

Semi-empirical quantum chemical study on structure–activity relationship in monocyclic- β -lactam antibiotics

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Abstract

β -Lactam antibiotics have been highly emphasized in theoretical research and practical synthesis for a long time. They have been the main drugs used in the clinical treatment of bacterial diseases. In this paper, PM3 semi-empirical quantum chemical method has been employed to optimize the molecular geometry, and quantitative structure–activity relationship in 23 kinds of monocyclic- β -lactam antibiotics systematically. Moreover, the structure–activity model of monocyclic- β -lactam antibiotics was studied. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Monocyclic- β -lactam antibiotics; Comparative molecular force analysis (CoMFA); Quantitative structure-activity relationship (QSAR)

1. Introduction

β -Lactam antibiotics are the most commonly prescribed medicines for treating bacterial diseases. The biochemical mechanism of β -lactam is to prevent cell-wall synthesis in bacteria [1]. It has a high order of selective toxicity to microorganisms which are pathogenic to human beings, and no obvious side effects in humans. Since the 1980s, a series of non-traditional β -lactam antibiotics and their precursors, such as cephalosporin and penicillin derivatives, have been developed. These compounds have higher biological activity, wider range of anti-microorganism activity and their stability and reliability have been improved. Among these antibiotics, monocyclic- β -lactam is a kind of new compound which is not only structurally simple for ease of synthesis, but also has a special feature in the

biological activity and range of antibiotics. So, from the beginning of its discovery, monocyclic- β -lactam antibiotics attracted attention in the research field of antibiotics [2–6]. In this paper, we used the semi-empirical quantum chemistry method PM3 [7] to study the molecular structure, energy, and atomic net charge of 23 kinds of monocyclic- β -lactam antibiotics. On the basis of these data, and using partial least square (PLS), the quantitative structure–activity relationship (QSAR) was obtained using least square analysis of quantitative structure factor and biological activity. The structure–activity model of monocyclic- β -lactam antibiotics was proposed.

2. Computational methodology

Comparative molecular force analysis (CoMFA) [8] was used to analyze the three-dimensional-QSAR of 23 kinds of β -lactam antibiotics (Fig. 2) and the possible active conformation was obtained. All parameters were optimized with PM3 method,

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and electron excitation energies ($\Delta E = E_{\text{LUMO}} - E_{\text{HOMO}}$) were obtained. Based on these data, the PLS method was used to analyze QSAR.

3. Results and discussion

3.1. Quantum chemistry study

Fig. 1 shows the biological mechanism of β -lactam. On the attack of the nucleophilic hydroxyl group of series, the peptide bond of the four-membered amide ring is cleaved [9].

This is a nucleophilic substitution reaction and so the strength of each bond of the four-membered amide ring and the atomic net charges are closely related to its biological activity. In this report, we emphasize on the four-membered amide ring. The structures of 23 kinds of monocyclic- β -lactam antibiotics are shown in Fig. 2. The atomic net charges and biological activity are listed in Table 1. The bond lengths, polar moment, and energies of β -lactam are listed in Table 2.

The four-membered amide ring is highly strained which makes the ring unstable, and easy to open. There are two neighboring atoms, N1 and O5, for atom C2 which possesses strong electronegativity and electron-withdrawing ability. This enhances the positive charge on the C2 atom and makes it favorable for the attack of the nucleophile. The nucleophilic substitution and ring opening reaction of the four-membered amide ring were discussed in an earlier research work and partial structure–activity relationship was established. From Tables 1 and 2, one can see that the bond lengths, atomic net charges, dipole moment of the molecule and the energy of the four-membered amide ring can affect the biological activity of monocyclic- β -lactam antibiotics. There is a specified correlation between the relative parameters listed in Tables 1 and 2 and molecular activity. That is to say, the relative parameters of the molecule will change along with the different activities of the molecule. So we choose them to simulate structure–activity models of molecular structures.

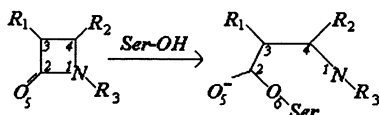


Fig. 1. Reaction mechanism of monocyclic- β -lactam antibiotics.

3.2. Quantitative structure–activity relationship study

After we use the definition of ‘activity’ as the response factor, bond order, atomic net charge, dipole moment of the molecule and frontier orbital excitation energy of the four-membered amide ring as various changing factors, the PLS method has been used to analyze the theoretical computational results and following QSAR model was obtained. The results are listed in Table 3 and Fig. 3.

