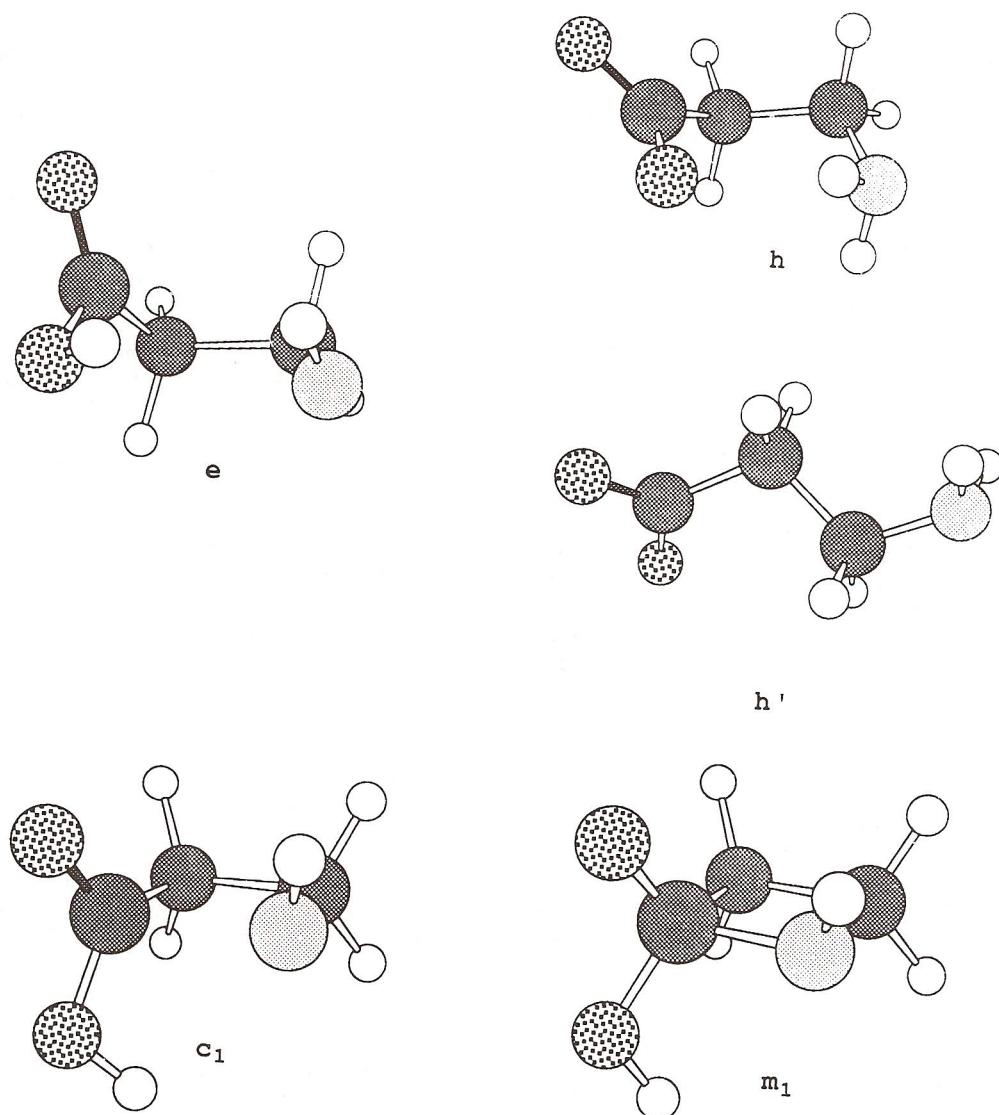


Figure 5. (continued)

The MINDO/3 method does not predict correctly the energies of small rings. This, together with the fact that, like MNDO, it cannot detect the occurrence of hydrogen bonds, gives rise to uncertain estimates of energy barriers.

Overall, the AM1 method can be considered the most suitable for studying the hydrolysis of β -lactam compounds, both in energy and in geometric terms.

Finally, we have to remark that water as solvent and different substituents in the β -lactam ring could change the mechanism of the alkaline hydrolysis of β -lactam compounds. However, recent calculations carried out in our laboratory²⁹ show that the presence of another ring (thiazolidine and dihydrothiazine) fused with the β -lactam ring modifies slightly the energy of the different structures but does not change the mechanism. In addition, the presence of five molecules of water, as a discrete representation of the solvent, does not affect essentially the mechanism of the alkaline hydrolysis of cephalosporins and just introduces a new energy barrier due to the dehydration of the hydroxyl ion when this approaches the carbonyl carbon.

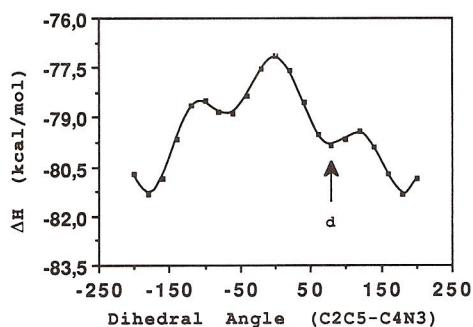


Figure 6. Energy profile by rotation of the C₅-C₄ bond in the structure **d** AM1 method.

