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QM/MM Model Study on Properties and Structure of Some Antibiotics in Gas Phase: Comparison of Energy and NMR Chemical Shift

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Abstract—The combination of Quantum Mechanics (QM) and Molecular Mechanics (MM) methods has become an alternative tool for many applications for which pure QM and MM are not suitable. The QM/MM method has been used for different types of problems, for example: structural biology, surface phenomena, and liquid phase. In this paper, we have used these methods for antibiotics and then we compared results. The calculations were done by the full *ab initio* method (HF/3-21G) and the (HF/STO-3G) and QM/MM (ONIOM) method with HF (3-21G)/AM1/UFF and HF (STO-3G)/AM1/UFF. We found the geometry obtained by the QM/MM method to be very accurate, and we can use this rapid method in place of time consuming *ab initio* methods for large molecules. Comparison of energy values in the QM/MM and QM methods is given. In the present work, we compare chemical shifts and conclude that the QM/MM method is a perturbed full QM method. The work has been done on penicillin, streptomycin, benzyl penicillin, neomycin, kanamycin, gentamicin, and amoxicillin.

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Key words: quantum mechanics, molecular mechanics, *ab initio* calculations, antibiotics

Various 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 compounds 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 many other attributes characterizing the various published methods. Chemical systems of interest in computational biology and reaction catalysis are occasionally systems in condensed phase that consist of thousands of participating atoms.

The combination of quantum and molecular mechanics gives very rapid results where only one part of the 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 of a molecule and a variety of its physical and chemical properties.

Using these calculations energy, bond lengths, bond angles, the strongest bonds, estimation of the active site of a molecule, recognition of reaction mechanism in the body, type of penetration in living cells, and 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 are widespread for biological systems, especially enzymes [1-8].

In this study, the QM/MM method is focused on antibiotics [4]. The geometries and NMR shielding tensors have been calculated. The calculated values from both methods (QM and QM/MM) were compared and the results were very close together except in time consumption. For example, optimization times for the largest molecules in this study—kanamycin, streptomycin, and gentamicin—are given in Table 1.

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Table 1. Comparison of time consumption for the three largest antibiotics

Antibiotic	Time consumption, sec	
	QM	QM/MM
Kanamycin	15659	344
Streptomycin	38441	125
Gentamicin	8374	24

METHODS OF INVESTIGATION

Computational details. The GAUSSIAN 98 software package [9] is used to perform Hartree–Fock (HF) and DFT calculations, B3LYP and LSDA, on the antibiotics. The semiempirical calculation is based on the AM1 method and because we use the Gaussian 98 program we must take UFF force field for the molecular mechanic part. Hybrid QM/MM runs were performed as implemented before in the 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 worthwhile to give 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 3.

II. Those based on a QM package incorporating the MM environment as a perturbation.

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

Methodology. On the basis of the ONIOM method, we divided every molecule into three parts (L, M, and H) and then optimized each point. This method cannot optimize some molecules 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 dummy atom to complete the QM subsystem. We must note that the link part should always be in the form of C_α–C_β for two subsystems QM/MM. In fact, the relation between the 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; this means that two link atoms are 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, $E^{\mathrm{REAL}}_{\mathrm{ONIOM}}(R_1 \ldots R_N; r_{m+1}, r_{m+2})$ is approximated by:

$$E^{\mathrm{REAL}}_{\mathrm{ONIOM}}(R_1 \ldots R_N; r_{m+1}, r_{m+2}) = E^{\mathrm{REAL}}_{\mathrm{MM}}(R_1 \ldots R_N) + $$
$$+ E^{\mathrm{MODEL}}_{\mathrm{QM}}(r_1 \ldots r_m, r_{m+1}, r_{m+2}) - E^{\mathrm{MODEL}}_{\mathrm{MM}}(r_1 \ldots r_m, r_{m+1}, r_{m+2}),$$

where the REAL system consists of N atoms at R_i (i = 1, 2...N) and the MODEL system consists of (m+2) atoms at r_j (j = 1, 2...m+1, m+2) [12].