The dipole moment, electron excitation energies ΔE , bond lengths in Table 2 and atomic net charges in Table 1 were used as descriptive factors in the p -least square analysis to investigate the structure–activity model. Non-cross-check method and pick-one method were used in the PLS analysis. In order to guarantee the reliability of returning model, the two groups of data with the largest deviation were deleted after each PLS analysis and the try PLS analysis is then reiterated once again. The activity values of the model are listed in Table 3. The correlation between experimental activity (EA) and predicted activity (PA) was shown in Fig. 3.

The model equation is:

$$\begin{aligned} -\log C = & 399.736 - 4.099 \times q_{\text{N1}} + 27.428 \times q_{\text{C2}} \\ & - 11.674 \times q_{\text{C3}} + 31.661 \times q_{\text{C4}} - 242.731 \\ & \times q_{\text{O5}} + 362.908 \times P_{\text{N1-C2}} + 311.297 \\ & \times P_{\text{C2-C3}} - 102.182 \times P_{\text{C3-C4}} + 375.352 \\ & \times P_{\text{C4-N1}} - 1573.715 \times P_{\text{C2-O5}} + 0.078 \\ & \times D - 0.295 \times \Delta E \end{aligned}$$

From the model, we learnt that the biological activity of the monocyclic- β -lactam antibiotics can be effected not only by the bond length of peptide, but also by the atomic net charge and other bond lengths of the four-membered amide ring.

The following conclusions can be drawn:

1. The higher the polarity of the molecule, the more active is the compound.
2. The coefficient of the electron excitation energy is negative, meaning that the bigger the ΔE value is, the less active is the compound.
3. The bond length coefficient of C3–C4, C2–O5 is

