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32. Theoretical Calculations of β-Lactam Antibiotics

Part VII

Influence of the Solvent on the Basic Hydrolysis of the β-Lactam Ring

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We used semi-empirical and *ab initio* calculations to investigate the nucleophilic attack of the OH⁻ ion on the β-lactam carbonyl group. Both allowed us to detect reaction intermediates pertaining to proton-transfer reactions rather than the studied reaction. We also used the PM3 semi-empirical method to investigate the influence of the solvent on the process. The AMSOL method predicts the occurrence of a potential barrier of 20.7 kcal/mol due to the desolvation of the OH⁻ ion in approaching the β-lactam carbonyl group. Using the supermolecular approach and a H_2O solvation sphere of 20 molecules around the solute, the potential barrier is lowered to 17.5 kcal/mol, which is very close to the experimental value (16.7 kcal/mol).

Introduction. – The nucleophilic attack on the carbonyl group has been the subject of extensive theoretical and experimental research on account of the wide variety of biological processes where the reaction is involved.

Recent literature abounds with theoretical studies usually involving *ab initio* or semi-empirical methods and aimed at elucidating the nature of the nucleophilic attack of the OH⁻ ion on carbonyl groups *via* a tetrahedral intermediate. In this way, nucleophilic attacks on esters [1–4], aldehydes [5–7], amides [8–10], and lactams [11–17] were investigated.

Solvent molecules are known to be able to alter potential barriers and even reaction mechanisms, particularly those for reactions involving charged species. In studying nucleophilic attacks on various esters, *Fukuda* and *McIver* [18] found proton-transfer elimination and nucleophilic substitution reactions to prevail over $B_{AC}2$ reactions. However, the presence of a single water molecule restored the prevalence of the $B_{AC}2$ reaction.

Theoretically, the influence of the solvent on this type of reaction was mainly studied by using two different methods, *viz.* the supermolecular approach and the continuum method. The former method involves wrapping the solute in a given number of H_2O molecules that varies with the computational procedure used. The latter deals with the solvent as a continuum with a given dielectric constant.

In a recent study on the alkaline hydrolysis of β-lactam antibiotics [16], our group simulated the presence of the solvent by adding a first solvation layer consisting of five H_2O molecules. The results showed no appreciable alteration of potential barriers or

reaction mechanisms by virtue of the solvent and thus seemingly support the assertion of *Weiner et al.* [8] that placing a few H_2O molecules around the solute does not permit correct assessment of solvation energies. On the other hand, using the supermolecular approach and 15 H_2O molecules in the solvation layer, *Rzepa* and *Yi* [19] found the PM3 semi-empirical method to predict solvation energies for the zwitterionic forms of small amino acids that were similar to their experimental counterparts.

In this work, we used *ab initio* and semi-empirical methods to investigate the nucleophilic attack of OH^- ion on the β-lactam carbonyl group. We also used the PM3 method to study the influence of the solvent on the process. The presence of the solvent was simulated by using the supermolecular approach (the solute was wrapped in 20 H_2O molecules, which allowed at least two full solvation layers to be formed); also, the solvent was modeled as a continuum (the AMSOL method, *Cramer* and *Truhlar* [20]).

Methods. – We chose the *N*-methylazetidin-2-one ring as the β-lactam model compound for semi-empirical calculations and azetidin-2-one for the *ab initio* calculations (in order to expedite computations, the *N*-methyl group was replaced by a proton).

All semi-empirical calculations were carried out by using the PM3 method [21] as implemented in the AMPAC 4.0 and 4.5 software packages [22]. The software was run on a *Silicon-Graphics Iris Indigo XZ4000* or a *VAX 9210VP* computer.

The semi-empirical structures obtained were used as the starting points for the *ab initio* calculations, which were done using the 4-31G and 6-31+G* bases. The latter, which included the effect of polarized and diffuse bases on heavy atoms, was imposed by the need for diffuse functions to obtain reliable results from small charge-localized anions such as OH^- [6]. The *ab initio* calculations were performed on a *VAX 9210VP* or an *ALPHA DEC 10620 AXP* computer running the program GAMESS [23] as modified by *Schmidt et al.* [24].

The solvation study was carried out by using the AMSOL continuum method (with the PM3–SM3 parametrization) [20] as implemented in the program AMPAC 4.5.

