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Computer Graphics / Molecular Mechanics Studies of β-Lactam Antibiotics. Geometry Comparison with X-Ray Crystal Structures

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Geometries for a number of representative β-lactam antibiotics (penams, cephems and monobactams) have been calculated by computer graphics/molecular mechanics energy minimization procedures using both MM2 and AMBER force fields. The calculated geometries have been found in reasonable agreement with the geometries reported in the X-ray crystal structures, especially in terms of the pyramidal character of the amide nitrogen in the β-lactam ring and the Cohen distance. Based on these calculations, it is suggested that the nitrogen atom in the monobactams may also have pyramidal geometries in the biologically active conformations.

Introduction

Computer-assisted molecular design (CAMD) is recently becoming on important new tool in the molecular research areas such as organic synthesis, enzyme catalysis, drug-receptor interactions and protein engineering.[1-10] The CAMD technique commonly involves the interactive manipulation of three-dimensional molecular structure information by means of a sophisticated computer graphics system; the requisite 3-D structural information is typically obtained from X-ray crystallographic data and from theoretical computations. In the case of "small molecules" (excluding proteins and other macromolecules) X-ray crystallographic methods provide highly precise unambiguous information of molecular structure and conformation in the solid state. Subject to certan limitations, *e.g.* disorder in the crystal littice, occluded solvent, polymorphism, unusual intermolecular interactions or crystal packing forces, the X-ray experiment provides a time-averaged model of the low energy conformations of the given molecule within a given crystal lattice environment. More recently, 2D-NMR techniques such as NOE measurments are becoming an increasingly powerful tool for exploring molecular conformations in solution.

Theoretical calculation methods including *ab initio,* semiempirical quantum mechanics and molecular mechanics (energy minimization, grid searching of conformational space, Monte Carlo searches and molecular dynamics simulations) have been employed to generate and study 3-D molecular conformations. *Ab initio* and semiempirical quantum mechanics calculations have profitably been applied to a wide range of chemical problems but they have not yet been shown practical for studying molecular interactions involved with, for example, enzyme catalysis and ligand-receptor interactions.[4] Molecular mechanics calculations have been very useful in studying organic molecules in non-polar solvents and in the gas phase. They use simple analytical functions to represent bond stretching, bending, and torsional and non-bonded (dispersion, attraction exchange repulsion and electrostatic interaction) energies of molecules.[11] Since evaluation of these analytical functions is computationally rapid and efficient the molecular mechanics methods can be applied to the study of complex molecular systems and interactions.

In connection with our research program of applying the CAMD techniques to the design of physiologically important molecules,[12] we desired to evaluate the reliability and utility of the computer graphics/molecular mechanics method in the molecular design of several types of antibiotics. Thus, we have generated a number of energy minimized molecular conformations of the β-lactam antibiotics by using molecular mechanics calculations, compared them with the corresponding solid state X-ray crystallographic conformation and herein report the results.

Results and Discussions

Among the representative β-lactam antibiotics whose X-ray crystal structures are available either through the published literature or accessible Cambridge Structures Database(CSD), we have selected three penams(**1-3**), two cephems(**4,5**), three oxa/carbapenams(**6-8**), and two monobactams(**9,10**) as test examples. The structures were interac-

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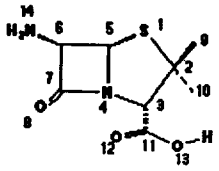
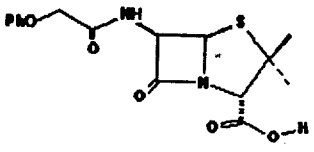


1. 6-Aminopenicillanic Acid



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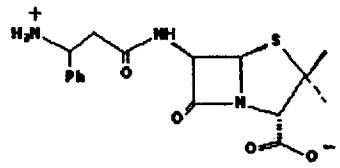
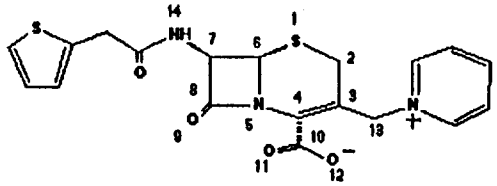
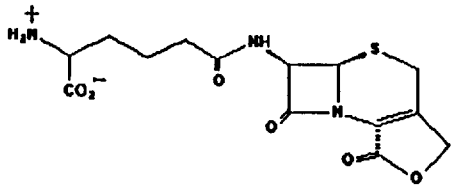