RESULTS AND DISCUSSION

According to [12], $E^{\mathrm{REAL}}_{\mathrm{ONIOM}}(R_1 \ldots R_N; r_{m+1}, r_{m+2})$ 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. $E^{\mathrm{REAL}}_{\mathrm{MM}}(R_1 \ldots R_N)$ is the total MM optimized energy for R_1 to R_N. $E^{\mathrm{MODEL}}_{\mathrm{QM}}(r_1 \ldots r_m, r_{m+1}, r_{m+2})$ is the total QM optimized energy for the medium region and link atoms and $E^{\mathrm{MODEL}}_{\mathrm{MM}}(r_1 \ldots r_m, r_{m+1}, r_{m+2})$ is the total MM optimized energy for the medium region and link atoms [10].

In the present work, we compare the result from pure quantum mechanical (*ab initio*) calculation of a molecule and the QM/MM results. The calculations were performed using the 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 chemical study. The optimized geometries are summarized in Table 2.

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 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 excellent agreement (maybe due to successful cancellation of errors) or serious disagreement between two sets of values. In the ONIOM method that we use in this work, particle exchanges between high-level and 4 low-level subsystems 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 Figs. 1-4.

As we see in NMR isotropy and anisotropy for all of the molecules (Table 3), in the high region of calculations a similar trend is obtained for the QM and QM/MM methods [17-19]. In the medium and low regions (semiempirical and molecular mechanic parts) some perturbations were observed in the form of the following equations:

Table 2. Geometric data comparison[a]

Method / Antibiotic	QM(HF/STO-3G)						QM/MM(ONIOM/AM1/STO-3G)[b]		
	Bond length		Angle		Torsion		Bond length	Angle	Torsion
Gentamicin	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[c]	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)				
	QM(HF/3-21G)						QM/MM(ONIOM/AM1/3-21G)[b]		
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	
Amoxicillin	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

[a] Bond length in Angstroms and angles in degrees.

[b] H, M, and L are related to the level of calculation.

[c] After optimization, the atom number is different in each method, so we wrote the equal positions. The upper is the nomenclature in QM and the lower in QM/MM.