The program MOBY 1.50 [25] was employed to perform a molecular-dynamics (MD) and molecular-mechanics (MM) study of the *N*-methylazetidin-2-one ring and the OH^- ion at a distance of 5.5 Å, the two being solvated by 20 H_2O molecules. The minimum-energy structure thus obtained was subsequently optimized by using the PM3 method and used to construct different reaction coordinates to identify maxima and reaction intermediates.

All structures produced by the semi-empirical and *ab initio* calculations were characterized by vibrational analysis.

Results. – *Geometry of the β-Lactam Ring. Fig. 1* shows the structure of the azetidin-2-one ring and the numbering convention used in this work. *Table 1* gives the major geometric and energy parameters for the β-lactam ring.

A comparison of the experimental bond distances provided by the X-ray [26] and electron diffraction/microwave (ED/MW) techniques [27] reveals that the former predicts a longer $O(1)-C(2)$ and a shorter $C(2)-N(3)$ distance relative to the latter. The difference may arise from the fact that, in the crystal state, $H(10)$ forms an intermolecular H-bond, which possibly increases π-electron resonance and hence shortens the above-mentioned distances. Accordingly, the theoretical results should be compared with the gas-phase ED/MW results.

Table 1. *Geometric Parameters [Å, °] for the β-Lactam Ring Obtained by Different Methods*

	PM3[a])[b]	4-31G*[a]	6-31+G*[a]	MINDO/3[c]	MNDO[c]	AM1[c]	6-31G**[d]	6-31G*[e]	X-Ray[f]	ED/MW[d])[g]	6-31G[h]
O(1)–C(2)	1.2024	1.2053	1.1888	1.202	1.212	1.225	1.186	1.18	1.225	1.201	1.211
C(2)–N(3)	1.4699	1.3637	1.3564	1.372	1.435	1.411	1.358	1.359	1.331	1.380	1.361
N(3)–C(4)	1.5184	1.4732	1.4575	1.435	1.483	1.466	1.455	1.456	1.467	1.479	1.488
C(4)–C(5)	1.5445	1.5572	1.5497	1.518	1.557	1.555	1.549	1.549	1.538	1.553	1.562
C(2)–C(5)	1.5283	1.5321	1.5312	1.530	1.538	1.539	1.533	1.532	1.522	1.537	1.512
N(3)–H(10)		0.9896	0.9969	1.019	0.999	0.983	0.994			0.990	0.990
O(1)–C(2)–N(3)	130.73	132.6	132.9	132.4	129.2	132.4		132.9			132.2
O(1)–C(2)–C(5)	137.88	135.8	135.8	138.9	139.1	136.6	135.9	135.8	135.9	136.6	
C(2)–N(3)–C(4)	91.17	95.9	96.1	97.1	92.6	94.3	96.2	96.0	96.2	95.3	93.0
N(3)–C(4)–C(5)	88.93	86.5	86.9	86.9	89.1	88.3	87.0	87.0	86.2	87.6	
O(1)–C(2)–N(3)–C(4)	175.1	180.0	180.0	180.0	174.8	183.5					
C(2)–N(3)–C(4)–C(5)	5.3	0.0	0.0	0.0	-6.2	-4.4					
H(10)–N(3)–C(4)–C(5)	135.9	180.0	180.0	180.0	136.0	211.5					180.0

a) This work. b) *N*-Methylazetidin-2-one ring. c) [14]. d) [27]. e) [29]. f) [26]. g) Electron diffraction/microwave measurements. h) [28].

Table 2. *Energy and Geometric Parameters [Å, °] for the Different Structures of the Nucleophilic Attack*

