Journal of Physical & Theoretical Chemistry
Islamic Azad University of Iran 2 (2)
Science and Research Campus
ISSN: 1735-2126

Quantum Mechanics-Molecular Mechanics Model Study of some Antibiotics and Vitamins in Gas Phases: Investigation of Energy and NMR Chemical Shift

M.Monajjemi[1*] H.Aghaie[1], and M.Heshmat [1]

[1] Science and Research Campus, Islamic Azad University, Ponack,Hessarack. Teharn, Iran

ABSTRACT

The combination of Quantum Mechanics (QM) and Molecular Mechanics (MM) methods has become alternative tool for many applications that pure QM and MM could not be suitable.
The QM/MM method has been used for different type of problems, for example: structural biology, surface phenomena, and liquid phase. In this paper we have performed these methods for some antibiotics and vitamins and then we compare results. The calculations have done by full ab initio method (HF/3-21g), (HF/6-31G) and (HF/STO-3G) and QM/MM (ONIOM) method with HF (3-21G)/AM1/UFF HF(6-31G)/AM1/UFF and HF (STO-3G)/AM1/UFF then we find out the geometry that has obtained by QM/MM method is very accurate and we can use this rapid method in place of time consuming ab initio methods for large molecule. The comparison of energy values in QM/MM and QM methods is given. In the present work we compare chemical shifts and conclude that QM/MM method is a perturbed full QM method.

INTRODUCTION

Different computational approaches have strengths and weaknesses. Dramatic progress has been made in the field of computational chemistry in recent years. Molecular mechanics can model very large compound rapidly. Quantum mechanics is able to compute many properties and model chemical reactions. Of course, QM/MM approaches are different and depend on the methods used for calculations in the QM and MM regions. However there are a lot of other attributes characterizing the various publishes methods. Chemical systems that we are interested in computational biology and reaction catalysis are occasionally systems in condensed phase that consist of thousands participating atoms. Presently the most promising theoretical/computational approach for studying large molecular systems (nanoscale systems, biological systems, supramolecular assembles) is the combined QM/MM method.

The combination of quantum and molecular mechanics give results that have very high speed were only one part of molecule needs to be modeled quantum mechanically. Today, it is well accepted that the QM method is the ultimate computational tool that can be used successfully in studying the structural aspects and a variety of its physical and chemical properties.

By use of these calculations energy, bond lengths, bond angles, the most strength bonds, estimation of the active site of the molecule , recognition reaction mechanism in the body , type of penetration in alive cells, also the presence of antibiotic drug residues in food products of animal origin that has potential health hazard to consumers can be obtained. For example sulfonamide residues in some species have been a problem for about 10-12 years. Such studies were done in widespread for biological systems, especially enzymes [1-8].In this study the QM/MM method is focused on antibiotics and vitamins [4].

* Corresponding Author

The calculations of the geometries and NMR shielding tensors have been performed. The calculated values in both methods (QM and QM/MM) were compared and the results were very close together except in the time consumption. For example optimization time for Kanamycin, Streptomycin and Gentamycin has been given in Table 4.

COMPUTATIONAL DETAILS:

GAUSSIAN 98software package [9] is used to perform Hartree-Fock HF, B3LYP, and LSDA calculations on antibiotics and vitamins The semi empirical calculation is based on AM1 method and because we use from Gaussian 98 program we must take UFF force field for molecular mechanic part. Hybrid QM/MM runs were performed as implemented before in ONIOM method. In many respects the issues governing implementation of QM/MM computer codes are similar to those associated with the individual QM and MM methods. Most of the coupling terms are readily computed using the machinery present in either the QM or MM packages. However, it is worth giving brief consideration to a couple of implementation issues. Given that the starting point is working QM and MM codes, QM/MM implementations can be considered to fall into three groups: [10]

(I)Those based on classical modeling packages, with a QM code integrated as a force field extension

(II)Those based on a QM packages, incorporating the MM environment as a perturbation

(III) Modular schemes in which a central control program is provided and a choice of bout QM and MM methods is left open.

METHODOLOGY:

In the basis of ONIOM method we divided every molecule in three parts (L, M, and H) and then optimizes each point. Some of molecules can't be optimized by this method, because of having a double bond or aromatic ring in the link part. The link bonds are a critical aspect of the QM/MM method. Usually, we use a domy atom to complete the QM subsystem. We must notice that the link part always should be in the form of C_α-C_β for two subsystems QM/MM in fact relation between link part and MM or QM subsystems must be through one atom. The QM/MM boundary should not cut across double, triple or aromatic bonds as [11].

Thus one link atom can only be bonded to one QM atom. But the reverse situation is allowed, it means that two link atoms bonded with one QM atom.

The separation of the partial atomic driving force is described as follows: In the ONIOM calculation of the total energy, $E^{REAL}_{ONIOM}(R_1\ldots R_N; r_{m+1},r_{m+2})$, is approximated by

$E^{REAL}_{ONIOM}(R_1,\ldots R_N;r_{m+1},r_{m+2})=E^{REAL}_{MM}(R_1,\ldots,R_N) + E^{MODEL}_{QM}(r_1,\ldots,r_m,r_{m+1},r_{m+2})-E^{MODEL}_{MM}(r_1,\ldots,r_m,r_{m+1},r_{m+2})$ where the REAL system consists of N atoms at R_i (i=1,2,…,N) and the MODEL system consist of (m+2) atoms at r_j(j=1,2,…,m+1,m+2)[12].

RESULT AND DISCUSSION:

According to [12], $E^{REAL}_{ONIOM}(R_1,\ldots R_N;r_{m+1},r_{m+2})$is the total ONIOM optimized energy for each antibiotic,$R_1,\ldots R_N$ are the coordinates for each atom 1…N of the molecules and r_{m+1},r_{m+2} are the coordinates for link atoms. $E^{REAL}_{MM}(R_1,\ldots,R_N)$ is the total MM optimized energyfor R_1toR_N. $E^{MODEL}_{QM}(r_1,\ldots,r_m,r_{m+1},r_{m+2})$ is the total QM optimized energy for medium region and link atoms. $E^{MODEL}_{MM}(r_1,\ldots,r_m,r_{m+1},r_{m+2})$is the total MM optimized energy for medium region and link atoms[10].

In the present work we compare the result test from pure quantum mechanic (ab initio) calculation of molecule and QM/MM results. The calculations were performed by the use of GAUSSIAN 98 software package [9]. We conclude that these two data groups are in good agreement. Then we can use the QM/MM method for recognizing the active site of antibiotic molecules and mechanism of their reactions in the body. In all test examples the results of QM/MM calculations were compared to the corresponding results of full quantum mechanical study. The optimized geometries are summarized in Table2.

In ab initio quantum chemistry, analytical derivative theories have made possible the

calculations of many important molecular properties. It should be pointed out that a direct comparison of the QM/MM predictions or to the experimental data available for the same molecular system is complicated by the fact that the empirical parameterization contained in the MM force fields is partly responsible either for an excellent agreement (may be due to successful cancellation of errors) or serious disagreement between two sets of values. In ONIOM method that we use in this work particle exchanges between high-level and low-level sub systems do not disturb the statistical ensemble. NMR shielding tensors (ppm) have been computed with the continuous set of the gauge independent atomic orbital (GIAO) method [13-16]. The δ values for isotropy and anisotropy are shown in figures 1-8.