3. Ampicillin



4. Cephaloridine



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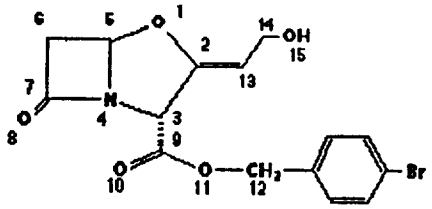
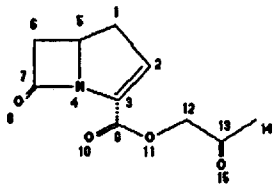


6. Clavulanate



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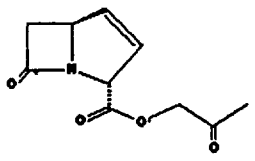

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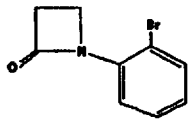

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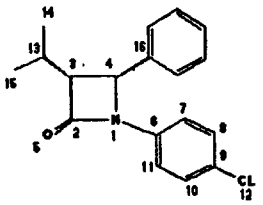

10

tively built on the molecular modeling system, and their geometries refined using the molecular mechanics algorithms of the MacroModel Molecular Modeling System.[13] In the geometry refinements based on the energy minimization procedures, we employed both the MM-2[14] and AMBER[15] force field parameters. It has generally been acknowledged that the MM-2 force field is an all-atom field which is useful for small molecules, whereas the AMBER is a unite-atom field which is useful for peptide and nucleic acid modeling.[3,4]

The molecular parameters obtained from the reported X-ray crystal structures and the molecular mechanics calculations are listed in Table 1 through 4 for penams, cepems, oxa/carbapenams, and monobactams, respectively. The bond distances of the calculated geometries generally agree with those of the solid state geometries within several percentage point deviation in all the structures studied, although some exceptions are noted where the deviation is as large as 10 percent in the cephaloridine(**4**) structure. No apparent and predictable advantages of one force field over the other has been observed.[16] The bond angles in the calculated structures differ from those in the X-ray structures substantially more than the usual standard deviations observed in the X-ray crystallography. Geometry calculations on the zwitter ionic form of 6-aminopenicillanic acid(**1**) and the non-ionized form of ampicillin(**3**) have also been carried out. No significant differences are observed between the gross molecular geometries of the non-ionized and zwitter ionic structures, although the molecular parameters in the immediate vicinity of the ionization sites have been somewhat altered.

It has generally been understood that the gas phase molecular structures agree reasonably well with those found in crystal, although some significant deviations are also observed in certain cases. For example, biphenyl has a twisted conformation in the gas phase, but is planar in the crystal. Furthermore, molecular mechanics calculations of the isolated molecule gave a conformation with a central bond length and torsional angle close to the gas phase values.[11] The deviations of molecular structures in crystal from the results of quantum mechanical or molecular mechanics calculations are most often explained in terms of crystal packing effects and the influence of the crystal forces on the geometry.[17]

Despite the extensive research work in both biology and medicinal chemistry of β-lactam antibiotics, the detailed understanding of the 3-D molecular geometry requirements for the biological activities is still limited. The origin of the biological mode of action of these antibiotics is believed to be related to their ability to irreversibly acylate the active site of the transpeptidase enzyme involved in the biosynthesis of the peptidoglycan moiety of the bacterial cell wall. It has been suggested by Strominger that the transpeptidase should recognize the D-ala-D-ala residues of the pentapeptide fragments of the nascent cell wall in order to carry out the necessary cross linking and that the antibiotic behaves as a structural analog of the endogenous substrate, thus aborting the cross linking.[18,19]

The currently recognized minimum structures of β-lactam antibiotics required to show the biological activity are the chemical reactivity of the β-lactam amide bond and a suitable distance geometry between the oxygen atom of the β-lactam amide functionality and the carbon atom of the carboxy group (Cohen Distance).[20] The chemical reactivity is related to the pyramidality of the amide nitrogen atom, thus hindering the amide resonance in the β-lactam ring. The required