	β-Lactam ring		Tetrahedral intermediate				Transition state	
	AMSOL[a]	Supermol. approach	AMSOL[a]	PM3[b]	4-31G[b]	6-31+G*[b]	AMSOL[a]	Supermol. approach
O(1)–C(2)	1.2125	1.2151	1.3365	1.2895 (1.2824)	1.3111 (1.2884)	1.2955 (1.2762)	1.2303	1.2242
C(2)–N(3)	1.4570	1.4538	1.5692	1.6114 (1.6209)	1.5264 (1.5207)	1.5093 (1.5101)	1.4858	1.4913
N(3)–C(4)	1.5234	1.5212	1.5117	1.5021 (1.5006)	1.4821 (1.4788)	1.4662 (1.4646)	1.5244	1.5183
C(4)–C(5)	1.5450	1.545	1.5272	1.5268 (1.5263)	1.5434 (1.5421)	1.5353 (1.5355)	1.5306	1.5416
C(2)–C(5)	1.5200	1.5190	1.5700	1.5800 (1.5867)	1.5686 (1.5703)	1.5642 (1.5660)	1.5300	1.5376
C(2)–O(nuc)		5.6376	1.4251	1.4106 (1.4199)	1.4528 (1.5072)	1.4275 (1.4657)	2.2471	2.0369
O(1)–C(2)–N(3)	130.7	130.3	118.0	119.1 (118.5)	116.0 (122.3)	115.7 (120.8)	127.3	125.8
O(1)–C(2)–C(5)	137.4	137.8	118.8	122.8 (124.4)	119.1 (124.4)	118.0 (123.1)	131.8	138.1
C(2)–N(3)–C(4)	91.1	91.2	90.6	90.7 (90.85)	91.4 (91.7)	90.7 (91.3)	90.1	90.8
N(3)–C(4)–C(5)	88.7	88.3	91.4	92.0 (92.1)	89.6 (89.1)	90.1 (89.7)	90.1	88.9
O(nuc)–C(2)–N(3)		124.7	107.1	109.5 (111.2)	110.2 (104.0)	110.2 (105.5)	103.2	117.5
O(1)–C(2)–N(3)–C(4)	174.0	172.1	113.5	120.9 (-131.4)	-105.1 (-146.3)	-102.3 (-145.1)	143.2	146.1
C(2)–N(3)–C(4)–C(5)	5.6	6.7	8.1	4.9 (4.5)	-16.3 (17.4)	-18.1 (18.2)	5.7	-10.7
H–O(nuc)–C(2)–O(1)		-109.7	20.9	6.0 (-5.1)	-7.2 (1.4)	-3.2 (1.7)	19.3	-145.8
Energy	-162.980 (-162.736)	-1306.63	-171.611 (-169.187)	-103.107	-320.731497 (-320.731646)	-321.233221 (-321.230668)	-142.314 (-141.660)	-1289.11

a) In parentheses AMSOL energy with electronic relaxation. Energy in kcal/mol. b) In parentheses pseudo-*cis*-conformation parameters. Energy in hartree.
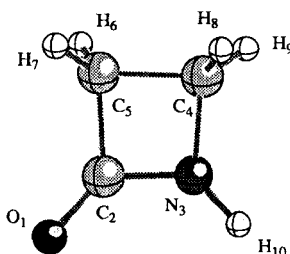
Fig. 1. *Structure and numbering scheme* (arbitrary) *for the azetidin-2-one ring*

Neither semi-empirical method predicts a geometry in accordance with the experimental geometry. Contrary to the experimental results, the MNDO, AM1, and PM3 methods predict the pyramidal structure for the β-lactam N-atom to be the most stable.

Ab initio calculations predict a significantly more accurate geometry for the β-lactam ring. *Ab initio* computations on a STO-3G minimal base predict the existence of two conformers, depending on whether the β-lactam N-atom is planar or pyramidal. On the other hand, all calculations based on a double-zeta basis set predict a single conformer, the planar one [27–29].

Nucleophilic Attack of the OH⁻ Ion on the β-Lactam C-Atom. In studying the nucleophilic attack of the OH⁻ ion on the β-lactam carbonyl group, we initially optimized the tetrahedral intermediate by using the PM3 method. The most stable structure was that with the nucleophile and the *N*-methyl group in the *anti*-periplanar conformation. *Table 2* lists the major geometric and energy parameters for different structures. We should emphasize the considerably increased O(1)−C(2) and C(2)−N(3) distances for this species. This tetrahedral intermediate is similar to that observed by *Petrongolo et al.* [12] using *ab initio* calculations and various basis sets. The stabilization energy, 58 kcal/mol, is similar to those obtained by using other semi-empirical methods [14–16], but lower than those provided by *ab initio* methods [12].