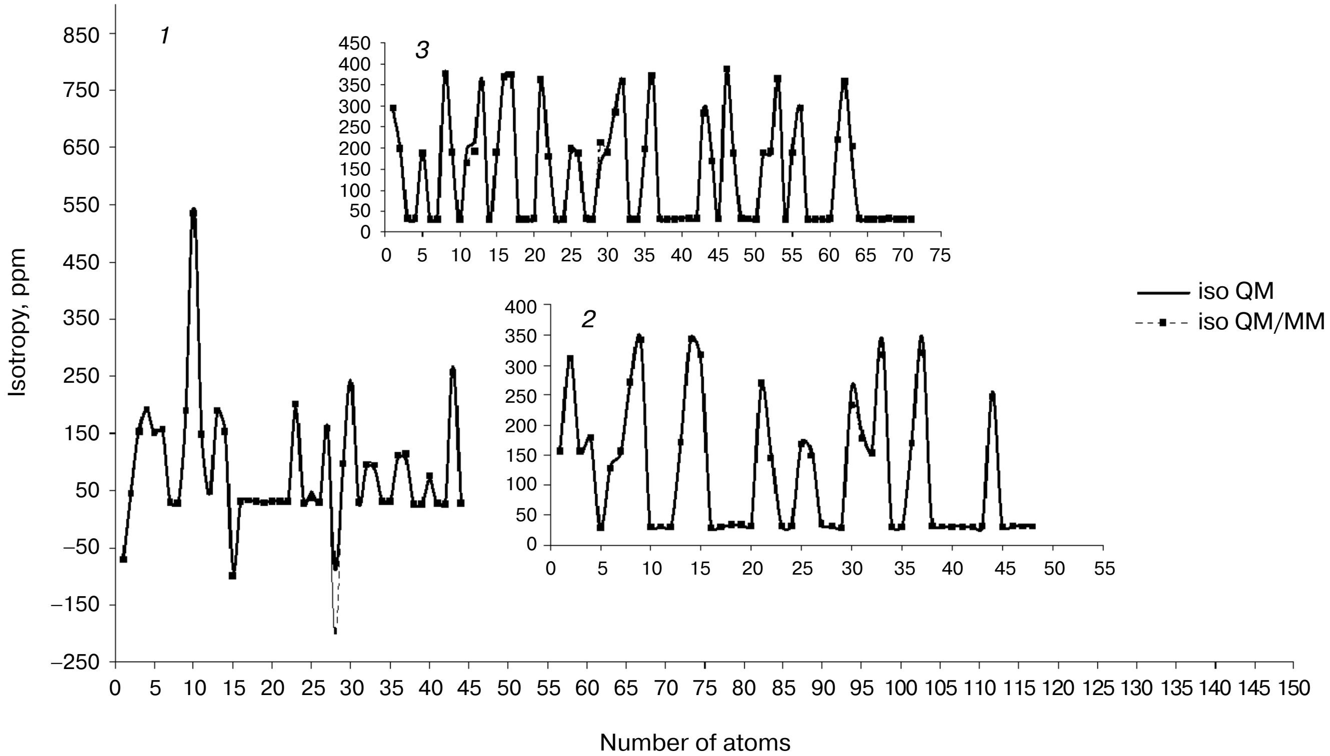


Fig. 1. Calculated NMR isotropy by QM and QM/MM methods for amoxicillin (*1*), neomycin (*2*), and gentamicin (*3*).

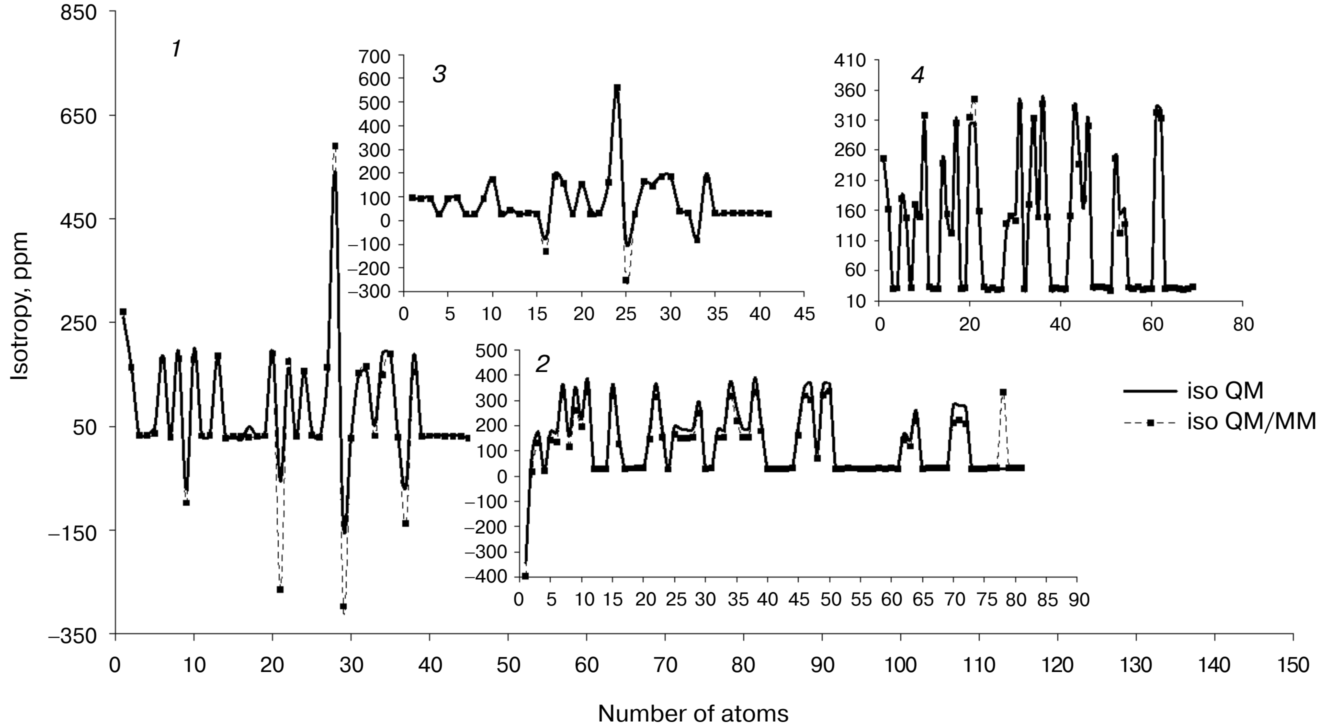


Fig. 2. Calculated NMR isotropy by QM and QM/MM methods for penicillin N (*1*), streptomycin (*2*), benzyl-penicillin (*3*), and kanamycin (*4*).