As we see in NMR isotropy and anisotropy for antibiotics (Table1), in the high region of calculations a similar trend has obtained for the QM and QM/MM methods [17,18]. In medium and low regions (semi empirical and molecular mechanic parts) some perturbations were observed in the form of the following equations:

$$H_{eff}=H^0_{qm}+H_{mm}+H^{elec}_{qm/mm}+H^{vdw}_{qm/mm} \quad (1)$$

Where:

$$H^{vdw}_{qm/mm}= \sum_{ss=1}\sum_{mm=1} 4\ \varepsilon_{sm}[(\sigma_{sm}/R_{sm})^{12}-(\sigma_{sm}/R_{sm})^{6}] \quad (2)$$

s: The number of atoms in MM part
m: The number of atoms in QM part
The ϭ and ε are experimental parameters.

$$E_{qm/mm} = \langle \Psi | H_{qm/mm} | \Psi \rangle + E^{vdw}_{qm/mm} \quad (3)$$

$$H^{elec}_{qm/mm} = \Sigma_{ss}=1\Sigma_{mm}=1\ q_s\ Z_m / R_{sm} \quad (4)$$

q_s: atomic charge on MM atom
Z_m: atomic charge on QM atom
R_{sm}: distances between particles
In the MM region we use total strain energy in the form of:

$$E_{total}=\Sigma\ (E_b+E_\theta+E_\varphi+E_{nb}+E_\varepsilon+E_{hb}+E_\delta+\ldots) \quad (5)$$

In this part of calculations two domy atoms (H) are entered in the molecule and chemical environment of atoms differ with the primary structure .In full ab initio method the hydrogen and carbon atoms have resemble chemical environment and their chemical shifts are approximately uniform. Therefor simply we can see the effect of isolation of parts in NMR spectra. Usually the heavy atoms that contain electron pairs have high δ values and display picks.

The energy values for some different ab initio and DFT methods and the comparison between the QM and QM/MM methods have been given in Table3.

As observed geometrical values are very close in two methods and where the ab initio calculations are not possible, for examples in molecules consist of 100 or graters number of atoms we can use from QM/MM results with completely assurance.

CONCLUSION:

This brief review of the QM/MM approach has emphasized the variety of ways that QM and MM calculations can be combined. As may be clear from the number of variations that are possible it will probably be difficult to get exactly the same answer with two separate implementations and like the force fields themselves the methodology will gradually gain acceptance on the basis of experience.

The QM/MM model for describing biomolecules, while successful still requires further development which will lead to a better integration of the QM and MM formalisms by solving the problem of the QM/MM boundary in a general way thus it is expected that both the development and the application of QM/MM method will continue to expand strongly in the current decade and that the information obtained from QM/MM calculations will be essential for a deep understanding of biochemical processes. A number of other systems are currently under study with the new QM/MM methods that have been developed recently in this group. Implementations of the algorithm to calculate NMR chemical shielding tensors in the QM/MM framework makes it possible to study the chemical shift of specific group in biomolecules.

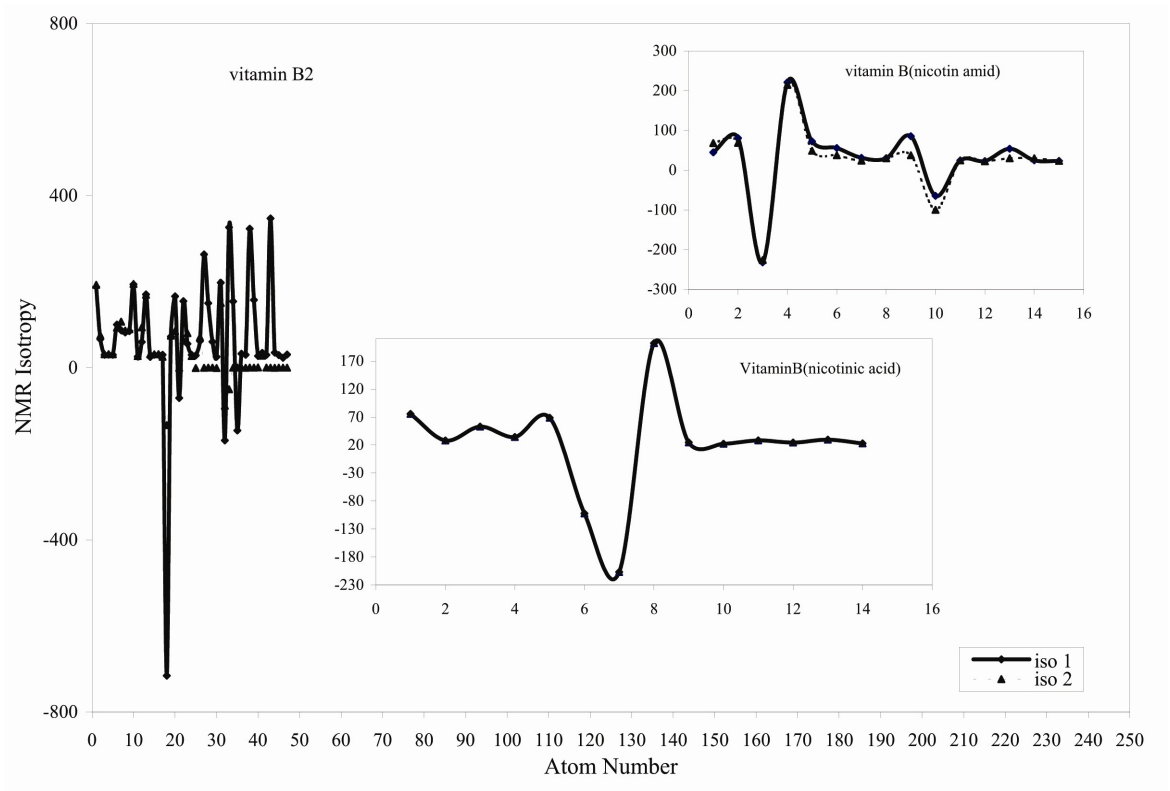


Figure 1. NMR Isotropy diagramsof Vitamins for QM Method (iso1)and QM/MM Method (iso2).