The approach of a C-atom in a carbonyl group by a nucleophile was the subject of much research. *Stone* and *Erskine* [7] claimed that, beyond a distance of 3 Å, the nucleophile approaches the C-atom colinearly with the O(1)−C(2) bond, thereby forming an O(1)−C(2)−O(nuc) angle of 180°; however, as the nucleophile distance to the target decreases, the angle rapidly decreases to *ca.* 107° at a distance of *ca.* 2 Å, from which the approach pathway is virtually normal to the O(1)−C(2) bond. Similar results were reported by *Madura* and *Jorgensen* [6] and *Yu* and *Karplus* [5]. *Alagona et al.* [9] who studied the attack of formamide by OH⁻ ion concluded that the nucleophile can approach its target *via* various pathways that are either colinear with N−H and C−H bonds or normal to the C=O bond – only the last, however, corresponds to a $B_{AC}2$ mechanism. These authors agreed that a normal approach of the OH⁻ ion to the carbonyl group in the gas phase entails overcoming no energy barrier.

We used two different procedures to investigate the nucleophilic attack in the gas phase. One involved having the OH⁻ ion attack the carbonyl group in a normal direction (at two fixed O(1)−C(2)−O(nuc) angles of 113 and 90°) from a distance of 5 Å to that where the tetrahedral intermediate was formed. The other involved the opposite process,

i.e., departing from the tetrahedral intermediate to a distance of 5 Å in a normal direction. The behavior was similar in all cases: the energy decreased steadily from the reaction products to the tetrahedral intermediate.

We carried out similar experiments with free optimization of the geometric parameters (*i.e.*, with the nucleophile attacking its target *via* non-normal pathways). At 10 Å, the OH⁻ ion had already switched from its initial position normal to the carbonyl group $(O(1)-C(2)-O(nuc) = 90°)$ to a nearly colinear position $(O(1)-C(2)-O(nuc) = 162°)$. As OH⁻ neared the carbonyl group, it interacted with H−C(4) to form a H-bond; as a result, the proton was eventually transferred to the nucleophile to form a H_2O molecule $(C(2)-O(nuc) = 4.4$ Å). In the gas phase, the negative charge on the nucleophile is less stable than that on the ring since the latter must be delocalized over the β-lactam group.

If the C−H distances were fixed to avoid an undesirable proton transfer, a profile such as that in *Fig. 2* was obtained. As can be seen, it includes two relative minima at C(2)−O(nuc) distances of 3.90 and 5.00 Å that correspond to two structures where the nucleophile is interacting with protons bonded to C(5) and C(4), respectively.
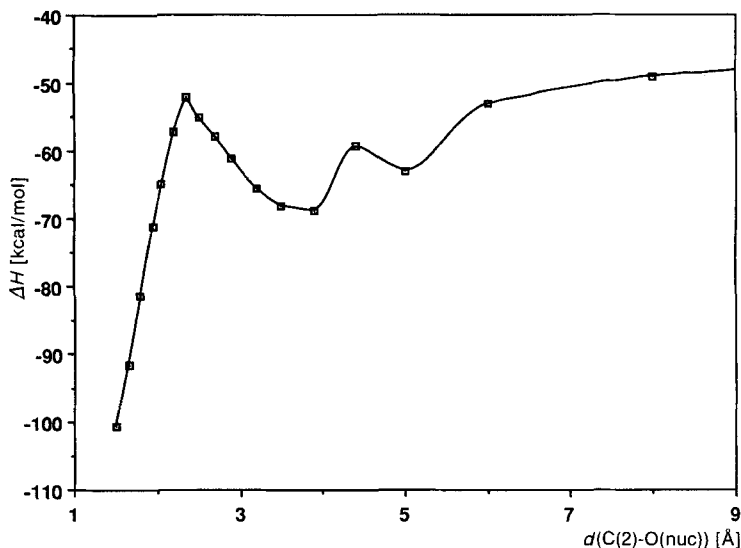

Fig. 2. *Reaction pathway for the nucleophilic attack of the OH⁻ ion obtained from PM3 calculations*

In characterizing these minima, the system always evolved with a proton transfer and the consequent formation of H_2O (*Fig. 3, a*), thus producing a highly stabilized structure (relative to the pseudo-minima) including H-bonds between H_2O and the *N*-methylazetidin-2-one anion.