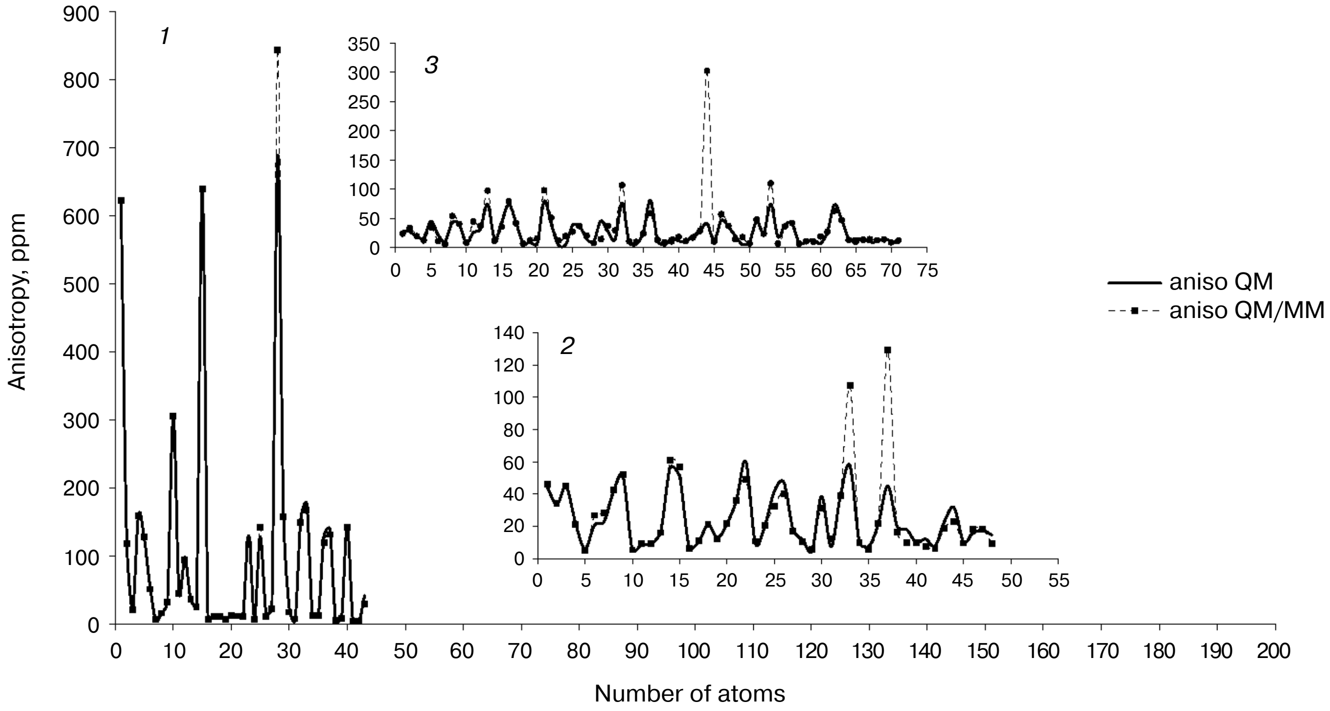


Fig. 3. Calculated NMR anisotropy by QM and QM/MM methods for amoxicillin (*1*), neomycin (*2*), and gentamicin (*3*).