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References

- J. Fischer, *Antimicrobial Drug Resistance: β -Lactam Resistant to Hydrolysis by the β -lactamases*, Academic Press, New York, 1984, chap. 2, p. 33.
- M.I. Page, *Adv. Phys. Org. Chem.*, **23**, 165 (1987) and references cited therein.
- R.B. Morin, B.G. Jackson, R.A. Mueller, E.R. Lavagnino, W.B. Scanton, and S.L. Andrews, *J. Am. Chem. Soc.*, **91**, 1401 (1969); M. Takasuka, J. Nishikawa, and K. Tori, *J. Antibiot.*, **35**, 1729 (1982); R.M. Sweet and L.F. Dahl, *J. Am. Chem. Soc.*, **92**, 5489 (1970); R.B. Herman, *J. Antibiot.*, **26**, 223 (1973); D.B. Boyd, *J. Med. Chem.*, **26**, 1010 (1983); D.B. Boyd, *J. Med. Chem.*, **27**, 63 (1984); K. Tori, J. Nishikawa, and Y. Takeuchi, *Tetrahedron Lett.*, **22**, 2793 (1981); J. Nishikawa and K. Tori, *J. Med. Chem.*, **27**, 1657 (1984).
- C. Petrongolo, G. Ranghino, and R. Scordamaglia, *Chem. Phys.*, **45**, 279 (1980); C. Petrongolo and G. Ranghino, *Theoret. Chim. Acta*, **54**, 239 (1980); C. Petrongolo, E. Pescatori, G. Ranghino, and R. Scordamaglia, *Chem. Phys.*, **45**, 291 (1980).
- R.C. Bingham, M.J.S. Dewar, and D.H. Lo, *J. Am. Chem. Soc.*, **97**, 1285, 1294, 1302, 1307 (1975); M.J.S. Dewar, D.H. Lo, and C.A. Ramsden, *J. Am. Chem. Soc.*, **97**, 1311 (1975).
- M.J.S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, **99**, 4899, 4907 (1977).
- M.J.S. Dewar, E.V. Zoebisch, E.F. Healy, and J.J.P. Stewart, *J. Am. Chem. Soc.*, **107**, 3902 (1985).
- S. Olivella, *QCPE Bull.*, **4**, 10 (1984); extended by S. Olivella and J.M. Bofill, unpublished data, (1987).
- J.J.P. Stewart, *QCPE Bull.*, **3**, 101 (1983).
- R. Fletcher and M.J.D. Powell, *Comp. J.*, **6**, 163 (1963); W.C. Davidon, *Comp. J.*, **11**, 406 (1968).
- J.A. Pople and R.K. Nesbet, *J. Chem. Phys.*, **22**, 571 (1954).
- J.W. Mc Iver and A. Komornicki, *J. Am. Chem. Soc.*, **94**, 2625 (1972).
- J. March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, McGraw-Hill, New York, 1963, p. 313.
- J. Frau, M. Coll, J. Donoso, F. Muñoz, and F. García Blanco, *J. Mol. Struct. (THEOCHEM)*, **231**, 109 (1991).
- J. Frau, J. Donoso, F. Muñoz, and F. García Blanco, *J. Mol. Struct. (THEOCHEM)*, **251**, 205, (1991).
- E. Sedano, J.M. Ugalde, F.P. Cossio, and C. Palomo, *J. Mol. Struct. (THEOCHEM)*, **166**, 481 (1988).
- J.L. Luche, H.B. Kagan, R. Parthasarathy, G. Tsoucaris, C. de Rango, and C. Zelwer, *Tetrahedron*, **24**, 1275 (1968).
- H.B. Bürgi, J.D. Dunitz, J.M. Lehn, and G. Wipff, *Tetrahedron*, **30**, 1563 (1974).
- H.B. Bürgi, *Angew. Chem. Int. Ed. Engl.*, **14**, 460 (1975).
- G. Alagona, E. Scrocco, and J. Tomasi, *J. Am. Chem. Soc.*, **97**, 6976 (1975).
- S. Scheiner, D.A. Kleier, and W.N. Lipscomb, *Proc. Natl. Acad. Sci. USA*, **72**, 2606 (1975).
- S. Scheiner, W.N. Lipscomb, and D.A. Kleier, *J. Am. Chem. Soc.*, **98**, 4770 (1976).
- S. Scheiner and W.N. Lipscomb, *Proc. Natl. Acad. Sci. USA*, **73**, 432 (1976).
- D.A. Kleier, S. Scheiner, and W.N. Lipscomb, *Int. J. Quant. Chem. Quant. Biol. Symp.* **3**, 161 (1976).
- W.N. Olmstead and J.I. Brauman, *J. Am. Chem. Soc.*, **99**, 4219 (1977) and references cited therein.
- M.J.S. Dewar and D.M. Storch, *J. Chem. Soc., Chem. Comm.*, **94** (1985).
- D.B. Boyd, *Chemistry and Biology of β -Lactam Antibiotics*, R.B. Morin and M. Gorman Eds., Academic Press, New York, 1982, vol. 1, chap. 5.
- J.J. Maraver, E. Sánchez Marcos, and J. Bertrán, *J. Chem. Soc. Perkin, Trans II* 1323 (1986).
- Frau J., PhD thesis, University of Balearic Islands, Palma de Mallorca, Spain, 1991.