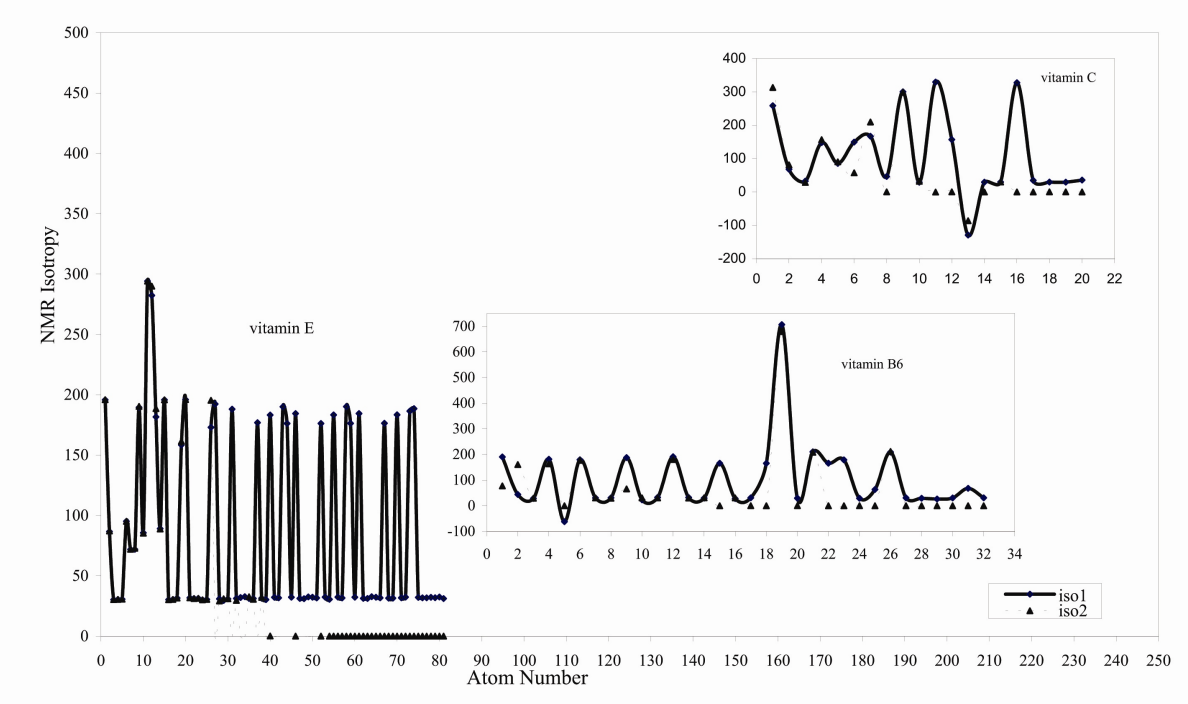


Figure 2. NMR Isotropy diagrams of Vitamins for QM Method (iso1)and QM/MM Method (iso2).

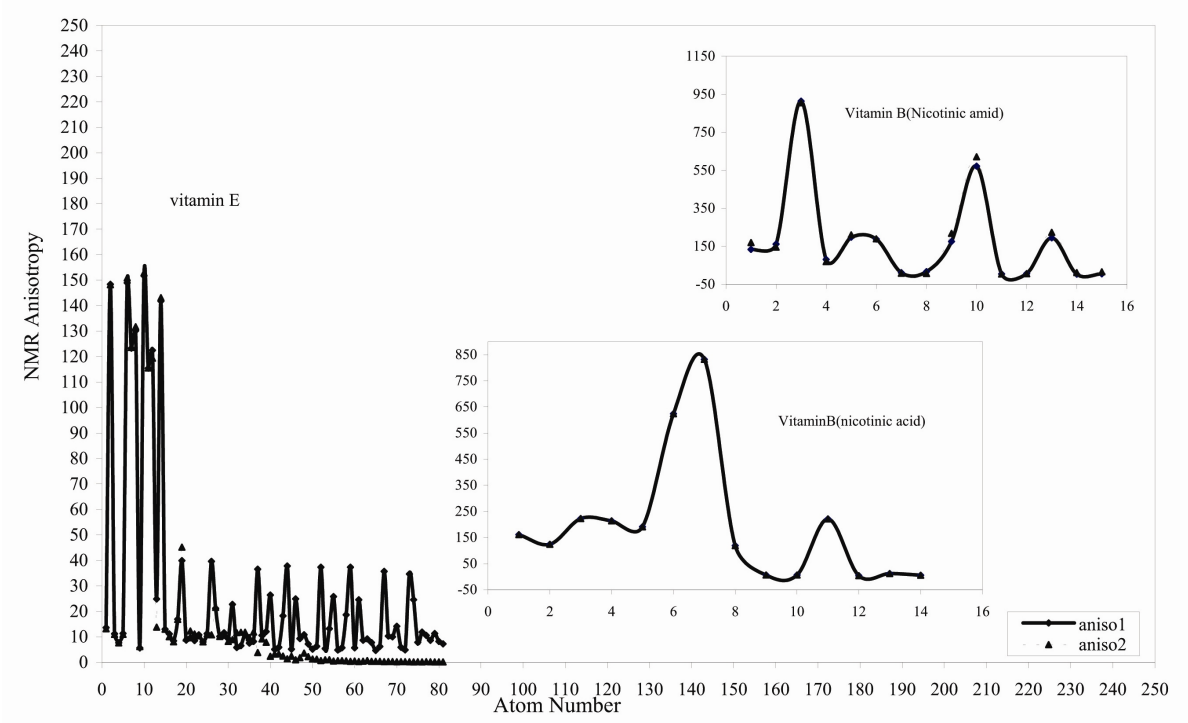


Figure 3. NMR Anisotropy diagrams of Vitamins for QM Method (aniso1)and QM/MM Method (aniso2).

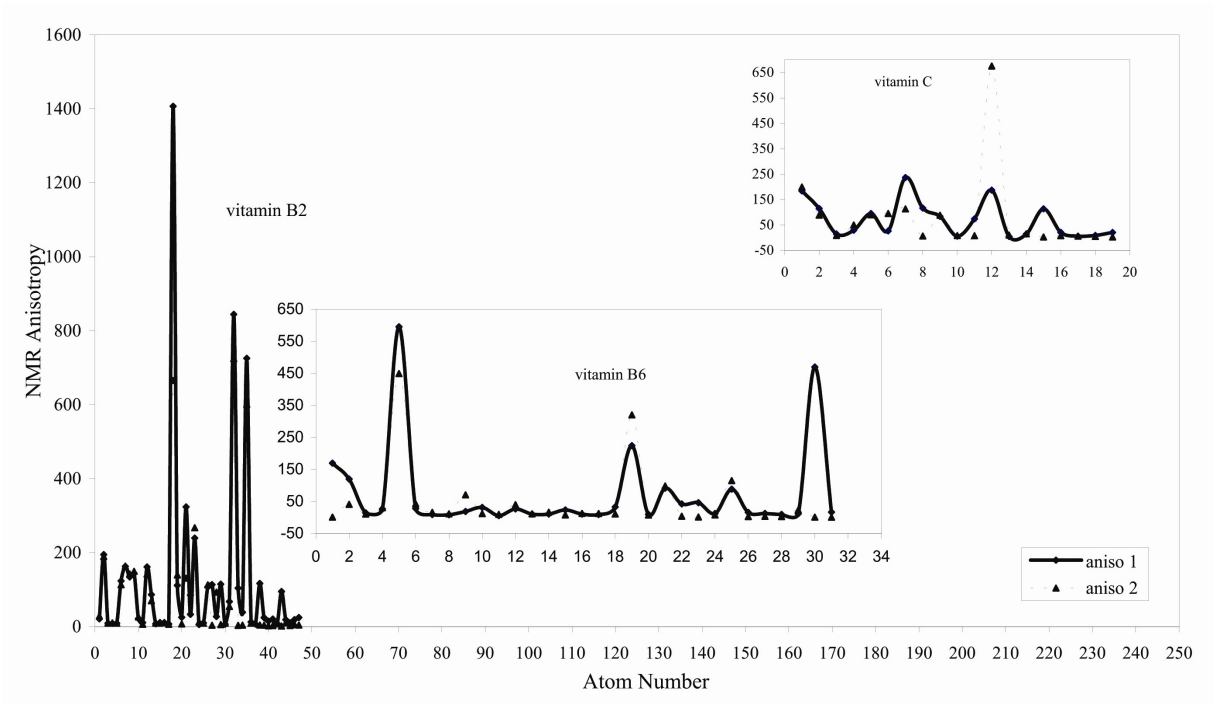


Figure 4. NMR Anisotropy diagrams of Vitamins for QM Method (aniso1)and QM/MM Method (aniso2).