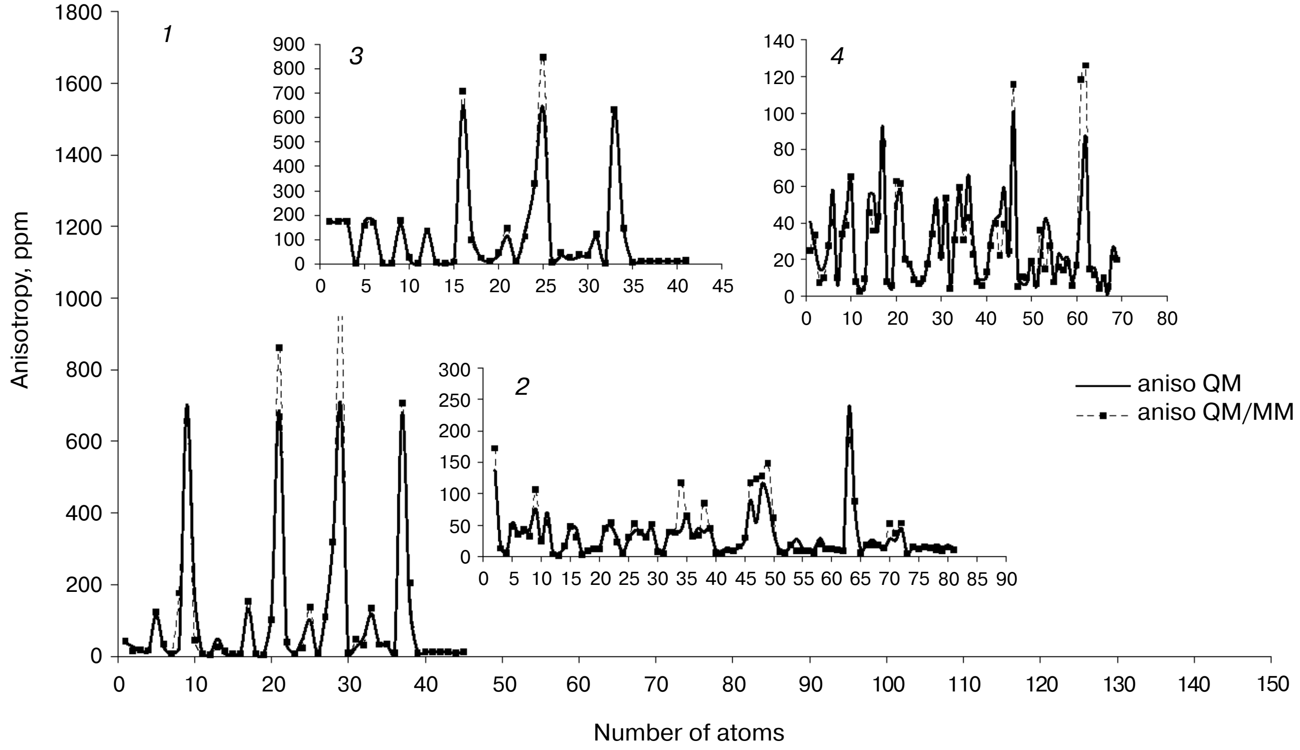


Fig. 4. Calculated NMR anisotropy by QM and QM/MM methods for penicillin N (*1*), streptomycin (*2*), benzyl-penicillin (*3*), and kanamycin (*4*).

Table 3. Comparison between resulting QM and QM/MM isotropy, anisotropy, and chemical shift anisotropy 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	1.8894
	N27	151.0595	114.8195	–0.4008	163.7063	57.6385	–0.1721
Gentamicin	N1	289.1194	26.5275	0.7262	295.1335	9.5498	3.0687
	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
Amoxicillin	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 4. Optimized structure of different antibiotics with their energies (Hartree) by QM and QM/MM methods

