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PM3 study of reactivity of non-classical β-lactam structures

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Abstract

Various mechanisms for the alkaline hydrolysis of aza-β-lactam (**na**), oxo-β-lactam (**oa**) and thio-β-lactam compounds (**sa**) were analysed on the basis of PM3 calculations in order to identify potential differences with classical β-lactam antibiotics. Changes in the tetrahedral intermediate were studied via the cleavage of not only the bond between atoms at 7 and 4 as in classical β-lactam antibiotics but also of that between those at 7 and 6, which was previously put forward as a plausible pathway for the hydrolysis of these compounds. Cleavage of the 7–6 bond was found to be the energetically more favourable pathway in the three compounds studied, both in the gas phase and in solution. Opening of the β-lactam ring at the 7–6 bond yields especially stable carbamates, which suggests a potential inhibitory action in serine-β-lactamases. Based on the computations, those hydrolysis products where the five-membered ring is opened by cleavage of the $C_5–S_1$ bond are highly stable.

Keywords: PM3; β-lactam; Alkaline hydrolysis; Aza-β-lactams; Oxo-β-lactam

1. Introduction

β-Lactam antibiotics have been widely used to treat bacterial diseases ever since their inception [1]; however, the appearance in the past few years of bacterial strains resistant to their action has raised the need for new, effective antibacterials [2].

The bactericide action of penicillins and cephalosporins originates from their ability to stop biosynthetic activity in cell walls by inhibiting a transpeptidase [3]. The mechanism via which the transpeptidase is inactivated involves the acylation of a serine residue at the enzyme's active site [4,5]. However, some bacterial strains have acquired the ability to synthesise β-lactamases. These enzymes can bind to β-lactam antibiotics and hydrolyse them to bacterially harmless substances. Like transpeptidases, some such enzymes (A and C types) contain a serine residue in their active sites, which facilitates their binding to β-lactam antibiotics [6,7].

The biological activity of β-lactam antibiotics depends on the structure of its constituent heterocycles and on the side chains they bear. Thus, some β-lactam derivatives bind irreversibly to β-lactamases and inactivate them as a result. One typical example is clavulanic acid [5,8,9], the inhibitory action of which involves cleavage of the C–O bond in the oxazolidine ring fused to the azethidin-2-one ring [10].

According to Ghosez et al. [11–13], some aza-γ-lactams (viz. bicyclic imidazolidinones) may also be active towards β-lactamases since the carbamoyl-enzyme intermediate potentially formed must be much more stable that the penicilloyl-serine intermediate. However, this type of molecule has been experimentally found to exhibit low antibacterial activity [12,13] as the likely result of a decreased

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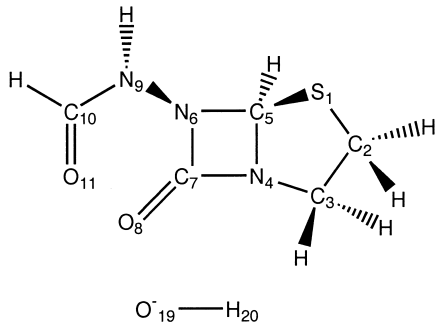

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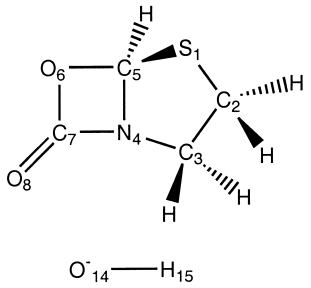
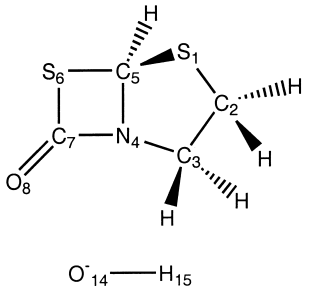
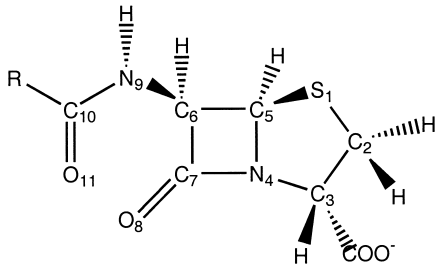


oa



sa

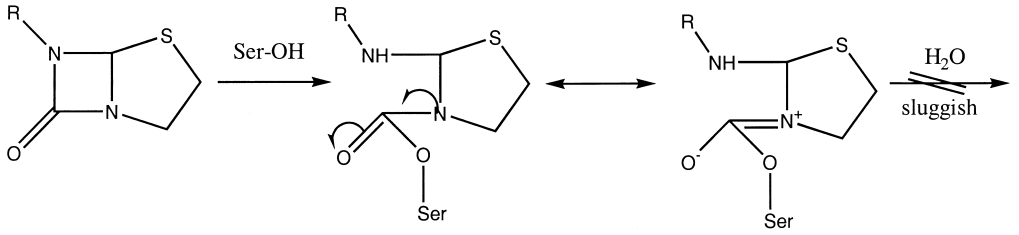


Penicillin

Scheme 1.

chemical reactivity and of topological changes involved in replacing a four-membered ring (azethidinone) with a five-membered one (imidazolidinone).

Recently, Nangia et al. [14–16] computed various structural parameters for aza-β-lactams. They concluded that 1,3-diazetidin-2-one bicyclic derivatives may possess not only substantial antibacterial activity but also some inhibitory activity against β-lactamases (Scheme 2) [14]. However, structural parameters are known to be inadequate for deriving



Scheme 2.

the chemical and antibacterial properties of these compounds. Based on the similarity between the mechanisms of enzyme acylation and alkaline hydrolysis (attack of a nucleophile on the carbonyl carbon to give a tetrahedral complex followed by cleavage of the four membered ring in both) [7,17], it has been suggested that the alkaline hydrolysis is a suitable model for the enzymatic hydrolysis, and that the alkaline hydrolysis constant for the carbonyl may strongly influence the antibacterial activity of β-lactams [18,19]. However, the reactivity of these and related compounds has never to date been studied by theoretical methods.