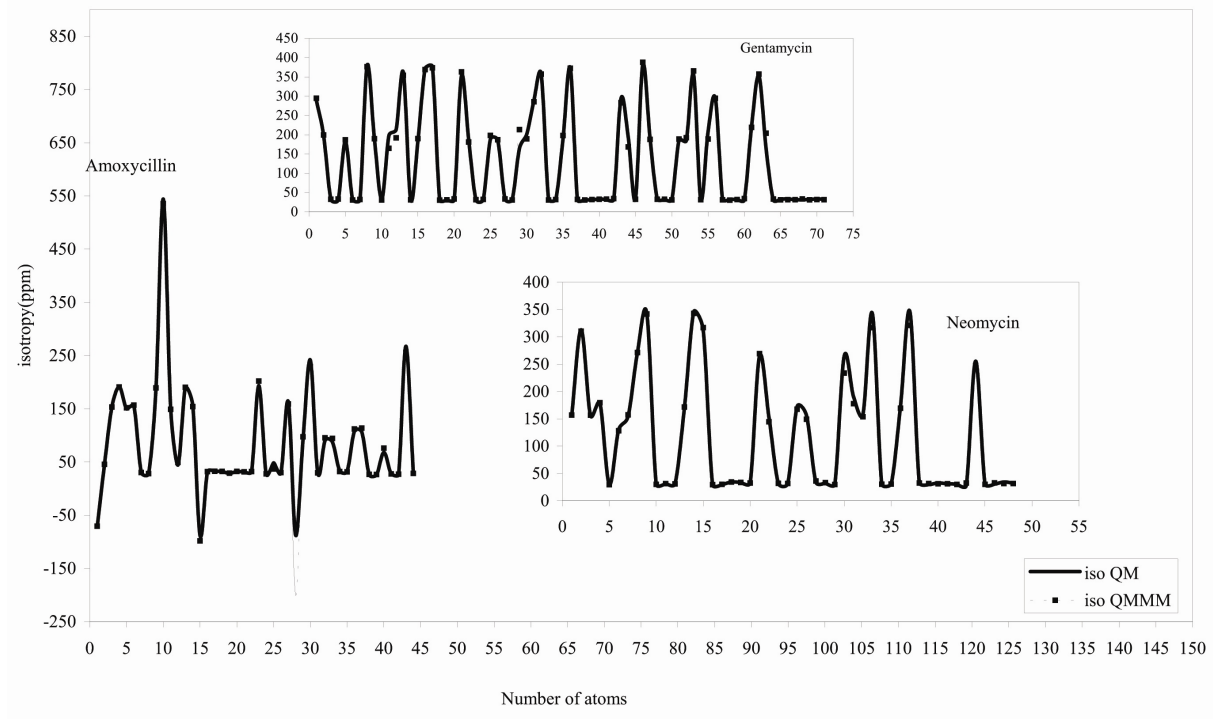


Figure 5. Calculated NMR Isotropy by QM and QM/MM methods.

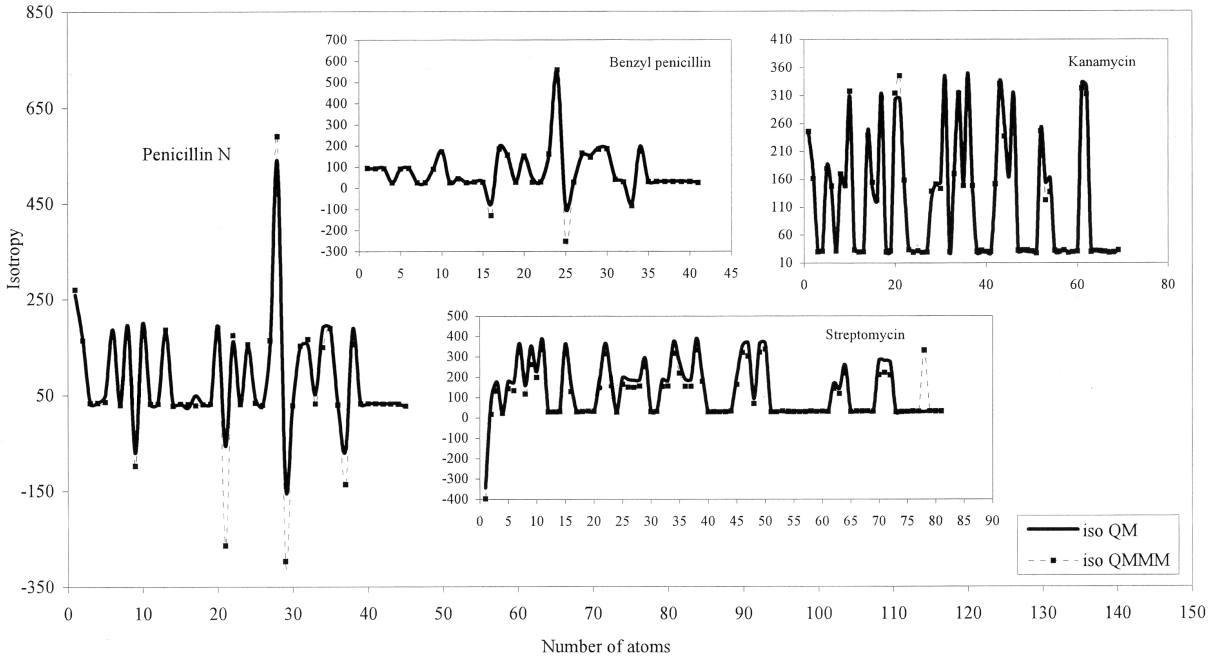


Figure 6. Calculated NMR Isotropy by QM and QM/MN.

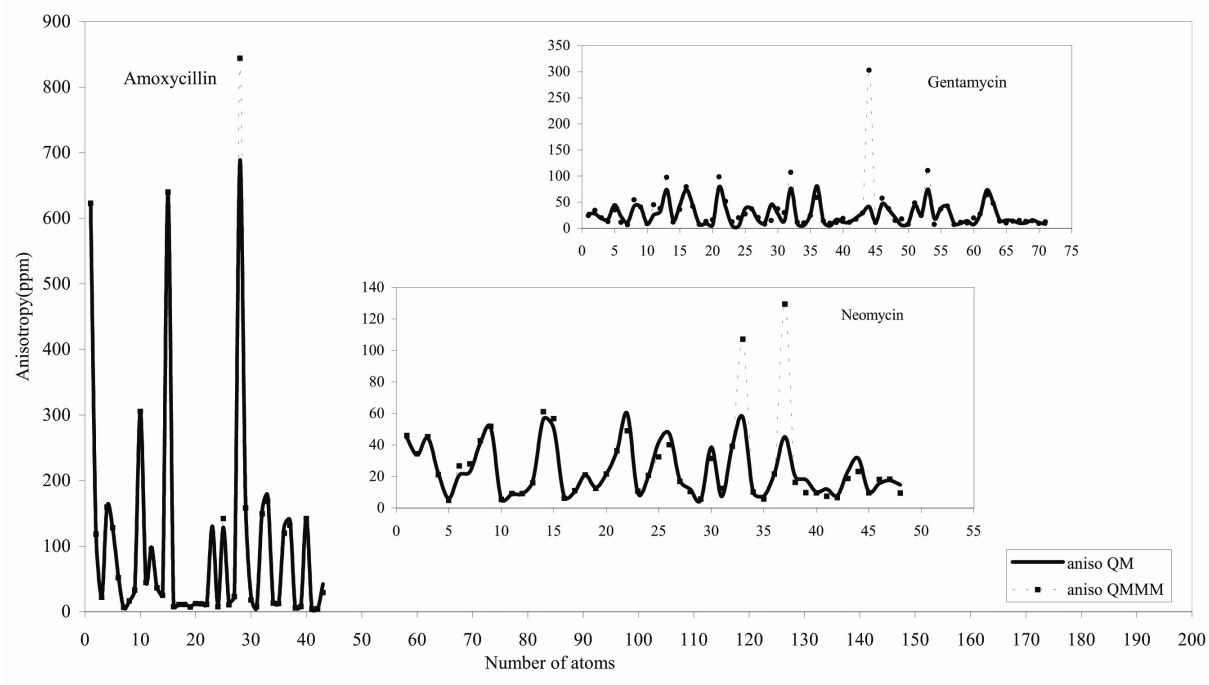


Figure7. Calculated NMR Anisotropy by QM and QM/MM methods.