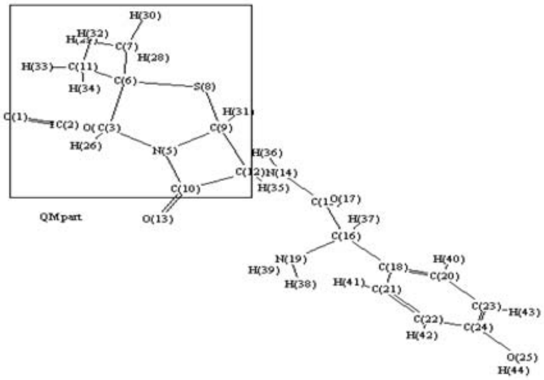
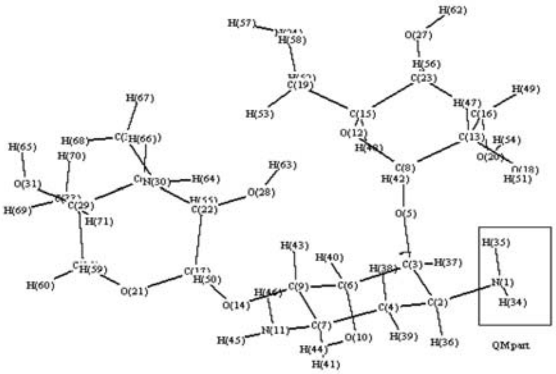
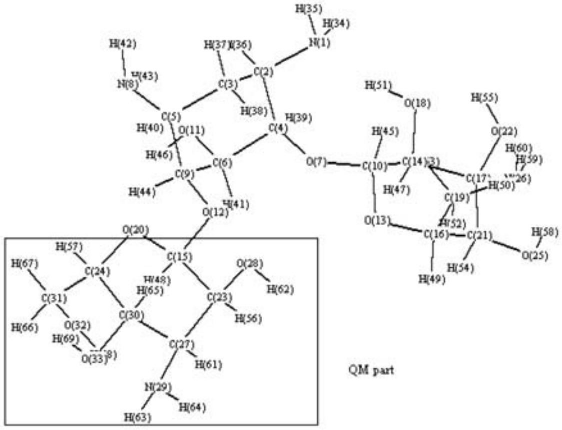
Structure		HF	B3LYP	LSDA
Amoxicillin 	QM / 3-21G	–1543.7406662	1551.3320605	–1544.2061673
	QM/MM / 3-21G	–1543.7051903	–1551.3007558	–1544.1770218
Gentamicin 	QM / 3-21G	1698.4550694	–1708.5923462	–1699.8719074
	QM/MM / 3-21G	–1698.3845529	–1708.5163471	–1699.7991278
Kanamycin 	QM / 3-21G	–1734.0996830	–1744.3167454	–1735.4697345
	QM/MM / 3-21G	–1734.0396267	–1744.2399020	–1735.3803990

Table 4. (Contd.)