In this work, we carried out a comprehensive study of the different potential mechanisms for the alkaline hydrolysis of aza-, oxo- and thio-β-lactams (**na**, **oa** and **sa**, respectively, in Scheme 1) where the CHR group next to the carbonyl one was isoelectrically and isosterically replaced with NR, O and S, respectively. Two different hydrolysis mechanisms were considered, namely: (a) the nucleophilic attack on the β-lactam carbonyl, followed by the formation of the tetrahedral intermediate and the cleavage of the C_7–N_4 bond to give the reaction end products, which is the typical mechanism for the alkaline hydrolysis of β-lactams; and (b) same as the previous one but with cleavage of the 7–6 bond.

2. Methodology

All computations were performed by using the standard version of PM3 [20,21] in the AMPAC 4.5 software package [22] which was run on VAX8820 computer, on a Silicon Graphics Iris Indigo XZ4000 and on a Pentium 200MMX personal computer. The results were derived from a single-determinant wavefunction (RHF) with exclusion of configuration interactions.

The carboxyl group of β-lactams is omitted from the core structures studied to exclude discrepancies from hydrogen bonding effects and also to simplify calculations [23,24].

A reaction coordinate was used to locate stationary points in the potential-energy surface. The geometries for stationary points were identified by minimisation of the energy with respect to all geometric parameters using the Broyden–Fletcher–Goldfarb–Shanno algorithm [25–29]. The approximate geometries for the transition states were refined by minimising the gradient norm of energy using the Powell algorithm [30]. Stationary points were characterised by FORCE frequency analysis, a zero number of imaginary frequencies being assigned to reactants, products and intermediates and a unity value of imaginary frequency to each transition state.

The PM3–SM3 method [31,32] implemented in AMPAC 4.5 has been used as a continuum model for the solvent. This methodology incorporates hydration free-energy effects in a continuum fashion and employs the PM3 hamiltonian for the solute. From the structures generated in the gas phase the solvent effects were studied with electronic relaxation without structure optimisation. AMSOL calculations with optimisation of geometries were accomplished in some of the studied structures. It was found that the difference of energy with those obtained in the AMSOL 1SCF calculations was less than 5% in all the cases.

3. Results and discussion

The three structures studied are similar to those of

Table 1
Main geometric parameters, heat of formation and imaginary frequencies of the reactants, intermediates, transition states and final products of the alkaline hydrolysis of the aza-β-lactam compound

	C_7–N_4[a]	C_7–N_6[a]	N_4–H_{20}[a]	N_6–H_{20}[a]	C_5–S_1[a]	$O_8C_7N_4$[b]	C_7N_4–C_5N_6[b]	ΔH_f[c]	Imaginary frequencies[d]	$\Delta H_{f(AMSOL)}$[c]
na	1.485	1.478	–	–	1.835	134.4	7.6	− 35.09[e]	0	− 163.56[e]
nb	1.598	1.669	2.523	2.564	1.861	121.6	8.0	− 118.57	0	− 193.98
nbc	2.176	1.510	2.450	2.518	1.912	119.9	6.8	− 107.98	1 (204.6i)	− 177.49
nc	2.811	1.459	1.708	2.456	1.957	171.5	16.4	− 121.33	0	− 192.87
ncd	2.804	1.465	1.766	2.476	2.539	171.3	14.4	− 113.80	1 (183.8i)	− 185.90
nd	2.603	1.455	1.783	2.462	2.866	123.5	31.3	− 126.53	0	− 194.26
nce	2.815	1.492	1.298	2.387	1.928	172.8	17.5	− 110.42	1 (2327.li)	− 179.25
ne	3.003	1.543	1.022	2.447	1.923	168.7	22.0	− 131.49	0	− 206.06
nbf	1.527	1.940	2.512	2.515	1.908	126.0	7.4	− 115.02	1 (140.8i)	− 185.73
nf	1.450	2.806	2.492	1.744	1.984	123.1	10.9	− 130.48	0	− 202.36
ng	1.450	2.816	2.595	2.452	1.878	121.6	47.5	− 137.83	0	− 204.03
nfh	1.484	2.939	2.431	1.256	1.927	119.7	6.5	− 111.88	1 (2360.4i)	− 182.65
nh	1.523	2.940	2.526	1.029	1.913	116.6	7.6	− 125.36	0	− 203.23
nfi	1.452	2.745	2.603	2.309	2.691	124.3	29.6	− 112.89	1 (280.8i)	− 183.78
ni	1.445	2.808	2.496	1.805	2.921	124.4	10.5	− 134.15	0	− 198.72

[a] Bond length in angstroms.
[b] Bond and dihedral angles in degreees.
[c] Heats of formation in kcal/mol.
[d] Frequencies in cm^{-1}.
[e] Addition of aza-β-lactam structure and OH^-.

penicillins where the carbon atom at 6 is replaced by a heteroatom. Compound **na** contains a nitrogen atom at that position, to which the R–CONH (with R = H) is bonded. The principal geometric parameters for this compound and its enthalpy of formation are listed in Table 1, and its structure depicted in Fig. 1.

In the oxo- and thio-β-lactams (**oa** and **sa**, respectively), the C_6 atom is replaced by oxygen and sulfur, respectively. The principal geometric parameters for these compounds and their energies are given in Tables 2 (**oa**) and 3 (**sa**); their structures are shown in Figs. 2 (**oa**) and 3 (**sa**).

The alkaline hydrolysis of β-lactams involves the nucleophilic attack of the hydroxyl group on the carbonyl, the formation of a tetrahedral intermediate and the cleavage of the C_7–N_4 bond (viz. a B_{AC2} mechanism) [33]. However, the structures studied here can also undergo cleavage of the C_7–heteroatom bond (viz. C_7–N_6 in **na**, C_7–O_6 in **oa** and C_7–S_6 in **sa**) of the tetrahedral intermediate to give different reaction products. A similar cleavage mechanism was considered by Ghosez et al. [12] to be the step preceding the formation of carbamoyl-enzyme intermediates. Figs. 1–3 show the different structures involved in the reaction and Figs. 4–6 the gas-phase reaction profiles.