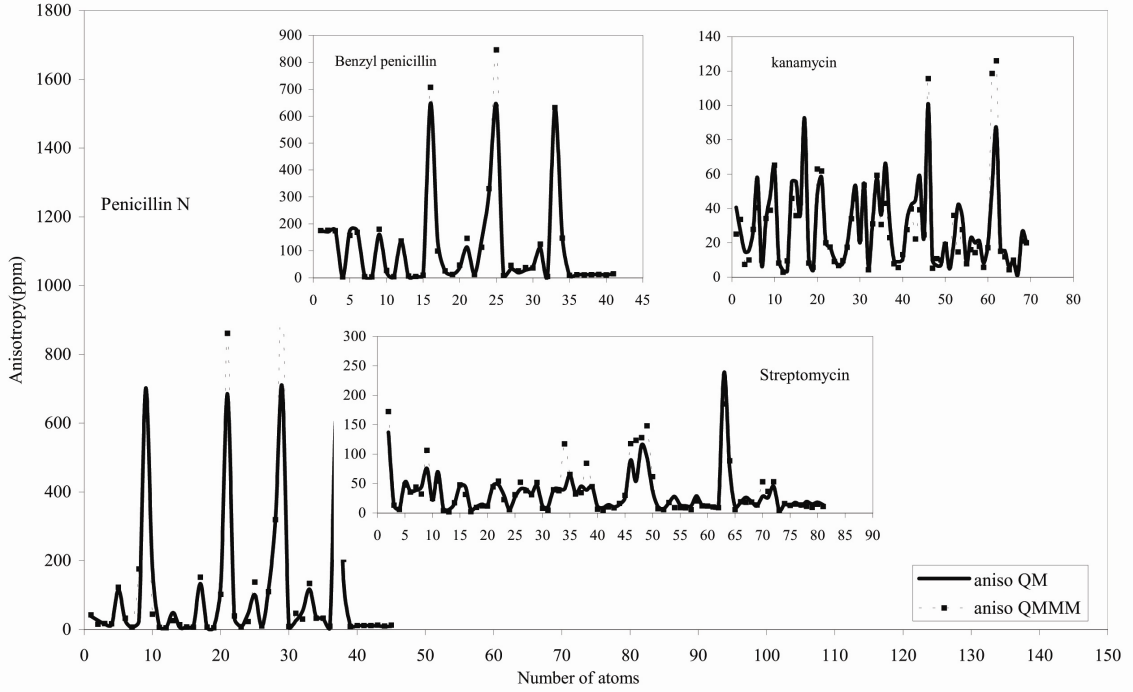


Figure 8. Calculated Anisotropy by QM and QM/MM method.

Table1. The comparison between resultant QM and QM/MM Isotropy,Anisotropy and Chemical shiftAnisotropy Asymmetry(Etha)

Antibiotic / Atom		QM			QM/MM		
		Isotropy (ppm)	Anisotropy (ppm)	Etha	Isotropy (ppm)	Anisotropy (ppm)	Etha
Penicillin N	N1	259.4764	-25.5084	1.8270	270.2220	-16.7483	0.4395
	O9	-70.6660	405.3953	-2.7435	180.7549	-50.1697	3.1016
	O10	199.3262	180.6477	0.2525	-97.5844	-27.3620	19.4987
	N20	-193.8844	37.8635	4.7432	-296.7816	393.7661	-2.1899
	O21	-55.9257	-265.0861	1.0835	190.3148	35.1709	1.8994
	N27	151.0595	114.8195	-0.4008	163.7063	57.6385	-0.1721
Gentamycin	N1	289.1194	26.5275	0.7262	295.1335	9.5489	3.6087
	O8	379.6643	-35.4001	1.1547	376.6949	38.9611	0.5754
	O16	361.1793	-35.4001	4.5864	369.2707	28.9016	-4.0937
	N17	288.9021	-11.2733	0.3245	285.8393	7.0689	0.2027
	O20	371.8920	13.4852	2.3133	357.3987	-49.1711	2.0225
	O22	376.2995	44.0402	-1.6170	372.5392	-6.1402	-2.6378
Benzyl-Penicillin	N16	192.6588	-46.6411	-3.8537	165.1936	45.8629	-3.4013
	O17	-84.0312	-358.3685	-0.4442	-130.0047	-342.1075	-0.6910
	N23	140.9620	81.8637	0.5216	161.8641	62.8843	-1.1014
	S24	530.2199	71.0631	2.5934	599.1027	168.3297	0.5887
	O25	-94.7227	385.2121	-2.2951	-251.1780	399.4710	-2.2297
	O33	-71.2745	-395.3331	-0.1769	-83.8716	-467.6284	-0.3328
Streptomycin	O1	-342.9533	999.0713	-0.1075	-397.7195	625.9290	1.8667
	O7	365.6820	21.0208	-1.7953	321.9443	15.0629	-0.2348
	O9	352.6940	51.4798	-0.8995	262.1071	88.8769	-1.0542
	O11	384.8125	46.2513	1.3498	334.5991	6.2631	3.4802
	N29	292.1538	11.8455	-6.3965	250.6474	3.4802	-11.9742
	N35	273.3409	14.4431	-6.1816	219.4225	-15.5077	-0.4228
Kanamycin	N1	243.7632	-6.9787	-11.2623	245.7689	16.4824	-0.9714
	O10	307.8146	31.4294	2.7652	345.2533	37.3437	-0.5195
	N14	247.7343	-6.7450	10.8454	238.5792	4.3886	-2.3674
	O17	313.0080	-27.7770	-4.4375	313.6998	40.4003	0.0917
	O20	301.7441	43.3493	0.6071	300.9153	-274.7366	0.5328
	O21	305.1157	-264.7204	5.7175	336.7489	19.1721	3.4834
Neomycin	O2	312.9844	-0.1071	164.8151	310.2457	-1.7443	11.4925
	N8	271.3593	0.8879	18.6109	271.2868	0.4523	-1.1814
	O9	341.8986	14.9862	3.2249	341.7557	19.4749	1.7089
	O14	346.0949	-32.9642	-0.2783	343.0432	-371.4624	-0.7607
	O15	312.6415	13.8043	0.1013	316.8814	16.4403	-0.1819
	N21	265.0583	-14.8125	0.4772	269.2565	22.6116	-0.3636
Amoxycilin	O1	-72.5490	109.0002	-2.1979	-70.6113	325.1847	-2.4406
	O4	191.2364	-117.3046	-0.2730	190.7483	-154.5213	1.6302
	N5	149.7623	125.5613	0.2812	151.8711	64.9583	-2.0875
	S10	543.9982	53.0307	5.8038	535.3778	165.8745	10.6828
	O15	-88.6107	209.0251	-3.2990	-98.3273	-406.6466	0.1350
	N23	193.4785	23.2478	9.5392	32.0677	123.5060	-0.5070