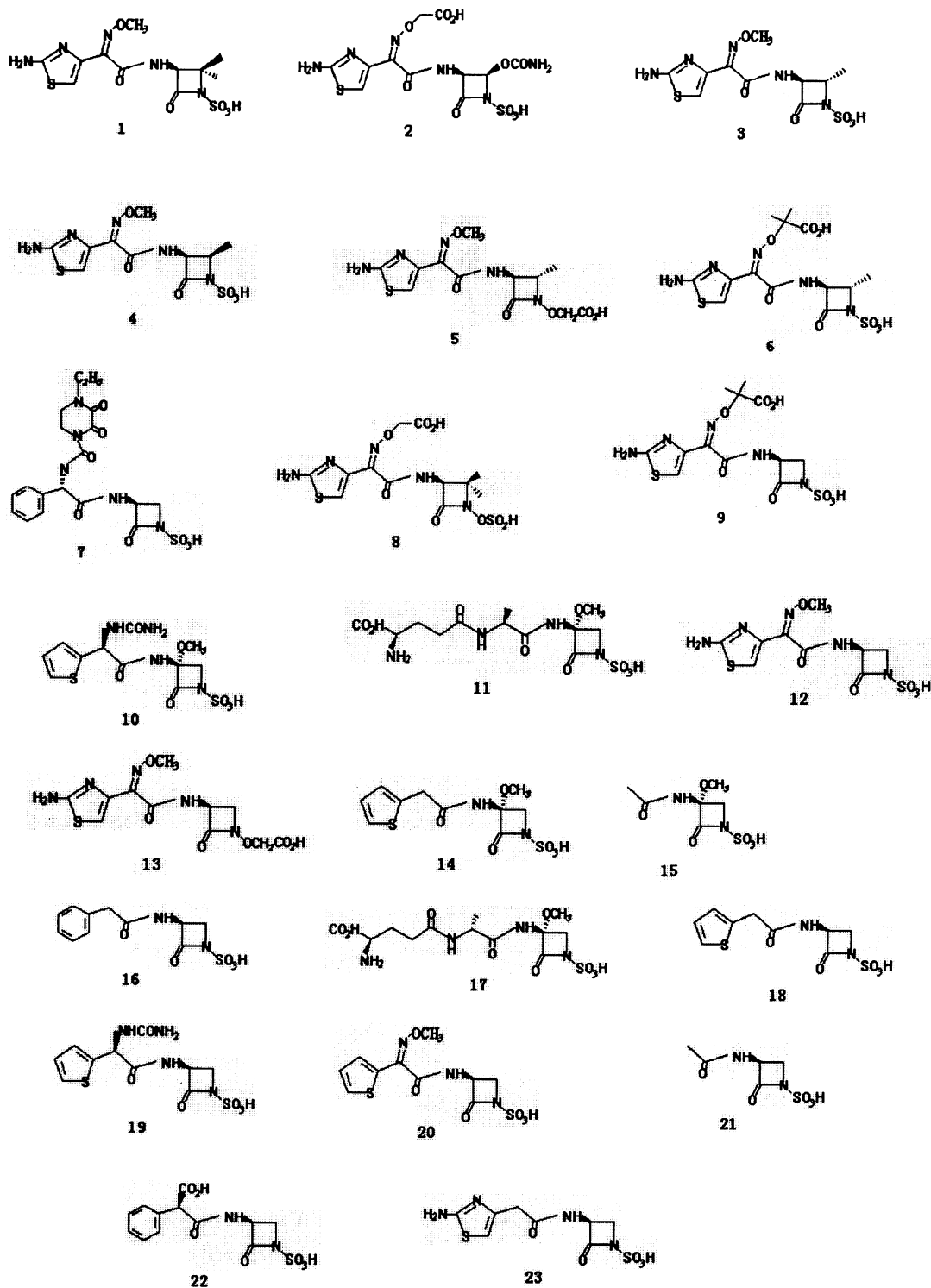


Fig. 2. Molecular structures of 23 monocyclic-β-lactam antibiotics.

Table 1

Atomic net charge and biological activity of monocyclic- β -lactam antibiotics (MIC₉₀ is minimal inhibition concentration; smaller this value, higher the level of its biological activity)

Entry	N1	C2	C3	C4	O5	MIC ₉₀ /-logC
1	-0.6223	0.3571	-0.1155	0.0700	-0.2943	0.1/1.0 [10]
2	-0.6644	0.3645	-0.1032	0.1659	-0.2707	0.12/0.92 [11]
3	-0.6296	0.3601	-0.1152	0.0362	-0.2894	0.125/0.90 [12]
4	-0.6043	0.3626	-0.1098	0.0598	-0.2796	0.15/0.82 [12]
5	-0.0370	0.2644	-0.1297	-0.0384	-0.2705	0.24/0.60 [13]
6	-0.6292	0.3599	-0.1147	0.0378	-0.2898	0.40/0.40 [14]
7	-0.6305	0.3341	-0.1020	0.0313	-0.2829	0.60/0.22 [14]
8	0.0076	0.2522	-0.1375	-0.0188	-0.2495	0.70/0.15 [15]
9	-0.6053	0.3485	-0.1030	0.0325	-0.3010	3.10/-0.49 [14]
10	-0.6140	0.3607	0.0575	-0.0084	-0.2627	3.10/-0.49 [14]
11	-0.6296	0.3601	-0.1152	0.0362	-0.2894	6.25/-0.80 [16]
12	-0.6235	0.3388	-0.1114	0.0276	-0.2872	6.30/-0.80 [14]
13	-0.6141	0.3607	0.0575	-0.0084	-0.2627	8.00/-0.90 [17]
14	-0.6235	0.3472	0.0757	-0.0164	-0.2355	8.50/0.93 [14]
15	-0.6112	0.3736	0.0519	-0.0078	-0.2601	25/-1.40 [18]
16	-0.6062	0.3721	-0.1022	0.0069	-0.2655	25/-1.40 [14]
17	-0.6206	0.3462	0.0807	-0.0078	-0.2607	50/-1.70 [16]
18	-0.6200	0.3366	-0.1047	0.0056	-0.2690	50/-1.70 [14]
19	-0.6168	0.3586	-0.1230	0.0308	-0.2923	50/-1.70 [14]
20	-0.6284	0.3599	-0.1107	0.0097	-0.2835	50/-1.70 [14]
21	-0.6057	0.3757	-0.1050	0.0048	-0.2652	50/-1.70 [18]
22	-0.6220	0.3391	-0.1255	0.0288	-0.2794	100/-2.0 [14]
23	-0.6298	0.3615	-0.0999	0.0118	-0.2877	100/2.0 [14]

Table 2

The bond length of amide ring, dipole moment and energies of monocyclic- β -lactam antibiotics