Table 1. Molecular Parameters for Penam Derivatives

		6-APA (**1**)			Pen V (**2**)			Ampicillin (**3**)		
		X-ray	MM-2	Amber	X-ray	MM-2	Amber	X-ray	MM-2	Amber
A. Interatomic distances (A)	S(1)-C(2)	1.859	1.844	1.805	1.87	1.854	1.806	1.855	1.857	1.811
	S(1)-C(5)	1.822	1.821	1.820	1.82	1.822	1.817	1.791	1.822	1.819
	C(2)-C(3)	1.575	1.547	1.541	1.57	1.550	1.540	1.573	1.549	1.527
	C(3)-N(4)	1.445	1.477	1.452	1.46	1.479	1.452	1.463	1.485	1.453
	N(4)-C(5)	1.450	1.463	1.465	1.52	1.492	1.464	1.470	1.487	1.467
	N(4)-C(7)	1.392	1.371	1.327	1.46	1.379	1.326	1.360	1.379	1.329
	C(5)-C(6)	1.554	1.563	1.547	1.58	1.587	1.549	1.554	1.589	1.546
	C(6)-C(7)	1.520	1.508	1.506	1.55	1.529	1.506	1.540	1.527	1.502
	C(7)-O(8)	1.228	1.228	1.229	1.21	1.223	1.227	1.198	1.224	1.228
	C(2)-C(9)	1.547	1.541	1.534	1.51	1.539	1.527	1.529	1.538	1.533
	C(2)-C(10)	1.502	1.544	1.527	1.58	1.541	1.534	1.514	1.542	1.528
	C(3)-C(11)	1.527	1.526	1.519	1.54	1.518	1.519	1.538	1.536	1.515
	C(11)-O(12)	1.273	1.332	1.326	1.35	1.334	1.326	1.240	1.242	1.247
	C(11)-O(13)	1.230	1.207	1.204	1.21	1.206	1.204	1.245	1.242	1.255
	C(6)-N(14)	1.474	1.445	1.477	1.44	1.482	1.460	1.420	1.486	1.475
	N(14)-CO	—	—	—	1.37	1.390	1.339	1.341	1.388	1.348
	C=O	—	—	—	1.29	1.229	1.227	1.226	1.230	1.226
	CO-C$_\alpha$	—	—	—	1.49	1.521	1.530	1.512	1.525	1.533
Bond angles (Deg)	C(2)-S(1)-C(5)	95.6	93.8	92.1	96	93.5	92.5	89.8	92.9	91.7
	S(1)-C(2)-C(3)	105.7	105.1	103.9	105	105.3	104.2	104.2	104.7	98.5
	C(9)-C(3)-C(10)	111.2	109.5	106.7	112	109.5	106.7	110.8	109.2	107.7
	C(2)-C(3)-N(4)	106.0	102.3	106.7	104	106.7	105.3	101.2	107.2	
	C(2)-C(3)-C(11)	111.8	114.7	115.7	113	114.6	115.8	114.6	113.1	121.0
	N(4)-C(3)-C(11)	109.8	114.7	109.9	114	114.9	209.9	113.3	118.8	111.1
	C(3)-N(4)-C(5)	118.0	125.5	117.9	120	125.7	118.0	117.8	125.5	110.9
	C(3)-N(4)-C(7)	132.5	122.0	122.8	129	121.9	122.5	127.7	123.5	119.6
	C(5)-N(4)-C(7)	93.5	95.8	91.2	88	95.4	91.2	93.4	95.7	91.5
	S(1)-C(5)-N(4)	103.4	97.8	103.8	103	96.9	104.0	103.7	96.7	106.5
	S(1)-C(5)-C(6)	120.2	119.2	120.1	122	117.9	120.2	118.4	117.8	121.9
	N(4)-C(5)-C(6)	88.1	86.0	89.8	92	85.9	89.8	88.4	85.8	89.2
	C(5)-C(6)-C(7)	84.6	86.4	81.6	83	86.0	81.6	83.6	86.1	82.2
	C(5)-C(6)-N(14)	118.4	115.7	115.3	115	117.2	114.6	118.2	113.7	118.4
	C(7)-C(6)-N(14)	117.3	113.4	116.7	115	119.7	116.4	114.6	128.5	115.7
	N(4)-C(7)-C(6)	91.7	91.5	97.1	96	92.3	97.2	93.1	92.2	96.5
	N(4)-C(7)-O(8)	131.7	133.0	132.2	128	132.0	132.1	132.3	133.2	132.3
	C(6)-C(7)-O(8)	136.4	135.4	129.2	136	135.6	129.2	134.5	134.6	125.7
	C(3)-C(11)-O(12)	116.1	128.0	126.5	115	127.9	126.4	117.4	119.3	120.3
	C(3)-C(11)-O(13)	118.2	112.1	110.0	122	112.1	110.1	116.6	117.3	111.9
	O(12)-C(11)-O(13)	125.7	119.9	123.5	122	120.0	123.5	126.0	123.0	127.8
	C(6)-N(14)-CO	—	—	—	125	122.4	125.3	123.3	126.5	130.4
	N(14)-C=O	—	—	—	125	118.8	120.6	124.5	120.2	119.9
	N(14)-CO-C$_\alpha$	—	—	—	120	119.1	119.9	113.8	124.6	121.9
	C$_\alpha$-C=O	—	—	—	116	122.1	119.5	121.6	115.3	118.1