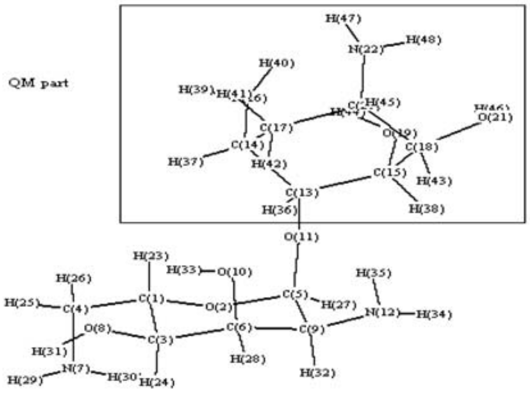
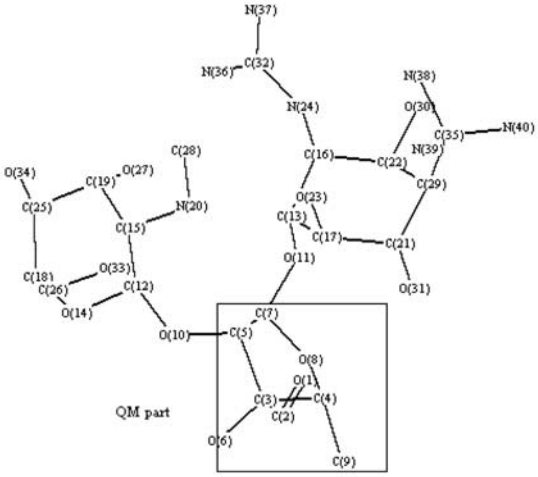
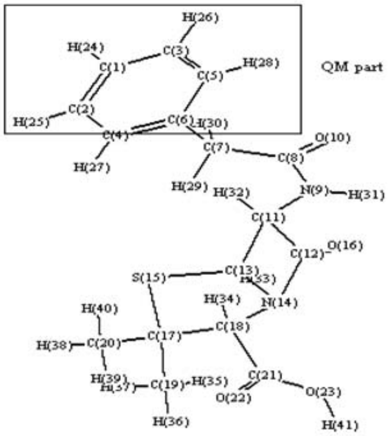
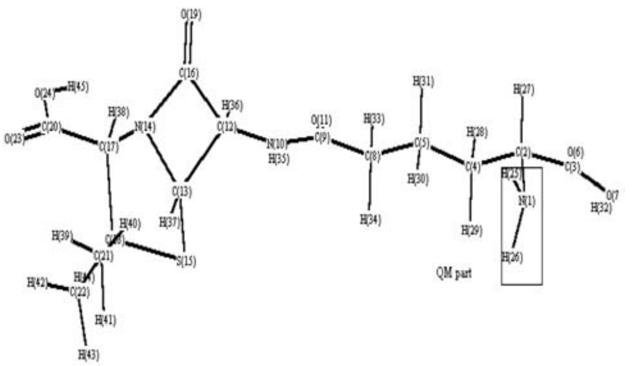
Neomycin	QM / 3-21G		
	HF	B3LYP	LSDA
	−1130.2036684	−1136.9499716	−1131.1477236
	QM/MM / 3-21G		
	HF	B3LYP	LSDA
	−1130.1302393	−1136.8790582	−1131.0697881
Streptomycin	QM / 3-21G		
	HF	B3LYP	LSDA
	−2086.8245071	−2099.1499472	−2088.4760577
	QM/MM / 3-21G		
	HF	B3LYP	LSDA
	−2086.7109075	−2099.0036450	−2088.3046473
Benzyl penicillin	QM / 3-21G		
	HF	B3LYP	LSDA
	−1414.5848985	−1421.4993239	−1414.9987423
	QM/MM / 3-21G		
	HF	B3LYP	LSDA
	−1414.5251216	−1421.4516870	−1414.9622243

Table 4. (Contd.)

Penicillin N	QM / 3-21G		
	HF	B3LYP	LSDA
	−1544.0668550	−1551.5906856	−1544.5587528
	QM/MM / 3-21G		
	HF	B3LYP	LSDA
	−1543.9504374	−1551.4922398	−1544.4569103

$$H_{eff} = H^0_{qm} + H_{mm} + H^{elec}_{qm/mm} + H^{vdW}_{qm/mm} \ , \qquad (1)$$

where

$$H^{vdW}_{qm/mm} = \sum_{s=1}^{S}\sum_{m=1}^{M} 4\varepsilon_{sm}\left[\left(\frac{\sigma_{sm}}{R_{sm}}\right)^{12} - \left(\frac{\sigma_{sm}}{R_{sm}}\right)^{6}\right], \qquad (2)$$

where ***s*** is the number of atoms in the MM part and ***m*** the number of atoms in the QM part. The σ_{sm} and ε_{sm} are experimental parameters;

$$E_{qm/mm} = \left\langle \Psi \middle| H_{qm/mm} \middle| \Psi \right\rangle + E^{vdW}_{qm/mm} \ , \qquad (3)$$

$$H^{elec}_{qm/mm} = \sum_{s=1}^{S}\sum_{m=1}^{M} \frac{q_s Z_m}{R_{sm}} \ , \qquad (4)$$

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

$$E_{Total} = \Sigma(Eb + E\theta + E\varphi + Enb + E\varepsilon + Ehb + E\delta + \ldots). \qquad (5)$$

In this part of the calculations two dummy atoms (H) are entered in the molecule and the chemical environment of atoms differ with the primary structure. In the full *ab initio* method, the hydrogen and carbon atoms have similar chemical environment and their chemical shifts are approximately uniform. Therefore, 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 peaks.

The energy values for some different *ab initio* and DFT methods and the comparison between the QM and QM/MM methods are given in Table 4. As observed geometrical values are very close in the two methods and where the *ab initio* calculations are not possible, for example, in molecules consisting of 100 or greater number of atoms, we can use QM/MM results with complete assurance.

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 5 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. Implementation 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.

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