The nucleophile approach is faced with no energy barrier and takes place on the α side of each structure, which is the energetically more favourable [34]; the result is the formation of the tetrahedral intermediate (**nb**, **ob** and **sb** in Tables 1–3 and Figs. 1–3). This intermediate is highly stabilised relative to the reactants, viz. by −83.48, −80.51 and −70.44 kcal/mol for **nb**, **ob** and **sb**, respectively; these values are similar to the energies for *N*-methylazethidin-2-one (−78.56 kcal/mol) [35] and the penicillin nucleus (−92.68 kcal/mol) [36] provided by other semi-empirical methods.

The tetrahedral intermediate **nb** can undergo cleavage of the $C_7 - N_4$ bond (with an activation energy of 10.59 kcal/mol) to form the intermediate **nc** via the transition state **nbc** (Fig. 1). The same cleavage in **ob** and **sb** gives the intermediates **oc** (Fig. 2) and **sc** (Fig. 3), with an energy barrier of 5.11 and 13.42 kcal/mol, respectively. These values are similar to those for clavulanic acid (8.6 kcal/mol) [10], the penicillin nucleus (8.57 kcal/mol) [36] and the *N*-methylazethidin-2-one (12.16 kcal/mol) [37]. The tetrahedral

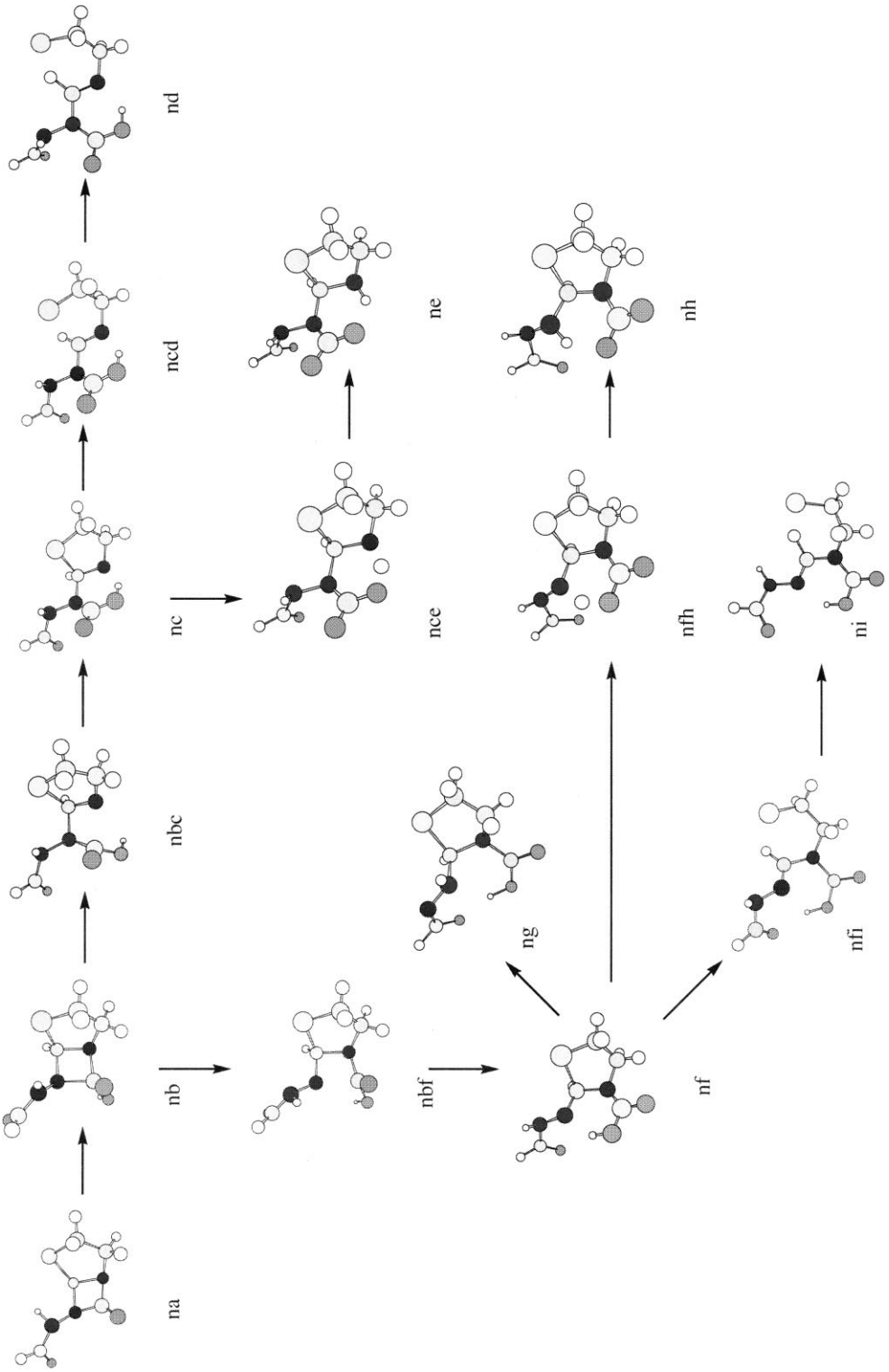


Fig. 1. Structures corresponding to the different intermediate and final states of the reaction pathway of alkaline hydrolysis of the aza-β-lactam compound in gas phase by the PM3 method.