Table 2. Geometric data comparison (a)

Method / Antibitic	QM(HF/STO-3G)						*QM/MM(ONIOM/AM1/STO-3G)		
	Bond Length		Angle		Torsion		Bond Length	Angle	Torsion
Gentamycin	R(1,2)	1.4872	A(2,1,3)	107.5508	D(3,1,2,5)	165.8139	1.4658(H)	106.2177	166.3004
	R(1,3)	1.0325	A(3,1,4)	105.5441	D(3,1,2,6)	43.2751	1.0335(H)	107.2584	48.1602
	R(2,6)	1.5539	A(1,2,6)	114.2216	D(4,1,2,5)	52.6942	1.1252(M)	107.5106	82.9067
	R(2,7)	1.0924	A(1,2,7)	108.3453			1.1209(M)	112.6706	
	R(2,5)	1.5539	A(1,2,5)	108.0114			1.5471(L)	110.7801	
			A(5,2,7)	107.6574				110.5552	
Streptomycin	R(1,2)	1.2166	A(1,2,3)	124.0378	D(1,2,3,5)	79.8769	1.2167(H)	124.2261	96.5851
	R(3,7)	1.4305	A(2,3,5)	111.4762	D(4,2,3,5)	99.9776	1.4318(H)	111.6398	83.4827
	R(5,10)	1.5414	A(6,11,16)	115.9816	D(3,5,10,18)	54.9853	1.5406(M)	113.6157	56.3064
	R(6,11)	1.4345	A(18,20,10)	109.1552	D(9,5,10,18)	63.4836	1.395(M)	109.013	61.033
	R(15,21)	1.4349	A(5,10,18)	110.1679	D(3,6,11,16)	156.032	1.3974(L)	110.2323	167.5119
	R(11,16)	1.4356	A(18,10,19)	108.9361	D(3,5,10,19)	65.1125	1.3985(L)	108.9551	64.0679
Neomycin	R(1,2)	1.4517	A(1,3,9)	108.7298	D(3,1,2,6)	63.7036	1.4454(H)	109.2582	66.9726
	R(8,18)	1.0042	A(8,4,12)	113.7329	D(9,3,7,13)	171.9786	1.0032(H)	113.971	171.0443
	R(15,22)	1.4458	A(6,15,22)	119.5938	D(15,6,13,7)	74.0331	1.4003(M)	113.3632	74.1027
	R(26,21)	1.0036	A(15,6,16)	110.9605	D(1,2,6,15)	62.4017	0.9835(L)	113.437	62.0783
	R(21,25)	1.0031	A(13,21,28)	110.5331	D(13,6,15,22)	170.5782	0.9782(L)	90.7267	161.1146
			A(25,22,26)	111.425	D(2,6,15,22)	67.3999		106.1211	78.7944
**Kanamycin	R(30,24)	1.5606	A(27,23,28)	111.8316	D(23,27,30,24)	30.8579	1.564(H)	112.242	28.0366
	R(1,2)		A(3,1,4)		D(3,1,2,6)				
	R(15,20)	1.4413	A(30,24,32)	110.255	D(5,29,30,24)	63.4242	1.4864(H)	108.069	65.6426
	R(5,9)		A(1,2,10)		D(1,2,8,14)				
	R(5,12)	1.0874	A(33,30,12)	1005.6652	D(33,30,24,12)	175.92	0.9905(M)	104.4232	173.9484
	R(4,12)		A(1,4,12)		D(2,1,4,12)				
	R(9,7)	1.5606	A(9,7,14)	111.5099	D(23,9,7,14)	107.4849	1.3896(L)	114.4554	106.2713
	R(13,21)		A(13,21,25)		D(6,13,21,25)				
	R(9,23)	1.4382	A(9,23,31)	112.3972	D(27,31,9,23)	18.5384	1.4471(L)	113.0142	21.8729
	R(6,13)		A(6,13,7)		D(3,7,13,6)				
Penicillin N	R(1,2)	1.4747	A((2,1,3)	114.4312	D(3,1,2,6)	92.1826	1.4367(H)	116.1293	76.4889
	R(1,4)	1.0063	A(7,3,6)	11.041	D(1,2,3,7)	150.3452	1.0031(H)	116.7761	162.0065
	R(2,7)	1.0851	A(2,5,9)	122.9126	D(6,7,2,8)	57.426	1.1287(M)	129.1952	88.3912
	R(5,9)	1.2015	A(6,2,7)	109.034			1.2314(M)	109.4599	
	R(13,17)	1.5149	A(1,2,6)	115.5248			1.5087(L)	112.268	
	R(20,22)	1.4228	A(5,2,6)	109.9593			2.9728(L)	108.2868	
Amoxycillin	R(6,13)	1.5291	A(6,9,16)	111.5394	D(6,3,5,11)	2.008	1.5287(H)	111.5615	1.1556
	R(12,14)	1.5479	A(20,13,22)	108.7822	D(9,6,13,20)	52.9199	1.587(H)	108.7355	52.7142
	R(26,23)	1.0015	A(23,14,24)	112.3918	D(5,11,14,23)	127.8987	0.9978(M)	112.0165	125.1758
	R(14,23)	1.4271	A(14,23,26)	116.7758	D(11,14,23,26)	32.5251	1.3968(M)	112.1836	75.1656
	R(31,27)	1.085	A(25,23,26)	113.7447	D(12,14,23,25)	104.612	1.1123(L)	114.9898	163.8114
	R(32,37)	1.3807			D(11,14,23,25)	156.3674	1.35023(L)		64.7453
penicillin B	R(1,2)	1.3816	A(2,1,3)	119.7149	D(3,1,2,5)	0.1162	1.3833(H)	119.7313	0.4789
	R(3,8)	1.0718	A(5,2,7)	119.721	D(2,1,3,8)	179.8691	1.0721(H)	119.8091	179.7936
	R(12,15)	1.0815	A(9,12,14)	110.5186	D(5,9,12,14)	8.1616	1.1251(M)	110.7938	15.0563
	R(12,14)	1.0813	A(14,12,15)	108.6868	D(3,6,9,12)	178.7708	1.1207(M)	106.3989	179.897
	R(12,13)	1.5194	A(13,12,15)	105.9928	D(5,9,12,13)	49.4916	1.5158(L)	109.2112	137.7132
			A(9,12,13	110.5651	D(6,9,12,13)	49.4916		113.9004	43.5595