Entry	N1–C2	C2–C3	C3–C4	C4–N1	C2–O5	<i>D</i>	<i>E</i> _{HOMO} (eV)	<i>E</i> _{LUMO} (eV)	ΔE (eV)
1	0.1457	0.1539	0.1578	0.1541	0.1200	4.972	-9.4196	-0.9725	8.4472
2	0.1469	0.1543	0.1578	0.1534	0.1196	2.961	-9.1362	-1.0901	8.0461
3	0.1460	0.1542	0.1566	0.1531	0.1199	4.409	-9.4045	-0.9941	8.4105
4	0.1460	0.1544	0.1568	0.1531	0.1198	6.281	-8.9485	-0.6536	8.2949
5	0.1481	0.1544	0.1569	0.1529	0.1200	2.934	-9.2464	-0.8103	8.4361
6	0.1459	0.1451	0.1566	0.1531	0.1199	5.021	-9.4421	-1.0673	8.3748
7	0.1461	0.1549	0.1554	0.1520	0.1198	4.239	-9.9427	-0.6816	9.2611
8	0.1483	0.1541	0.1582	0.1545	0.1198	4.054	-9.3973	-0.9142	8.4831
9	0.1456	0.1549	0.1554	0.1522	0.1200	6.461	-9.3327	-0.9524	8.3802
10	0.1461	0.1572	0.1567	0.1511	0.1195	3.323	-9.6717	-1.0322	8.6395
11	0.1465	0.1571	0.1565	0.1515	0.1195	5.675	-10.2531	-0.5996	9.6535
12	0.1460	0.1548	0.1556	0.1520	0.1198	4.286	-9.3132	-0.8198	8.4934
13	0.1485	0.1549	0.1558	0.1517	0.1198	4.547	-9.2524	-0.8645	8.3879
14	0.1470	0.1571	0.1568	0.1511	0.1192	5.801	-9.8765	-0.7684	9.1081
15	0.1463	0.1569	0.1566	0.1512	0.1194	3.601	-10.3275	-0.9130	9.4145
16	0.1466	0.1549	0.1554	0.1517	0.1195	7.175	-9.8267	-0.5027	9.3239
17	0.1464	0.1568	0.1568	0.1513	0.1195	5.724	-10.2279	-0.7626	9.4653
18	0.1463	0.1547	0.1553	0.1522	0.1197	4.429	-9.7843	-0.8383	8.9460
19	0.1457	0.1550	0.1555	0.1519	0.1199	3.092	-9.8353	-0.9037	8.9317
20	0.1463	0.1546	0.1556	0.1518	0.1198	3.280	-9.8028	-0.7191	9.0837
21	0.1467	0.1548	0.1554	0.1518	0.1195	7.451	-10.2872	-0.5258	9.7614
22	0.1459	0.1549	0.1555	0.1519	0.1198	1.832	-10.0906	-0.8728	9.2178
23	0.1462	0.1544	0.1556	0.1519	0.1198	2.781	-9.3398	-0.8711	8.4687

Table 3
PLS analysis results of experimental activity (EA), predicted activity (PA) and deviation (δ)

Entry	EA	PA	δ
1	1.0	1.14	-0.14
2	0.92	-	-
3	0.90	0.79	0.11
4	0.82	0.70	0.12
5	0.60	0.57	0.03
6	0.4	0.31	0.09
7	0.22	0.21	0.01
8	0.15	-	-
9	-0.49	-0.41	-0.08
10	-0.49	-0.51	0.02
11	-0.80	-0.61	-0.19
12	-0.80	-0.78	-0.02
13	-0.90	-0.88	-0.02
14	-0.93	-0.68	-0.25
15	-1.40	-1.28	-0.12
16	-1.40	-1.37	-0.03
17	-1.70	-2.06	0.36
18	-1.70	-1.73	0.03
19	-1.70	-1.67	-0.03
20	-1.70	-1.74	0.04
21	-1.70	-1.72	0.02
22	-2.00	-1.92	-0.08
23	-2.00	-1.66	-0.34

negative, then these bond lengths have inversely proportional relationship with biological activity; the weaker the bond is between these atoms, the less active is the compound.

- The coefficients of bond lengths N1–C2, C2–C3, N1–C4 are positive, their effect on the biological activity of the compound is opposite these or the above-mentioned bonds.
- It is obvious that the atomic net charges of N1, C2, C3, C4 and O5 have inverse relationship with molecular biological activity. The more positive C2 and C4 are

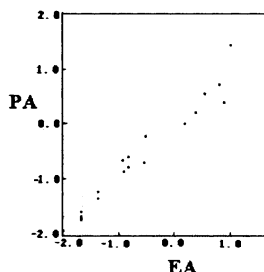


Fig. 3. PA and EA relationship of monocyclic- β -lactam antibiotics.

the more active the compound is. N1, C3, O5 atomic net charges are negative. The more negative charge they possess, the more active the compound is.

From the above conclusions, we can predict that, when new monocyclic- β -lactam antibiotics are designed, putting a strong electron-withdrawing group on C4 and a strong electron-donating group on N1 and C3 may improve the biological activity of the molecule.

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