Table 2
Main geometric parameters, hear of formation and imaginary frequencies of the reactants, intermediates, transition states and final products of the alkaline hydrolysis of the aza-β-lactam compound

	C_7–N_4[a]	C_7–O_6[a]	N_4–H_{15}[a]	O_6–H_{15}[a]	C_5–S_1[a]	$O_8C_7N_4$[b]	C_7N_4–C_5O_6[b]	ΔH_f[c]	Imaginary frequency[d]	$\Delta H_{f(AMSOL)}$[c]
Oa	1.482	1.400	–	–	1.836	139.4	2.9	− 62.41[e]	0	− 184.35[e]
Ob	1.616	1.599	2.526	2.457	1.902	122.4	4.2	− 142.92	0	− 215.73
obc	2.095	1.416	2.462	2.443	1.918	118.4	6.8	− 137.81	1 (208.0i)	− 203.63
oc	2.756	1.363	1.715	2.458	1.957	171.6	12.3	− 153.85	0	− 219.04
ocd	2.733	1.373	1.770	2.472	2.538	169.7	8.7	− 144.82	1 (208.7i)	− 210.29
od	2.726	1.374	1.776	2.477	2.900	172.5	− 0.7	− 159.88	0	− 219.72
oce	2.757	1.391	1.284	2.391	1.934	170.6	11.8	− 141.82	1 (2318.7i)	− 204.29
oe	2.921	1.426	1.022	2.474	1.935	159.6	16.8	− 161.68	0	− 230.69
obf	1.993	1.663	2.523	2.461	1.913	123.3	4.2	− 142.90	1 (187.7i)	− 216.30
of	1.442	2.797	2.477	1.734	2.069	124.7	15.5	− 168.12	0	− 237.41
ofh	1.481	2.690	2.354	1.147	1.983	121.7	15.9	− 151.69	1 (1377.9i)	− 214.96
oh	1.523	2.921	2.469	0.972	1.949	116.3	22.1	− 167.25	0	− 236.81
ofi	1.452	2.777	2.498	1.772	2.696	124.5	13.3	− 163.28	1 (127.8i)	− 229.89
oi	1.436	2.777	2.460	1.779	2.916	126.2	6.2	− 175.54	0	− 234.75

[a] Bond length in angstroms.
[b] Bond and dihedral angles in degrees.
[c] Heats of formation in kcal/mol.
[d] Frequencies in cm^{-1}.
[e] Addition of oxo-β-lactam structure and OH^-.

intermediate **sb** is unstable and undergoes unrestricted cleavage of the C_7–S_6 bond, the distance of which had to be fixed in optimising **sb**.

On the other hand, the cleavage of the 7–6 bond is much more favourable. Thus, ring opening to **nf** via the transition state **nbf** is subject to an activation energy of only 3.55 kcal/mol. Similarly, opening of **ob** to **of** involves overcoming virtually no activation

Table 3
Main geometric parameters, heat of formation and imaginary frequencies of the reactants, intermediates, transition states and final products of the alkaline hydrolysis of the sulfo-β-lactam compound

	C_7–N_4[a]	C_7–S_6[a]	N_4–H_{15}[a]	S_6–H_{15}[a]	C_5–S_1[a]	$O_8C_7N_4$[b]	C_7N_4–C_5S_6[b]	ΔH_f[c]	Imaginary frequencies[d]	$\Delta H_{f(AMSOL)}$[c]
sa	1.482	1.829	–	–	1.815	126.6	5.3	− 15.43[e]	0	− 137.68[e]
sb[f]	1.670	1.830	2.572	2.754	1.839	116.4	5.8	− 85.87	–	− 159.84
sbc	2.578	1.876	1.802	2.766	1.821	169.2	− 13.1	− 72.45	1 (455.3i)	− 138.31
sc	3.622	1.794	2.606	2.775	1.865	171.6	18.6	− 99.89	0	− 172.92
sd	3.059	1.835	1.824	2.753	2.868	172.4	0.0	− 107.18	0	− 168.22
sce	3.015	1.898	1.292	2.730	1.844	173.3	− 13.8	− 91.15	1 (2404.4i)	− 157.59
se	3.224	2.008	1.020	2.825	1.848	175.0	− 14.9	− 112.20	0	− 175.59
sf	1.461	3.197	2.485	1.847	1.875	122.0	20.1	− 118.23	0	− 184.89
sfh	1.488	3.272	2.576	1.625	1.871	118.9	22.2	− 109.02	1 (1440.4i)	− 175.18
sh	1.519	3.335	2.719	1.483	1.872	116.9	23.7	− 112.27	0	− 179.44
sfi	1.466	3.171	2.482	1.916	2.444	123.0	17.5	− 92.66	1 (412.9i)	− 161.47
si	1.471	3.177	2.482	1.950	2.921	123.9	0.0	− 101.70	0	− 175.36

[a] Bond length in angstroms.
[b] Bond and dihedral angles in degrees.
[c] Heats of formation in kcal/mol.
[d] Frequencies in cm^{-1}.
[e] Addition of sulfo-β-lactam structure and OH^-.
[f] Unstable structure with the C_7–S_6 bond fixed.