pyramidalization of the amide bond is usually created by either the strain of the ring fusion as in penams or by electron delocalization through enamine resonance outside the lactam ring as in cephems. In the biologically active compounds the Cohen distances range 3.0-3.9 A. Presumably, this distance has something to do with the 3-D stereochemical features necessary for the recognition of the antibiotics by the enzyme.

The molecular parameters considered to be important for biological activities are listed in Table 5 for compounds **1-10**. It is instructive to note that in the Cohen distance comparisons, the X-ray crystal structures agree far better with the results obtained from the MM-2 than the AMBER calculations. On the other hand, in comparing the sums of the bond angles around the amide nitrogen (a measure of pyramidality), the MM-2 calculations tend to overestimate the pyramidality while the AMBER tends to underestimate it. The average values between these two numbers agree reasonably well with the experimental values found in the crystal structures. It is very intriguing that the AMBER calculations show significant pyramidalities for the amide

Table 2. Molecular Parameters for Cephem Derivatives

		Cephaloridine (**4**)			Cephalosporin C_c (**5**)		
		X-ray	MM-2	Amber	X-ray	MM-2	Amber
A. Interatomic Distances (A)	S(1)-C(2)	1.817	1.828	1.806	1.802	1.829	1.813
	S(1)-C(6)	1.787	1.810	1.817	1.798	1.816	1.832
	C(2)-C(3)	1.501	1.520	1.504	1.486	1.502	1.498
	C(3)-C(4)	1.360	1.351	1.418	1.329	1.336	1.375
	C(4)-C(13)	1.500	1.527	1.515	1.476	1.499	1.484
	C(4)-N(5)	1.393	1.333	1.345	1.419	1.321	1.340
	C(4)-C(10)	1.514	1.360	1.480	1.459	1.480	1.468
	N(5)-C(6)	1.463	1.485	1.465	1.479	1.489	1.470
	N(5)-C(8)	1.382	1.378	1.382	1.385	1.374	1.379
	C(6)-C(7)	1.567	1.584	1.555	1.535	1.587	1.554
	C(7)-C(8)	1.499	1.531	1.504	1.527	1.533	1.505
	C(7)-N(14)	1.440	1.480	1.456	1.442	1.480	1.455
	C(8)-O(9)	1.214	1.224	1.228	1.209	1.223	1.227
	C(10)-O(11)	1.183	1.237	1.246	1.188	1.207	1.204
	C(10)-O(12)	1.304	1.246	1.249	1.358	1.354	1.350
	N(14)-CO	1.352	1.388	1.334	1.332	1.388	1.333
	C=O	1.224	1.229	1.228	1.245	1.229	1.228
	CO-C_α	1.528	1.517	1.526	1.489	1.520	1.522
B. Bon Angles (Deg)	C(2)-S(1)-(6)	94.4	94.0	97.9	96.9	95.8	101.0
	S(1)-C(2)-(3)	115.7	115.1	112.7	113.0	111.3	110.6
	C(2)-C(3)-(4)	123.1	122.3	120.6	124.0	125.8	124.7
	C(2)-C(3)-(13)	114.5	113.3	116.8	128.6	124.6	127.3
	C(4)-C(3)-C(3)	122.4	124.4	122.6	107.2	109.5	108.0
	C(3)-C(4)-N(5)	120.3	118.6	120.5	125.6	120.3	123.2
	C(3)-C(4)-C(1)	126.0	118.1	119.9	110.0	106.1	109.6
	N(5)-C(4)-C(1)	113.4	123.2	119.4	124.3	133.6	127.1
	C(4)-N(5)-C(6)	126.3	150.0	130.2	119.5	127.8	127.5
	C(4)-N(5)-C(8)	130.4	133.1	117.6	130.5	134.0	116.8
	C(6)-N(5)-C(8)	94.0	96.0	91.1	93.7	96.5	90.8
	(S)-C(6)-N(5)	110.7	102.7	111.0	111.9	104.5	112.6
	S(1)-C(6)-C(7)	116.5	116.6	118.3	114.5	117.7	117.2
	N(5)-C(6)-C(7)	86.7	85.8	89.9	86.6	85.4	89.8
	C(6)-C(7)-C(8)	85.5	86.3	83.3	86.1	86.5	83.1
	C(6)-C(7)-N(1)	120.4	118.6	115.6	121.0	118.4	114.6
	C(8)-C(7)-N(1)	116.3	117.2	115.2	115.6	117.1	115.6
	N(5)-C(8)-C(7)	92.4	91.8	95.2	90.3	91.6	95.5
	N(5)-C(8)-O(9)	131.1	134.5	135.0	132.1	133.4	133.7
	C(7)-C(8)-O(9)	136.3	133.6	127.2	137.5	134.9	127.8
	C(4)-C(10)-O(1)	120.9	123.6	116.9	132.1	127.3	127.7
	C(4)-C(10)-O(12)	113.4	116.1	117.1	107.7	110.5	106.4
	O(11)-C(10)-O(12)	125.7	119.7	125.5	120.0	122.2	125.9
	C(7)-N(14)-CO	121.6	117.0	123.2	122.6	116.9	122.4
	N(14)-C=O	123.4	121.5	122.1	119.3	121.5	122.5