Optimization of the maximum corresponding to a C(2)−O(nuc) distance of 2.4 Å in *Fig. 2* produced a structure with a single negative force constant but a C(5)−H bond distance of 1.161 Å (*Fig. 3, b*). This is, therefore, a true transition state, though not for the $B_{AC}2$ reaction, but rather for an *E1cB* mechanism. A similar behavior was previously
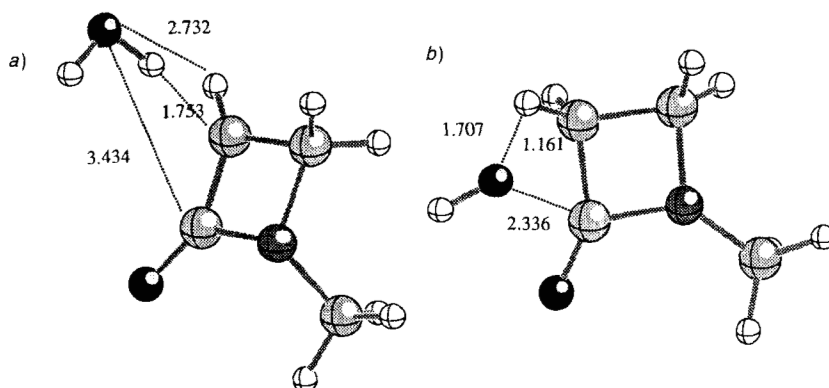
Fig. 3. *Structures of various reaction intermediates*

observed by *Katagi* [30] in a theoretical study of the alkaline hydrolysis of *N*-methylcarbamates by semi-empirical methods.

We used *ab initio* computations to carry out a similar study to that performed with the PM3 method. *Table 2* gives the major geometric and energy parameters for the tetrahedral intermediate, and *Fig. 4* depicts the reaction pathways obtained.
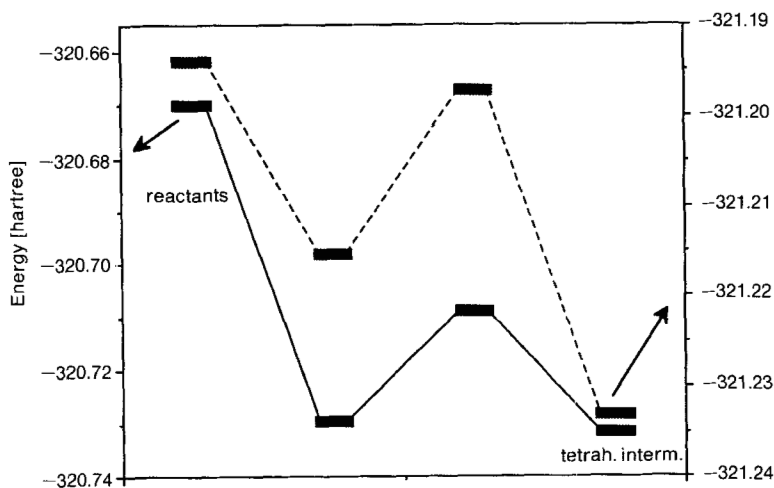

Fig. 4. *Reaction pathway for the nucleophilic attack of the OH^- ion obtained from* ab initio *calculations: 4-31G* (solid line) *and 6-31 + G** (dashed line)

Binding of OH to C(2) leads the N-atom to adopt a pyramidal structure that in turn gives rise to two possible conformers. *Ab initio* calculations using a 4-31G basis set predict that the more stable structure for the tetrahedral intermediate is that where the proton bonded to the N-atom and the OH group are in the *syn*-periplanar conformation; the energy difference between the two conformations is only 0.1 kcal/mol, however. On the

other hand, calculations with the 6-31+G* bases predict a *syn*-periplanar conformer that is 1.5 kcal/mol less stable than the *anti*-periplanar conformer.