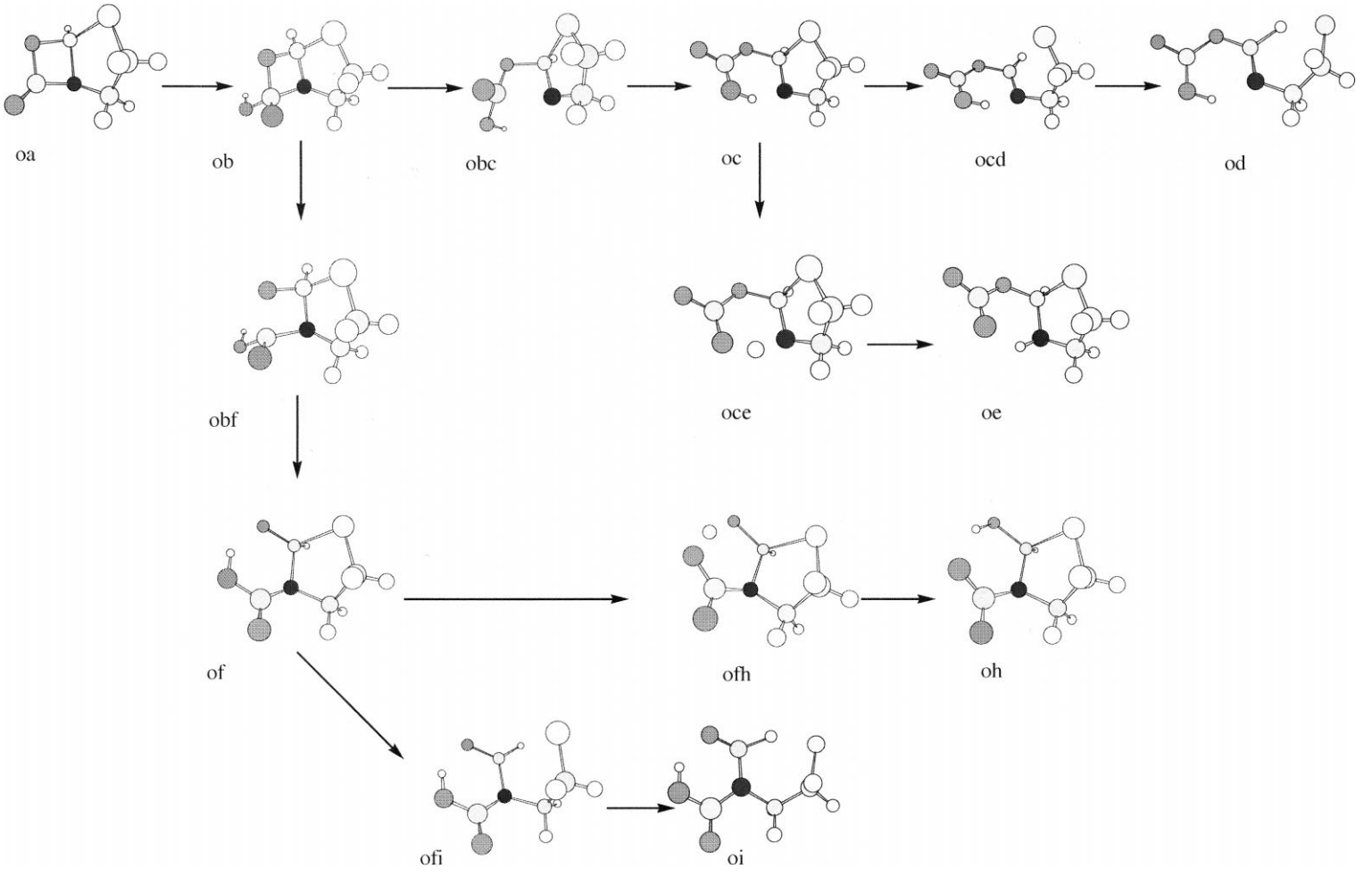


Fig. 2. Structures corresponding to the different intermediate and final states of the reaction pathway of alkaline hydrolysis of the oxo-β-lactam compound in gas phase by the PM3 method.