nitrogen in the monobactams **9** and **10**. The antibacterial activities observed in monobactams such as sulfazecin have been considered to be rather puzzling from the standpoint of established structure-activity relationships. The β-lactam nitrogens in all monobactams whose structures are investigated by X-ray diffraction is planar, although the distance between the oxygen of the amide group and the sulfur atom (3.355 A) is reportedly compatible with the Cohen distance.[20]

It appears possible that monobactams may exist in pyramidal conformation in gas and solution phases, although they show planar geometry in crystals, perhaps due to the crystal packing and other effects. This possibility may be examined by molecular mechanics calculations with included crystal packing effects,[17] or by 2D-NMR NOESY experiments.[21,22] We further suggest that since the monobactam ring is considerably more susceptible to conformational distortions than the bicyclic systems such as penams and cephems, a substantial degree of pyramidality may also be induced upon its interaction with the enzyme active site. In other words, the biologically active conformation of the monobactams inside the enzyme cavity might possess a substantial degree of pyramidality, thus showing an enhanced chemical reactivity towards the enzymic nucleophiles.

Experimental Methods

The molecular modeling system at POSTECH consists of Evans & Sutherland PS 390 graphics station linked to VAX 8800 running the MacroModel Molecular Modeling Software (version, 2.0 update)[13]. The MacroModel implementation of MM-2 differs from the standard version[14] in several ways. The major distinction is in electrostatics-whereas the standard version uses dipole/dipole interactions, MacroModel uses partial atomic charges which correspond to the MM-2 dipoles. The field is also set for a distance-dependent dielectric to mimic polarization effects. MacroModel also uses an improper torsion calculation in place of the MM-2 out-of-plane bending. Also incorporated is a preliminary set of parameters for Lennard-Jones hydrogen bonding as used in AMBER. The AMBER field[15] used in the MacroModel is set up for distance-dependent dielectric electrostatics which functions as a crude approximation of polarization effects.

The energy minimizations were carried out to the preset convergence criterion (RMS energy gradient 0.05 KJoule/A) initially by the Steepest Descent(SD) method followed by block diagonal Newton-Raphson(BDNR) method.[14] For the the given structure, molecular hydrogens were added in the Organic Input Mode before the MM-2 calculations. Since the AMBER method requires hydrogens only at the heteroatoms, other types of hydrogens were deleted from the MM-2 minimized structures before the AMBER

Table 3. Molecular Parameters for Oxa/Carbapenams

	6			**7**			**8**		
	X-ray	MM-2	Amber	X-ray	MM-2	Amber	X-ray	MM-2	Amber
X(1)-C(2)	1.401	1.374	1.372	1.485	1.511	1.501	1.325	1.343	1.338
X(1)-C(5)	1.446	1.410	1.438	1.530	1.537	1.534	1.503	1.506	1.496
C(2)-C(3)	1.567	1.524	1.506	1.359	1.341	1.402	1.535	1.515	1.510
C(2)-C(13)	1.345	1.342	1.381	—	—	—	—	—	—
C(3)-N(4)	1.493	1.471	1.437	1.437	1.332	1.337	1.463	1.482	1.452
C(3)-C(9)	1.572	1.515	1.511	1.467	1.484	1.481	1.514	1.517	1.512