Table2. Continued

Method / Vitamins	QM (HF/ 3-21G)				* QM/MM (ONIOM /AM1)				
	Bond Length		Angle		Torsion Angle		Bond length	Angle	Torsion Angle
C	R(1,2)	1.3816	A(4,1,3)	111.1057	D(1,4,8,5)	-3.8013	1.37531(H)	110.6768	-3.0425
	R(1,4)	1.3122	A(13,7,6)	123.8991	D(6,7,4,8)	179.911	1.3132(H)	123.2899	179.2442
	R(3,5)	1.5179	A(14,5,12)	110.1637	D(3,5,12,18)	68.9468	1.5127(M)	109.2405	60.425
	R(5,12)	1.5297	A(5,11,3)	106.2457	D(11,5,12,16)	-50.0886	1.5417(M)	109.6989	-57.6097
	R(16,20)	0.9663	A(18,12,16)	112.3905	D(18,12,16,20)	38.0644	0.9929(L)	109.6995	47.5355
	R(12,16)	1.4498	A(12,16,20)	111.0731	D(5,12,16,20)	-86.0398	1.4022(L)	106.6118	-74.6647
B (nicotinic acid)	R(9,5)	1.3285	A(9,5,12)	117.2779	D(5,3,9,1)	0.0001	1.3296(H)	116.8618	-0.0206
	R(1,2)	1.3852	A(1,2,60)	118.5809	D(2,6,9,5)	-0.0001	1.3859(H)	118.7821	-0.0063
	R(3,7)	1.4688	A(7,3,5)	118.8294	D(1,3,7,11)	179.998	1.4601(M)	119.5119	179.9284
	R(7,10)	1.3517	A(7,10,14)	113.3603	D(10,7,3,1)	0.0021	1.3673(M)	112.2713	0.0557
	R(10,14)	0.9539	A(11,7,3)	125.2126	D(14,10,7,11)	0.0019	1.0143(L)	121.3259	0.0613
B(nicotinic amid)	R(6,11)	1.3317	A(1,4,3)	118.1458	D(15,11,6,4)	-179.839	1.3307(H)	118.1459	-179.785
	R(1,4)	1.3863	A(6,11,5)	122.5205	D(10,4,1,2)	-0.2963	1.3902(H)	122.4868	0.1336
	R(1,2)	1.4914	A(1,2,7)	121.0364	D(2,1,3,9)	-0.8097	1.4632(M)	121.0169	-0.1262
	R(2,8)	1.3547	A(2,8,14)	117.6448	D(2,1,3,5)	-179.276	1.4088(M)	120.2057	-179.523
	R(8,14)	0.9976	A(14,13,8)	118.1665	D(13,8,2,7)	168.923	1.0443)L)	118.5687	177.7076
	R(8,13)	0.993	A(2,7,8)	122.2829			1.0443(L)	119.7286	
B6	R(6,14)	1.2126	A(9,8,3)	104.4162	D(3,1,2,10)	173.298	1.212(H)	106.8842	176.0137
	R(4,9)	1.8864	A(7,6,14)	126.8767	D(8,9,4,13)	13.501	1.8766(H)	127.0039	156.6553
	R(15,8)	1.5333	A(15,8,19)	107.5325	D(8,15,18,22)	-54.9452	1.4897(M)	108.6561	-50.5763
	R(15,18)	1.537	A(15,18,20)	109.0694	D(19,15,18,21)	62.3115	1.5415(M)	109.4322	66.7461
	R(27,31)	1.2026	A(31,30,27)	122.1328	D(31,27,30,32)	0.4158	1.2221(L)	120.2845	0
	R(24,21)	1.5315	A(27,30,32)	111.7642	D(29,24,27,31)	-0.3174	1.5363(L)	112.98	-0.0163
B2	R(7,2)	1.3762	A(1,2,7)	119.4352	D(1,2,7,10)	-179.854	1.3765(H)	119.5124	-179.924
	R(19,22)	1.2815	A(10,18,12)	120.3268	D(33,27,22,19)	-179.971	1.2752(H)	120.5583	-179.896
	R(20,13)	1.478	A(13,20,24)	108.742	D(10,13,20,24)	37.8963	1.4571(M)	108.0603	39.7116
	R(20,23)	1.5302	A(20,23,28)	105.0153	D(10,13,20,23)	-81.2697	1.5525(M)	108.6775	-80.3923
	R(29,35)	1.5253	A(29,34,35)	107.5426	D(20,23.28,36)	178.748	1.5586(L)	110.68	178.9318
	R(23,28)	1.4397	A(45,39,35)	109.3799			1.4033(L)	109.8044	
E**	R(1,30)	1.3814	A(26,28,30)	119.4697	D(5,4,26,6)	164.256	1.3814(H)	119.4387	163.7499
	R(1,4)		A(4,7,14)		D(12,5,14,19)				
	R(5,6)	1.4552	A(6,5,4)	120.2836	D(25,23,24,6)	62.0159	1.4581(H)	120.1011	59.9185
	R(12,19)		A(12,19,5)		D(34,13,19,27)				
	R(7,8)	1.5398	A(7,6,23)	112.5452	D(5,6,7,35)	-62.8713	1.5428(M)	111.0211	-63.5962
	R(26,31)		A(26,19,27)		D(33,26,19,12)				
	R(6,7)	1.5351	A(7,8,38)	108.0207	D(7,8,9,10)	-176.298			
	R(26,19)		A(26,31,32)		D(26,31,37,40)		1.5033(M)	107.9848	-171.751
	R(8,9)	1.5421	A(10,11,12)	111.0577	D(18,19,20,22)	171.571			
	R(31,37)		A(40,43,44)		D(6,67,70,74)		1.5379(L)	111.1261	169.3888
	R(21,20)	1.541	A(20,21,22)	109.5977	D(22,20,21,62)	-56.4022			
	R(74,70)		A(73,70,74)		D(74,70,73,76)		1.5344(L)	109.772	-52.7193

(a) Bond length in Angestrom and angles in deg; (b) calculations in QM were performed by 3-21g except for tnevitamin B(nicotinic acid), which have been done by 6-31g

* H,M,L are related to the level of calculations

** After optimization,the atom number is different in each method,so we wrote the equal positions ,the upper is the nomen clature in QM and the lower in QM/MM

Table3. The Optimized Structure of Different Antibiotics with Their Energies(in Hartree) by QM and QM/MM Methods

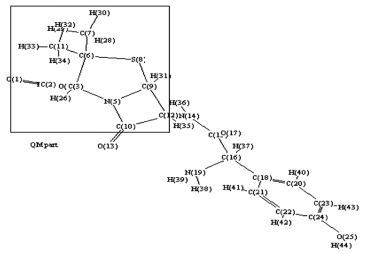
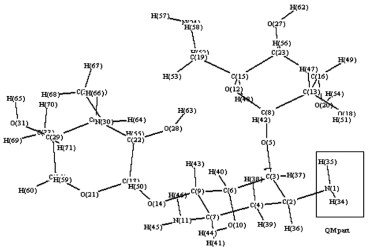
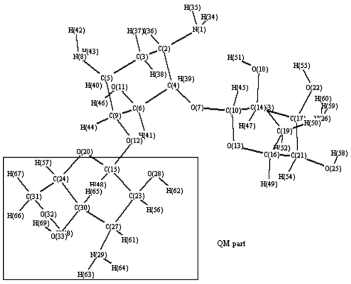
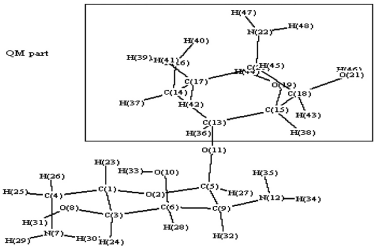
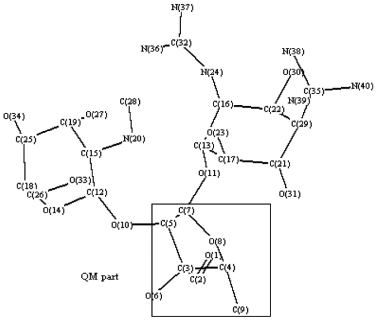
Structure	QM /3-21G			QM/MM /3-21G		
	HF	B3LYP	LSDA	HF	B3LYP	LSDA
Amoxycilin 	-1543.7406662	-1551.3320605	-1544.2061673	-1543.7051903	-1551.3007558	-1544.1770218
Gentamycin 	-1698.4550694	-1708.5923462	-1699.8719074	-1698.3845529	-1708.5163471	-1699.7991278
Kanamycin 	-1734.0996830	-1744.3167454	-1735.4697345	-1734.0396267	-1744.2399020	-1735.3803990
Neomycin 	-1130.2036684	-1136.9499716	-1131.1477236	-1130.1302393	-1136.8790582	-1131.0697881
Streptomycin 	-2086.8245071	-2099.1499472	-2088.4760577	-2086.7109075	-2099.0036450	-2088.3046473