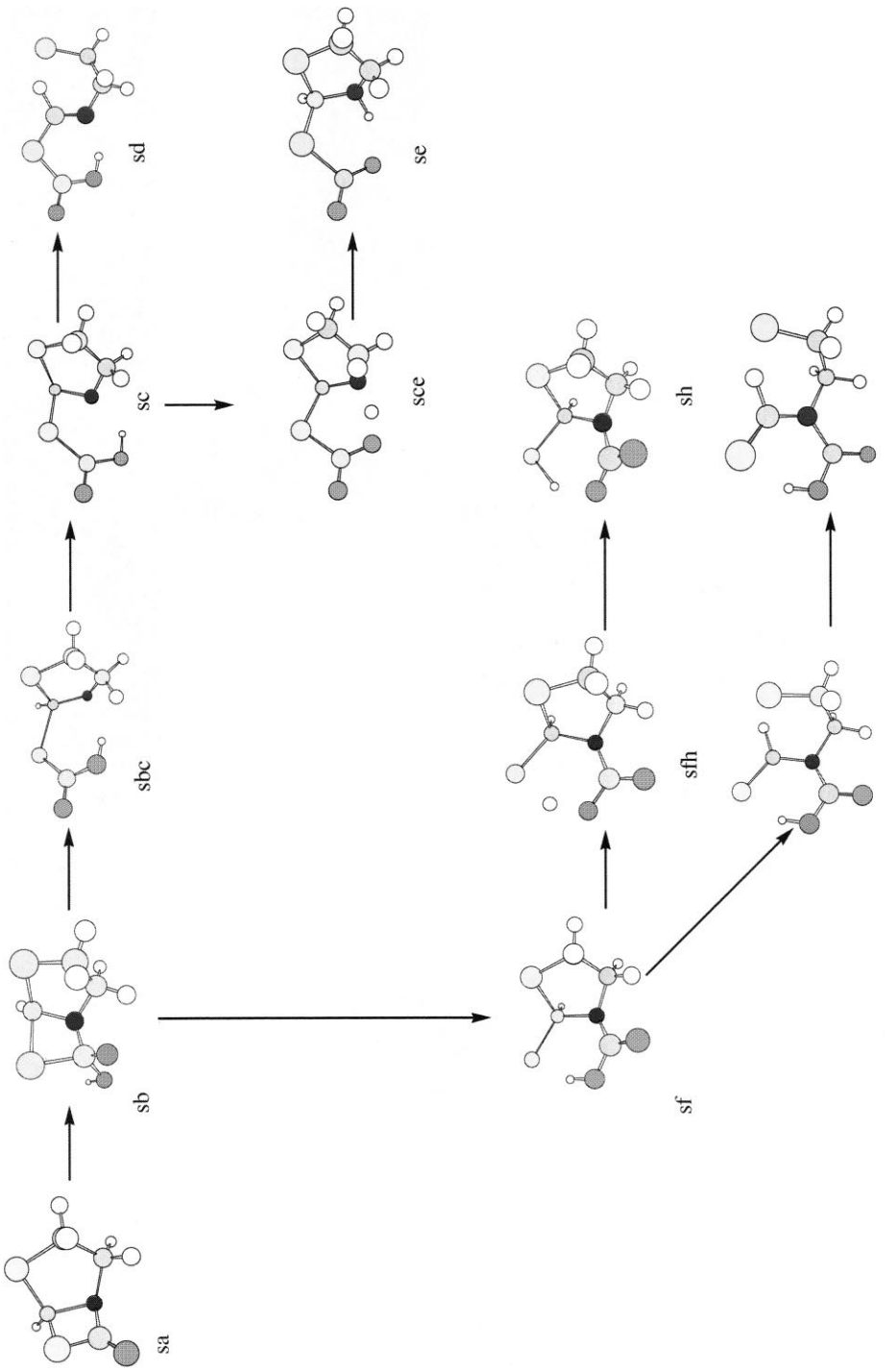


Fig. 3. Structures corresponding to the different intermediate and final states of the reaction pathway of alkaline hydrolysis of the tio-β-lactam compound in gas phase by the PM3 method.

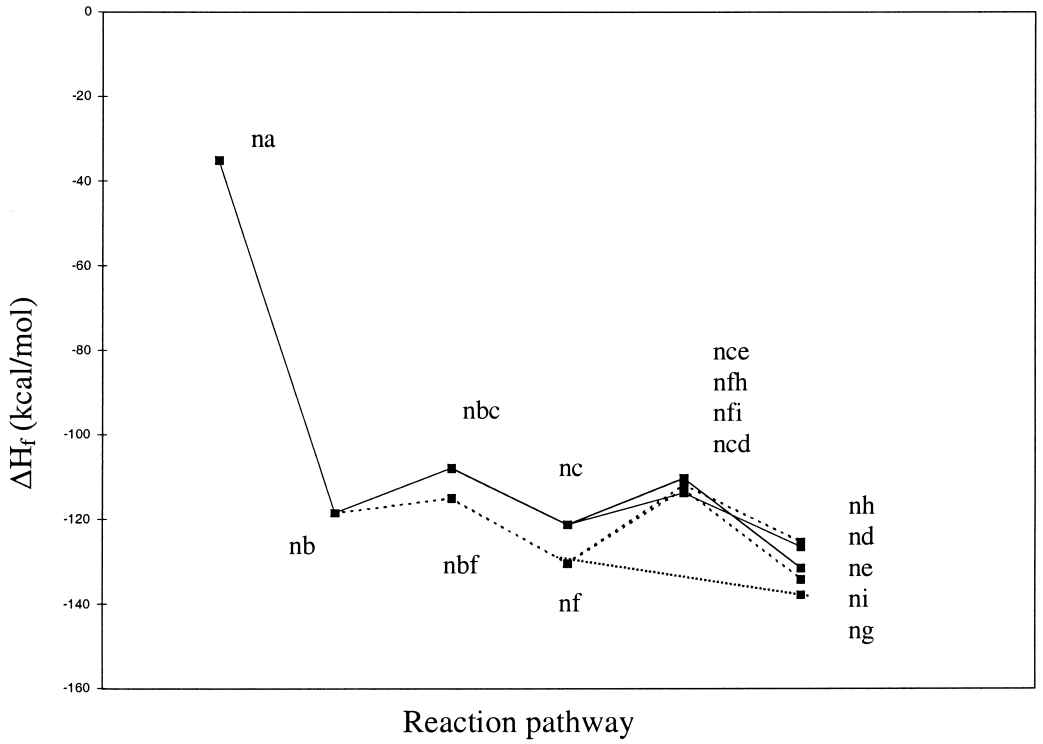


Fig. 4. Reaction pathway for the alkaline hydrolysis of the aza-β-lactam compound in gas phase.

barrier (0.02 kcal/mol). Also, as noted earlier, the conversion of **sb** into **sf** proceeds unrestrictedly. Therefore, opening via the 7–6 bond in these structures is energetically much more favourable than it is via the 7–4 bond.

The C_7–N_6 distance in intermediate **nc** is 0.020 Å shorter than in the reactant (**na**). Similarly, the C_7–N_4 distance in **nf**, of and **sf** is 0.035, 0.040 and 0.020 Å shorter, respectively, than in the reactants; this suggests the presence of carbamates (Scheme 2). The effect is more marked in **nf** (obtained by 7–6 cleavage) than in nc (reached via 7–4 cleavage). These results contradict those of Nangia et al. [14], who claim that no C_7–N_6 cleavage takes place and that N_6 has a lower electron-releasing capacity than N_4. These conclusions, however, were based solely on a structural study and on the Mulliken charge distribution in the initial structure of the β-lactam compound, the reactivity of which was not directly studied.

Structures **nc** and **nf** can lead to various end products (Fig. 1) via cleavage of the C_5–S_1 bond (**nd** and **ni**) or hydrogen transfer between O_{19} and N_3 (**ne**), O_{19} and N_5 (**nh**) or N_9 and N_6 (**ng**). Of these, **ng** (Table 1, Fig. 4) is the most stable product; however, the activation energy for the underlying process is unknown since the transition state could not be characterised. Also, especially stable is **ni**, with $\Delta H = -99.06$ kcal/mol relative to the reactants; however, the activation energy for the underlying process is somewhat high (17.59 kcal/mol).

As can be seen from the changes in **oc** and **of** (Fig. 2), **oi** is the most stable product (Table 2, Fig. 5), with $\Delta H = -113.13$ kcal/mol relative to the reactants; this product also results from cleavage of the C_5–S_1 bond. Its formation is subject to a very low energy barrier (only 4.84 kcal/mol).

Unlike the previous two compounds, the alkaline hydrolysis of the thio-β-lactam yields **sf** (Fig. 3), with no C_5–S_1 bond cleavage or proton transfer, as the most stable product. In addition, the formation of **sf** is subject to no energy barrier (Fig. 6).