A. Interatomic Distances (A)									
N(4)-C(5)	1.526	1.488	1.445	1.494	1.510	1.452	1.517	1.508	1.442
N(4)-C(7)	1.419	1.383	1.338	1.419	1.381	1.393	1.401	1.381	1.340
C(5)-C(6)	1.563	1.569	1.516	1.525	1.575	1.524	1.561	1.572	1.56
C(6)-C(7)	1.512	1.521	1.523	1.518	1.523	1.522	1.524	1.520	1.526
C(7)-O(8)	1.152	1.223	1.227	1.194	1.223	1.228	1.210	1.223	1.221
C(9)-O(10)	1.140	1.210	1.208	1.180	1.211	1.208	1.192	1.210	1.209
C(9)-O(11)	1.360	1.345	1.338	1.367	1.349	1.337	1.345	1.346	1.335
O(11)-C(12)	1.522	1.408	1.433	1.436	1.409	1.431	1.436	1.409	1.431
C(12)-C(13)	—	—	—	1.496	1.518	1.512	1.498	1.518	1.512
C(13)-C(14)	1.452	1.507	1.500	1.480	1.517	1.510	1.500	1.517	1.510
C(13)-C(15)	—	—	—	—	—	—	1.211	1.210	1.211
C(14)-O(15)	1.500	1.411	1.425	—	—	—	—	—	—
B. Bond Angles (Deg)									
C(5)-X(1)-C(2)	113.5	110.7	103.3	113.8	102.5	101.9	111.9	114.7	108.7
X(1)-C(2)-C(3)	109.3	115.2	114.5	111.5	113.7	109.0	111.9	114.8	111.5
X(1)-C(2)-C(13)	121.4	123.4	122.9	—	—	—	—	—	—
C(3)-C(2)-C(13)	129.4	121.3	122.6	—	—	—	—	—	—
C(2)-C(3)-N(4)	98.2	92.0	102.4	110.2	106.5	111.9	101.9	93.2	103.7
C(2)-C(3)-C(9)	110.8	112.5	114.8	131.1	124.0	124.2	109.5	111.2	112.4
N(4)-C(3)-C(9)	106.3	114.2	112.3	118.5	129.4	123.8	112.4	116.0	110.7
C(3)-N(4)-C(5)	112.1	118.0	107.7	107.8	115.6	109.8	111.1	121.6	109.8
C(3)-N(4)-C(7)	123.6	119.4	122.4	124.2	122.7	111.0	118.5	120.4	122.6
C(5)-N(4)-C(7)	91.7	94.2	87.2	92.1	95.2	86.5	90.8	94.7	87.3
N(4)-C(5)-C(6)	87.2	86.9	95.0	88.6	85.4	95.6	88.6	85.7	95.2
N(4)-C(5)-X(1)	101.0	99.7	118.8	105.1	99.8	106.8	101.8	93.1	106.2
X(1)-C(5)-C(6)	113.6	115.3	115.7	119.2	120.4	117.4	117.7	119.3	118.9
C(5)-C(6)-C(7)	86.9	85.8	78.4	87.5	87.1	79.6	84.8	86.8	78.3
C(6)-C(7)-N(4)	93.1	92.7	99.3	91.7	92.1	98.2	94.5	92.3	99.1
C(6)-C(7)-O(8)	139.7	134.8	128.7	137.7	134.2	128.4	135.4	134.9	128.6
N(4)-C(7)-O(8)	127.1	132.3	131.1	130.6	133.3	132.1	130.0	132.6	131.2