To avoid the proton transfer, the reaction pathway in *Fig. 4* was obtained by fixing the H−N(3) distance. The figure clearly shows a maximum at a C(2)−O(nuc) distance corresponding to a structure with three labile H-bonds between the nucleophile O-atom and the protons in the H−C(5) (2.49 Å), H−C(4) (2.21 Å), and H−N(3) bonds (2.43 Å). The structure possesses a single negative force constant that involves the atoms in the OH group and the proton bonded to the β-lactam N-atom; therefore, this is clearly not a transition state for the nucleophilic attack. At the energy minimum (C(2)−O(nuc) = 4.1 Å), a single, strong H-bond between the nucleophile O-atom and the H−N(3) bond is formed, with OH⁻ lying roughly in the same plane as the β-lactam ring. The energy of this structure is similar to that of the tetrahedral intermediate, which suggests a strong stabilizing effect of the H-bond formed.

The 6-31G* bases produce a similar reaction profile (*Fig. 4*). However, no interaction between the nucleophile and the H−N(3) bond takes place in the *anti*-periplanar conformation. The energy minimum corresponds to a structure including a strong H-bond (1.98 Å) between O(nuc) and the H−C(4) bond; the maximum occurs at a nucleophile distance to the C(2) atom and the H−C(4) bond of 2.50 and 2.17 Å, respectively.

Influence of the Solvent on the Nucleophilic Attack. The presence of solvent molecules can substantially alter reaction mechanisms. We studied the potential effect of the solvent on the nucleophilic attack on the β-lactam carbonyl by using PM3 calculations and two different strategies, *viz.* the solvation continuum method and the supermolecular approach.

The gas-phase geometries of *N*-methylazetidin-2-one and the tetrahedral intermediate produced by the PM3 method were used as the starting points for studying the alkaline hydrolysis of the ring using the AMSOL method [20]. The AMSOL solvation energy was calculated with allowance for electron and geometric relaxation, which obviously altered the ring geometry relative to the gas phase.

In implementing the supermolecular approach, the β-lactam ring was previously wrapped in 20 H₂O molecules with the aid of the MM-MD method. Then, the whole system was fully optimized by using the PM3 semi-empirical method.

Table 2 gives the major geometric and energy parameters for the solvated structures produced by both methods.

A comparison of the geometry of the β-lactam ring in the gas phase (*Table 1*) and in the presence of the solvent (*Table 2*) reveals that both the AMSOL method and the supermolecular approach predict a longer O(1)−C(2) distance and a shorter C(2)−N(3) distance. This suggests that the presence of the solvent favors the resonant form ⁻O−C(2)=N(3)⁺−, which is logical since polar solvents tend to stabilize charged species. This effect is even stronger on the tetrahedral intermediate.

The energy obtained with allowance for electron relaxation only (single-point SCF calculations) is very similar to that arrived at with geometric and electron relaxation provided the species concerned is uncharged (*e.g.* the β-lactam ring). The energy difference between the structure amounts to 2.4 kcal/mol for the tetrahedral intermediate, a charged species.

Fig. 5 shows the reaction profile obtained for the attack of the OH⁻ ion on the β-lactam ring in solution. The nucleophile was initially placed normal to the β-lactam
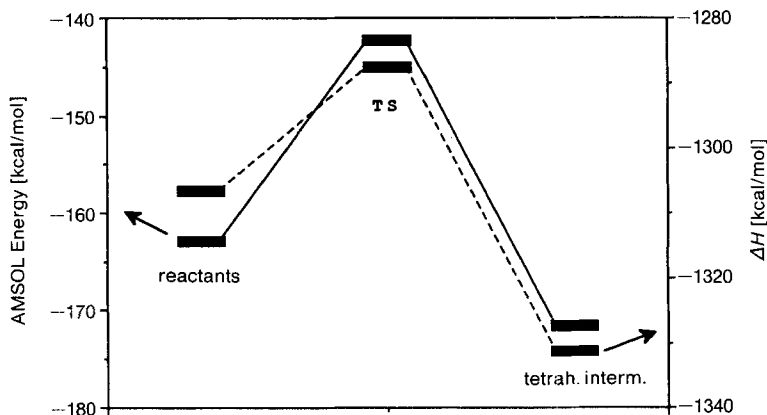
Fig. 5. *Reaction pathway for the nucleophilic attack of the OH⁻ ion in solution: AMSOL method* (solid line) *and supermolecular approach* (dashed line)

carbonyl group (5.63 Å and 20 Å away from it for the supermolecular approach and AMSOL calculations, resp.) and led along the reaction pathway (OH⁻ ion was gradually brought nearer to C(2) until the tetrahedral intermediate was formed). No variable other than the reaction coordinate was fixed, so all approach pathways were in principle available.