As can be seen, **ni** and **oi**, the formation of which involves cleavage of the C_5–S_1 bond, are markedly

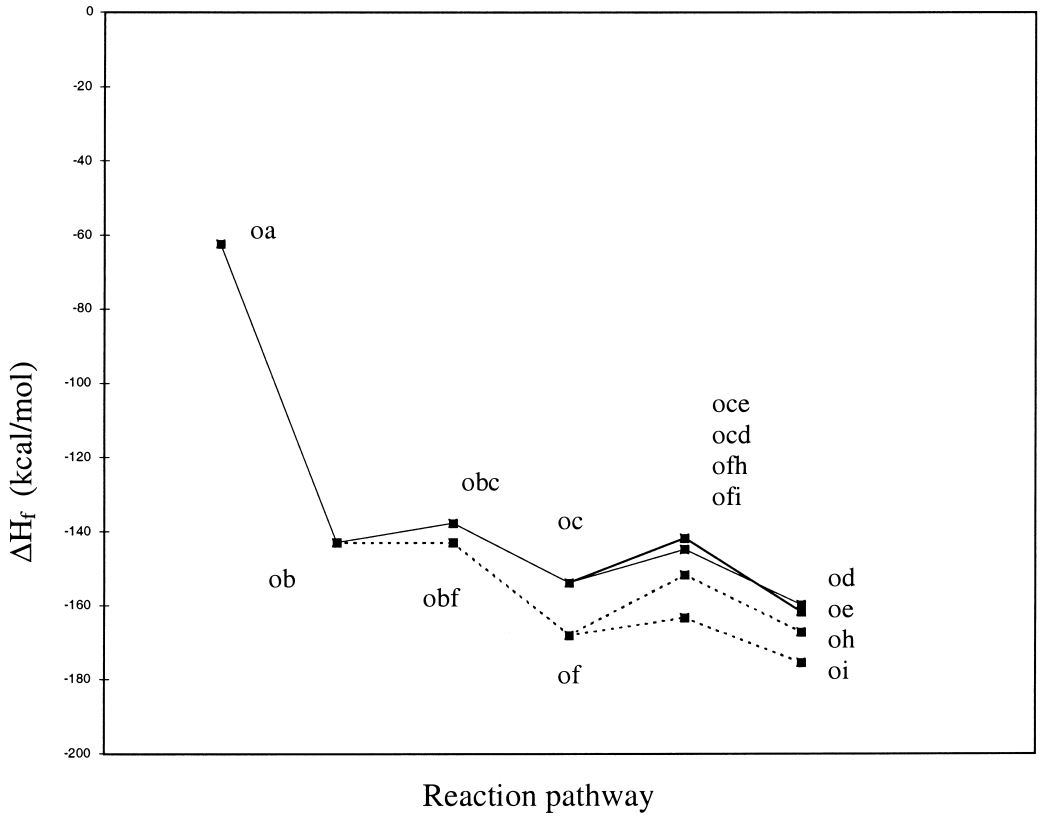


Fig. 5. Reaction pathway for the alkaline hydrolysis of the oxo-β-lactam compound in gas phase.

stabilised relative to the reactants. This is also the case with clavulanic acid, with $\Delta H = -45.1$ kcal/mol, but generally not with penicillins or cephalosporins. It should also be noted that the cleavage activation energy for the oxo-β-lactam (viz. 3.00 and 4.84 kcal/mol for the **oc**/**ocd**/**od** and **of**/**ofi**/**oi** process, respectively) is comparable to that of clavulanic acid (3.9 kcal/mol) [10]. The transformation of the aza-β-lactam involves somewhat higher energies (viz. 7.53 kcal/mol for **nc**/**ncd**/**nd** and 17.59 kcal/mol for **nf**/**nfi**/**ni**). Finally, the energy barrier for the cleavage in the thio-β-lactam compound is much higher (viz. 25.57 kcal/mol for the **sf**/**sfi**/**si** process).

The gas-phase results suggest that the three structures studied are markedly prone to cleaving of the 7–6 bond in the tetrahedral intermediate. The most stable end products (**ng**, **ni**, **oi** and **sf**) contain the carbamate unit, as do those of the classical hydrolysis of the aza-β-lactam (**nd** and **ne**). Based on the similarity between the alkaline and the enzymatic hydrolysis [6,7], the acyl-enzyme intermediate may not evolve to the elimination of penicillanic acid but rather to the formation of a highly stable carbamoyl-enzyme intermediate (Scheme 2), thereby potentially inhibiting β-lactamases.

Solvents are known to strongly influence the potential energy surface of many reactions. The effects are especially significant in reactions involving charged reactants or intermediates. There are two broad categories of methods for including solvent effects on theoretical calculations, viz. those based on the supermolecular approach, where computations include explicit solvent molecules [38], and those where the solvent is treated as a continuum [31,39–42]. Although more precise, the supermolecular approach involves time-consuming computations. Also, the high mobility of solvating water results in many imaginary force constants that hinder the identification