Table 3. Continued

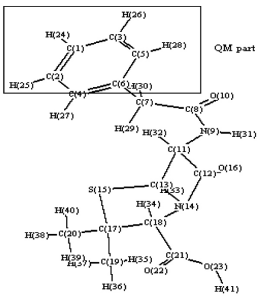
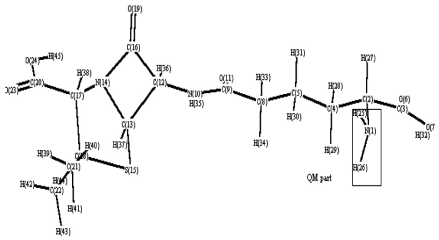
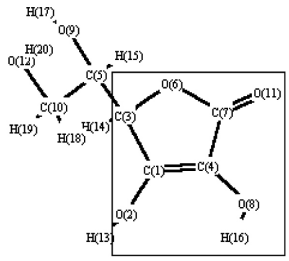
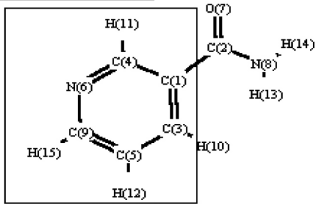
Structure	QM/3-21G			QM/MM/3-21G		
	HF	B3LYP	LSDA	HF	B3LYP	LSDA
Benzyl Penicillin 	-1414.5848985	-1421.4993239	-1414.9987423	-1414.5251216	-1421.4516870	-1414.9622243
Penicillin N 	-1544.0668550	-1551.5906856	-1544.5587528	-1543.9504374	-1551.4922398	-1544.4569103
Vitamin C 	-677.199766	-717.51221	-713.948978	-667.19976	-680.9442525	-677.5082932
Vitamin B(Nicotinic amid) 	-434.1213417	-436.716137	-434.3644688	-434.1151957	-436.7155297	-434.3644309

Table 3. Continued

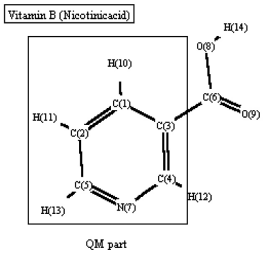
	QM/3-21G			QM/MM		
	HF	B3LYP	LSDA	HF	B3LYP	LSDA
Vitamin B (Nicotinicacid)  QM part	-412.1578258	-414.6767787	-412.4300262	-412.1578153	-434.4321184	-432.1087647

Table3. Continued

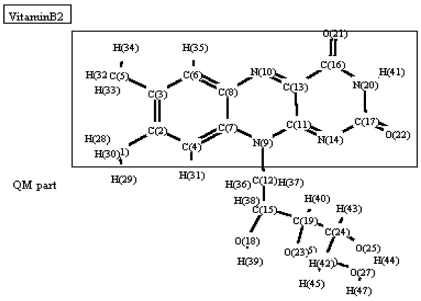
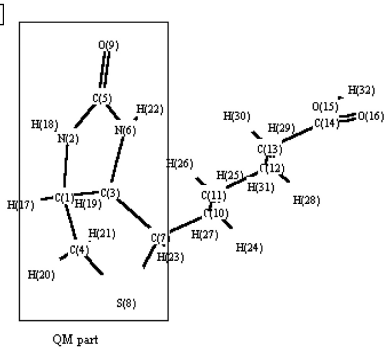
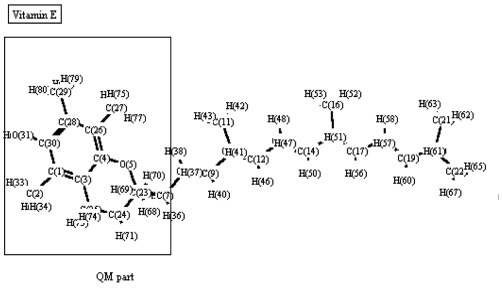
VitaminB2  QM part	-1315.034385	-1322.838881	-1315.9028	-1314.995636	-1322.873542	-1315.940476
VitaminB6  QM part	-1113.662355	-1118.156323	-1113.328608	-1113.073894	-1118.148479	-1113.325304
Vitamin E  QM part	-1269.996881	-1278.717119	-1271.736894	-1269.977009	-1278.710773	-1271.74198

Table 4. The comparison of time consumption

Antibiotic / Time(s)	Methods	
	QM	QM/MM
Kanamycin	15659	344
Streptomycin	38441	125
Gentamycin	8374	24

REFERENCES

1. Jason C. Hart, Neil A. Burton, Ian H Hillier, 1997, Chem.Commun. 1431-32.
2. Haiyan Liu, Yingkai Zhang, weitao Yang, 2000, J.Am. Chem. Soc., 122, 6560-70.
3. Thom Vreven, Keiji Morokuma, Michael J. Frisch, 2003, J. Comp. Chem., 24,760-69.
4. Gherman BF, Goldberg SD, Cornish VW, Friesner RA., 2004, J.Am. Chem. Soc., 126(24), 7652-64.
5. Jose A. Gascon and Victor S. Batista, 2003, Dep. Chem. Yale University, PO Box 208107, New Haven.
6. Milan Remko, Piet Th. Van Duijnen, and Marcel, 2003, Structural Chem., 14(3), 271-78.
7. U. Roethlisberger, P. Vidossich, P. Carloni, 2003, Science& Supercomputing at Cineca, 432-36.
8. Atsushi Yamada, Takakazu Ishikura, Takahisa Yamato, 2004, Proteins:structure,function,bioinformatics, 55, 1063-69.
9. Gaussian 98, Revision A.7, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Brent, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui,
   K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1998.
10. Paul Sherwood Hybrid Quantum Mechanics/Molecular Mechanics approaches John Von Neumann Institute for Computing.
11. SCM Vrije Universiteit; Theoretical Chemistry ADF QM/MM Program System Release 2002.01
12. Atsushi Yamada,Takakazu Ishikura, Takahisa Yamato,2004, Proteins: Structure, Function, and Bioinformatics, 55, 1070-77.
13. R.Ditchfield, 1974, Mol.Phys, 27, 789.
14. J.R.Cheesman, M.J.Frisch, F.J.Devlin, and P.J.Stephens, 1996, Chem.Phys.Lett.
15. R.Mac.Weeny, 1962, Phys.Rev., 126, 1028.
16. K.Wolinsky, J.F.Hilton and P.Pulay, 1990, J.Am.Chem.Soc, 112, 8251.
17. Q.Cui and M.Karplus, 2000, J.Phys.Chem.B 104:3721-3743.
18. Pablo A.Molina, R. Steven Sikorski, Jan H.Jensen , 2003,Theor.Chem.Acc. 109:100-7.