The presence of the solvent stabilizes OH⁻, thereby hindering its tendency to form H-bonds with protons on the β-lactam ring. As a result, the approach pathway is always normal to the carbonyl group.

We should note that both methods predict the occurrence of an energy barrier in the approach process, since the nucleophilic attack is impossible without partial desolvation. This barrier is 20.7 and 17.5 kcal/mol for the continuum method and supermolecular approach, respectively. These values are similar to those obtained from theoretical calculations for various nucleophilic attacks and virtually coincident (particularly the supermolecular-approach value) with the experimental energy for the hydrolysis of the N-methylazetidin-2-one ring (16.1 kcal/mol) [31].

Water-solvated OH⁻ ions form 6 strong H-bonds at an average distance of 1.76 ± 0.012 Å. In the transition state (*Fig. 6*), the OH⁻ ion, lying 2.037 Å away from the carbonyl group, can only form 5 H-bonds (average distance 1.79 ± 0.02 Å), which are slightly weaker than the previous ones. These results are in contradiction with those reported by *Madura* and *Jorgensen* [6], who observed no decrease in number, but only in strength of H-bonds.

There are some differences between the transition states provided by the two methods, foremost of which is the distance between the β-lactam C-atom and the nucleophile O-atom, *viz.* 2.247 Å for the solvation continuum model and 2.037 Å for the supermolecular approach. The latter value virtually coincides with that obtained independently by *Madura* and *Jorgensen* [6] and *Yu* and *Karplus* [5] for the hydrolysis of formaldehyde (2.00–2.05 Å).

In a recent paper, *Liu* and *Shi* [32] studied the nucleophilic attack in solution of OH⁻ on formaldehyde by a combined molecular-mechanical and quantum-mechanical (AM1)
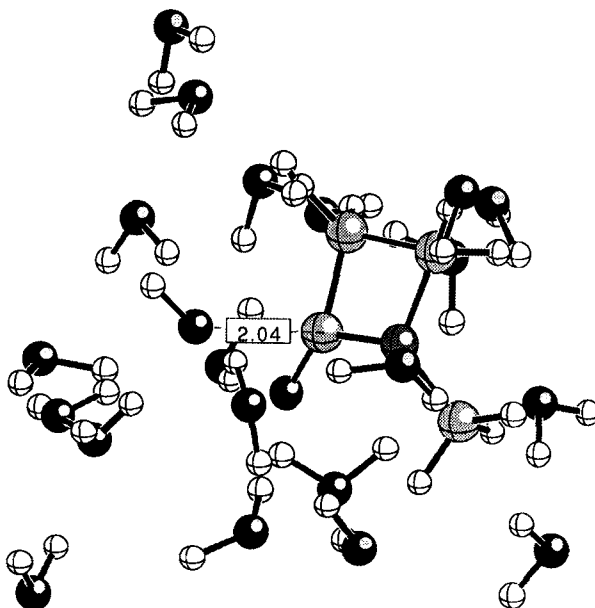
Fig. 6. *Structure of the reaction intermediate for the approach of the OH⁻ ion to the β-lactam ring*

method. The authors found a small approximate barrier of *ca.* 5 kcal/mol at a C—O(nuc) distance of 2.65 Å. These values are smaller and longer, respectively, than the value obtained by other methods [5] [6].

In the aqueous medium, the tetrahedral intermediate is not so markedly stabilized relative to the reactants as in the gas phase; in fact, the energy difference is only 8.6 or 24.6 kcal/mol, depending on the calculation method used (see *Table 2*). The last value coincides with that obtained by *Liu* and *Shi* [32].

In summary, 20 H_2O molecules can mimic the solvent quite appropriately. The primary difference between the gas phase and the aqueous phase lies in the occurrence of a reaction maximum and the smaller stabilization of the tetrahedral intermediate relative to the products. The potential barrier for the aqueous phase arises from partial desolvation of the OH⁻ ion as it approaches the ring as a result of the gradually decreased number and strength of H-bonds between the nucleophile and H_2O molecules. This effect is impossible in the gas phase, so the maxima observed in it are solely due to interactions between the OH⁻ ion and the protons on the β-lactam ring.

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