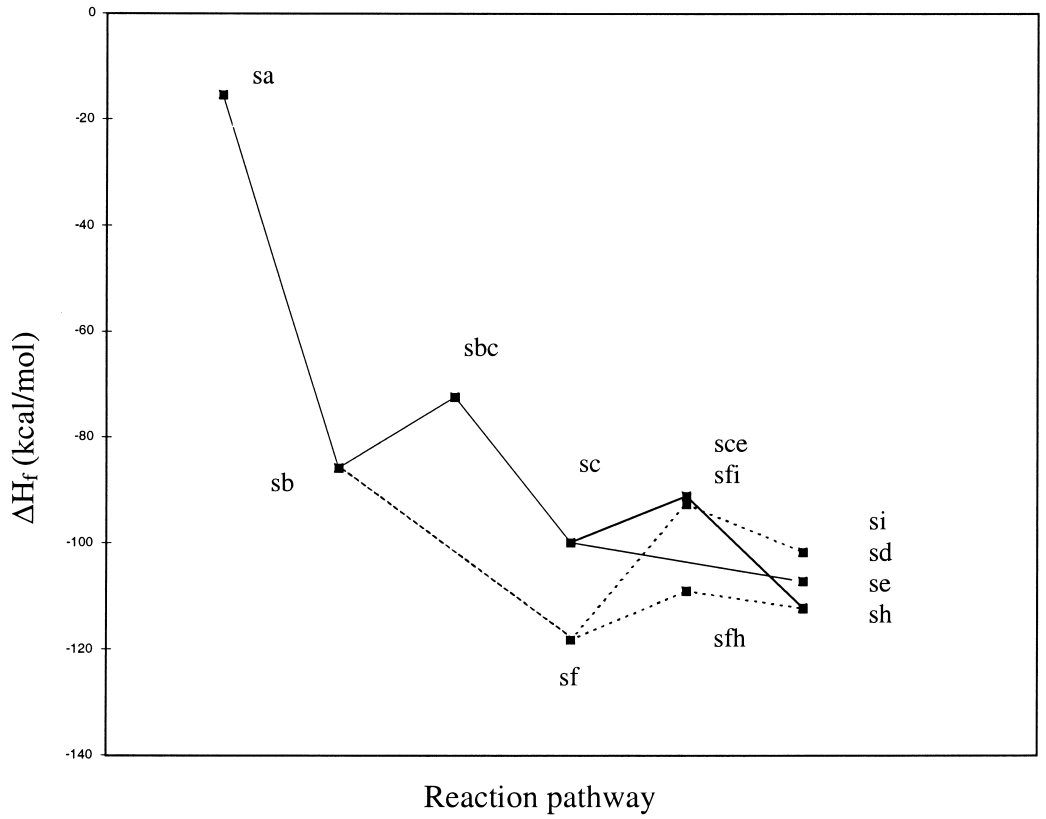


Fig. 6. Reaction pathway for the alkaline hydrolysis of the tio-β-lactam compound in gas phase.

of transition states. Qualitative studies of the solvent effect therefore usually rely on the continuum model. In fact, the solvent effect has been studied by using the AMSOL model, developed by Cramer and Truhlar [31,32], and implemented in the AMPAC 4.5 software package. According to Cramer and Truhlar, more than 90% of the free energy change in an aqueous solution is due to electron relaxation. Furthermore, in AMSOL calculations with optimisation of geometries accomplished in several of the studied structures, it was found that the difference of energy with those obtained in the AMSOL 1SCF calculations was less than 5% in all the cases. As a result, 1SCF calculations based on gas-phase geometries afford an expeditious qualitative analysis of solvating effects.

The primary effect of the solvent is stabilising the reactants without significantly altering the activation energies for the different possible reaction pathways, so the most favourable processes remain the same as in the gas phase. The formation of tetrahedral intermediates is not so markedly exothermal (ΔH is −30.42, −31.38 and −22.16 kcal/mol for **nb**, **ob** and **sb**, respectively). These values are comparable to those for the *N*-methylazethidin-2-one ring provided by the supermolecular approach, the AMSOL method [43] and by ab initio methods using a continuum model of solvation [37] (−24.6, −8.63 and 6.07 kcal/mol, respectively); that for cephalothin obtained with five water solvating molecules (−13.6 kcal/mol) [44]; and that for penicillin G provided by the AMSOL method (−13.1 kcal/mol) [10].

In theoretical studies based on optimised geometries, the nucleophilic attack of a hydroxyl ion on a carbonyl group in the presence of a solvent is known to involve an activation energy in the formation of the tetrahedral intermediate, both in β-lactams [35,37,43,45,46] and in other types of compounds

[47–49]. This energy arises from the hydroxyl desolvation barrier and is thus virtually independent of the particular β-lactam. Such a barrier should be similar to that for classical β-lactams, so structures **na**, **oa** and **sa** must react similarly eagerly with hydroxyl ion in the aqueous solution to form the tetrahedral intermediates.

A comparison of the activation energies for the different cleavage routes for the tetrahedral intermediate reveals that the cleavage of the 7–6 bond continues to be more favourable than that of the 7–4 bond. Thus, the **nb**/**nbf**/**nf** process (7–6 cleavage of the tetrahedral intermediate for the aza-β-lactam compound) is subject to an activation energy of 8.25 kcal/mol, compared to almost twice that value (viz. 16.49 kcal/mol) for the 7–4 cleavage in the **nb**/**nbc**/**nc** process. The classical 7–4 cleavage in the **ob**/**obc**/**oc** process is subject to an activation energy of 12.1 kcal/mol, whereas the non-classical 7–6 cleavage in the **ob**/**obf**/**of** process has virtually no energy barrier. These values are similar to those obtained for the cleavage of the tetrahedral intermediate of *N*-methylazethidin-2-one [37,43].

The most stable products of the different reactions are **ne** and **nh** for the aza-β-lactam, **oi** for the oxo-β-lactam and **sf** for the thio-β-lactam. All possess the carbamate unit, so their aqueous structures can form carbamoyl-serine intermediates at active sites in β-lactamases.

The structures studied by Ghosez et al. (bicyclic imidazolidinones) exhibited virtually no antibacterial activity [12,13]. This can be ascribed to two effects, namely: the topological changes involved in replacing a five-membered ring with a four-membered one; and the fact that the urea function present in the imidazolidinone is much less liable to undergo nucleophilic attack by the serine residue at the active site of a β-lactamase than is the carbonyl group usually involved in classical β-lactamases [6,7]. In our structures, however, the four-membered ring is preserved, albeit highly stressed, and, as noted by Nangia et al. [15], the three-dimensional structure of the molecules is compatible with antibacterial activity. In addition, as noted earlier, the formation of the tetrahedral intermediate is highly favoured, as much as in classical β-lactamases. Consequently, the factors that decrease antibacterial and inhibitory activity in bicyclic imidazolidinones are theoretically absent from our structures, which might thus be of pharmacological interest as inhibitors for serine enzymes. The high potential of these compounds warrants a deeper study of their reactivity and interactions with serine enzymes that will be undertaken in future work.

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