Table 4. Molecular Parameters for Monobactams

	9			**10**		
	X-ray	MM-2	Amber	X-ray	MM-2	Amber
A. Interatomic Distances (A)						
N(1)-C(2)	1.387	1.392	1.386	1.366	1.385	1.385
N(1)-C(4)	1.498	1.509	1.466	1.480	1.505	1.464
N(1)-C(6)	1.408	1.349	1.343	1.409	1.343	1.341
C(2)-C(3)	1.517	1.515	1.506	1.518	1.521	1.510
C(2)-O(5)	1.200	1.225	1.229	1.210	1.224	1.229
C(3)-C(4)	1.574	1.564	1.536	1.574	1.575	1.551
C(3)-C(13)	—	—	—	1.524	1.533	1.537
C(4)-C(16)	—	—	—	1.505	1.507	1.516
C(6)-C(7)	1.393	1.406	1.413	1.387	1.398	1.408
C(7)-C(8)	1.386	1.399	1.406	1.394	1.394	1.405
C(7)-Br(12)	1.908	1.911	1.898	—	—	—
C(8)-C(9)	1.364	1.392	1.405	1.371	1.394	1.405
C(9)-C(10)	1.391	1.390	1.404	1.376	1.394	1.405
C(9)-Cl(12)	—		—	1.741	1.737	1.729
C(10)-C(11)	1.375	1.393	1.405	1.389	1.395	1.405
C(11)-C(6)	1.398	1.402	1.409	1.389	1.397	1.409
C(13)-C(14)	—	—	—	1.511	1.538	1.529
C(13)-C(15)	—	—	—	1.527	1.539	1.528
B. Bond Angles (Deg)						
C(2)-N(1)-C(6)	129.9	134.5	112.1	132.7	135.5	115.5
C(2)-N(1)-C(4)	94.5	91.8	88.6	95.0	93.0	90.1
C(4)-N(1)-C(6)	135.5	133.7	127.7	131.1	131.4	127.2
N(1)-C(2)-C(3)	92.6	94.8	97.0	93.0	94.1	96.2
N(1)-C(2)-O(5)	133.1	133.8	132.8	130.9	132.7	133.3
C(3)-C(2)-O(5)	134.2	131.5	129.0	136.1	133.2	129.3
C(2)-C(3)-C(4)	86.6	85.5	81.8	85.5	85.3	82.4
C(2)-C(3)-C(13)	—	—	—	119.1	116.6	116.8
C(4)-C(3)-C(13)	—	—	—	121.0	119.7	115.5
C(3)-C(4)-N(1)	86.3	88.3	92.4	86.5	87.5	91.3
C(3)-C(4)-C(16)	—	—	—	119.6	117.6	118.4
N(1)-C(4)-C(16)	—	—	—	115.9	114.5	114.2

Table 5. Structural Characteristics of β-Lactams

	Bond Angle around N (Deg)			Cohen Distance (A)			**N-CO** Bond Distance (A)			C=O Bond Distance (A)		
	X-ray	MM-2	Amber	X-ray	MM-2	Amber	X-ray	MM-2	Amber	X-ray	MM-2	Amber
1	344	343.3	331.9	—	3.829	3.725	1.392	1.371	1.327	1.228	1.228	1.229
2	377	343	331.7	—	3.830	3.712	1.46	1.379	1.326	1.21	1.223	1.227
3	338.9	344.7	331.0	3.899	3.906	3.302	1.360	1.379	1.329	1.198	1.224	1.229
4	350.7	359.1	338.9	3.198	3.277	2.899	1.382	1.378	1.382	1.214	1.224	1.228

5	343.7	358.3	335.1	—	3.520	3.092	1.385	1.374	1.379	1.209	1.223	1.227
6	327.4	331.6	317.3	4.396	4.329	4.194	1.419	1.383	1.338	1.152	1.223	1.227
7	324.1	333.5	307.3	3.613	3.508	3.254	1.419	1.381	1.393	1.194	1.223	1.228
8	320.4	336.7	319.7	4.276	4.280	4.208	1.401	1.381	1.340	1.210	1.223	1.227
9	359.9	360	328.4	—	—	—	1.387	1.392	1.386	1.200	1.225	1.229
10	358.2	359.9	332.8	—	—	—	1.366	1.385	1.385	1.210	1.224	1.229

Table 6. Total Calculated Potential Energies (K Joules/mole)

Compound	MM-2	AMBER
1	170.06	289.10
2	242.67	254.90
3	277.36	154.22
4	133.26	173.54
5	152.09	215.5
6	231.01	311.75
7	242.69	352.85
8	207.75	321.44
9	173.98	294.01
10	176.49	295.27

calculations. The total force field potential energy values are listed in **Table 6.** The X-ray crystal molecular parameters were obtained from literature for compoudns **1-5**,[23] and from the CSD sources for compounds **1-5**,[23] and from the CSD sources for compounds **6-10.**

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