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STRUCTURE OF MATTER AND QUANTUM CHEMISTRY

Theoretical Study of Vitamin Properties from Combined QM–MM Methods: Comparison of Chemical Shifts and Energy*

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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 the liquid phase. In this paper, we have implemented these methods for vitamins, an important kind of biological molecule, and then compared results. The calculations were done by the full ab initio method (HF/3–21 g and HF/6–31 g) and QM–MM (ONIOM) method with HF(3–21 g)/AM1/UFF; then, we found that the geometry obtained by the QM–MM method is very accurate and this rapid method can be used in place of time consuming ab initio methods for large molecules. A comparison of energy values in the QM–MM and QM methods is given. We compare chemical shifts and conclude that the QM–MM method is a perturbed full QM method.

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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 compounds rapidly. Quantum mechanics is able to compute many properties and model chemical reactions. Of course, QM and MM approaches are different and depend on the methods used for calculations, i.e., in the QM and MM regions. However, there are many other attributes characterizing the various published methods. The chemical systems we are interested in computational biology and reaction catalysis are systems in condensed phase that consist of thousands of participating atoms.

The combination of quantum and molecular mechanics works at a very high speed, and only one part of a molecule needs to be modeled quantum mechanically. Today, it is accepted that the QM method is the ultimate computational tool for studying structural aspects and a variety of physical and chemical properties. The hybrid QM–MM approach splits the system under study into two parts: the electronically more important one is treated with QM, whereas the other part is treated on a classic level (MM system). The division into two subsystems is conventionally used in the case of solvation of an organic compound when solvent is treated in the MM system and solute treated in the QM system.

Several approaches have been applied to discuss the division of QM–MM systems, for instance, localized orbitals [1], pseudopotentials [2–5], density matrix, electron density partitioning [6], and so on. But the simplest and the most commonly chosen solution is to use link atoms [7, 8].

The QM–MM Hamiltonian is used in conjunction with molecular dynamics (MD) for studying the dynamic behavior of matter (formation/breaking of a chemical bond into a complex intermolecular environment).The hybrid QM–MM potential was proposed in 1976 by Warshel and Levitt for the study of the catalytic mechanism of lysozyme [9]. Many of the basic ideas were formed using their works: the partitioning into QM and MM regions, the construction of the hybrid QM–MM Hamiltonian, the evaluation of the total energy for the mixed system, and the treatment of the QM–MM boundary. More than a decade later, Field, Bash, and Karplus compared the performance of the QM–MM approach with the full QM and introduced the concept of link atoms for treating the QM–MM boundary [10].

One of the main driving forces in the development of the QM–MM method is the need to investigate the reactivity of enzymes. The benefits from understanding the fine details of the mechanism of enzyme reactions fully justify the considerable amount of work already

* The text was submitted by the authors in English.

invested in the development and refinement of the QM–MM method. The large number of papers published in the last decade shows that the QM–MM approach is now largely accepted as a valuable research tool that is well suited for studying biomolecular and nanoscale systems. This is emphasized in Field's recent review on the challenges and perspectives of the simulation of reactions.

The increasing number of publications that present the application of the QM–MM method to a variety of biochemical reactions is a clear evidence of the importance of the QM–MM approach as a theoretical tool for our understanding of the fine details of the structure and function of biological molecules. There is no question that, at present, the QM–MM method, together with the computer simulation methods, is the most sophisticated theoretical tool for determining the reaction mechanism of enzyme catalysis or in calculation of such quantities as binding constants and pK_a values.

THEORETICAL IMPLEMENTATION

The availability of implementations of commercial packages (e.g., CHARMM and Gaussian 98) and improvements in available computational resources will doubtless contribute to a continued increase in their popularity. Recent reviews of the subject include those by Mordasini and Thiel [11] and Gao.

Before doing the QM calculation, the MM system is optimized. In this stage, the atoms in the real QM system are kept fixed in their positions and interact with atoms in the MM system through classical MM interaction. During the optimization procedure, the charges of the QM system are updated after each QM optimization cycle.

In this paper we benefit from the "our own n-layered integrated MO and MM method" (ONIOM) [12–14], which allows for three or more different techniques to be used in successive layers.

The acronym ONIOM is often used to refer to a generalization of the technique. This technique can be used to model an entire system as a small model system and the rest system. The rest system is computed using only a classical model (MM); similarly, a three-layer system can be broken into small, medium and large regions to be computed with low, medium, and high theoretical levels (L, M, and H, respectively). The energy expression would then be

$$E_{\text{total}} = E_{\text{low, complete}} + E_{\text{high, model}} - E_{\text{low, model}} \quad \text{(low: MM, high: QM)}. \tag{1}$$

The advantage of this model is that it does not require a parameterized expression to describe the interaction of the various regions. The geometry of one region will affect geometry of the other, because this is not a systematic effect. Since the methods of molecular mechanics are defined atom by atom, having a carbon atom without all of its bonds does not have a large affect on the other atoms in the system. In contrast, quantum mechanical calculation uses a wave function that can incorporate second atom effects. An atom with an unfilled valence will behave differently than with the valence filled. A number of methods fill the valence of the interface atoms with an extra orbital sometimes entering the connecting MM atoms.

Link Atom Method

To fill a valence of the QM part, we use a dummy (H) atom. Also for maintenance of QM to the MM part, we use a link atom. Always, we must place a QM–MM link atom or have the smallest possible charge distribution at the border. In fact, the accuracy of ab initio methods is better than that of semi-empirical ones, but, as the former require a much greater computational effort, they are worth using only with a QM–MM implementation that preserves the accuracy. The suitability of different QM computational approaches must be considered, e.g., using either plane waves or a localized orbitals as the basis set. For example, QM implementations using plane waves and pseudopotentials are advantageous because they are able to treat systems up to a size of 1000 atoms fully quantum mechanically. When good quality force fields are available, the approach can be very accurate, as there are no problems with interactions between the link atom region and the classical environment.

The choice of QM method will not be dealt with in detail here, as it does not fundamentally affect the design of a QM–MM scheme and will largely be governed by the same criteria that apply to pure QM calculations. Since the first study by Warshel and Levitt [9], schemes based on semi-empirical methods have dominated the field for biological applications, and, for reasons of computational cost, such schemes are likely to remain important for applications incorporating molecular dynamics. A large number of ab initio schemes based on Hartree–Fock and density functional approaches have been implemented [15, 16].

Charge equilibration schemes, which determine the MM charges as a function of geometry, have also been employed.

In ab initio schemes, it is clear that the electrostatic embedding scheme should be implemented, at least at long ranges, by adding the contribution of the MM point charges to the one-electron Hamiltonian. However, within semi-empirical formalism, the definition of the electrostatic potential is more ambiguous as a result of the overlap approximations used, and alternative formulations for the one-electron integral terms have been suggested [17].

In this section, we review the mathematical basis of QM–MM methods and then we discuss the works had done in this paper.

Mathematical Treatment

The Hamiltonian of the QM–MM system is expressed by the formulation

$$H_{\text{eff}} = H^0_{qm} + H_{mm} + H^{\text{elec}}_{qm/mm} + H^{\text{vdw}}_{qm/mm}. \quad (2)$$

In fact, the Hamiltonian of molecular mechanics enters into the form of a perturbation in the Hamiltonian of the fundamental system.

The terms in Eq. (2) are

$$H^{\text{vdw}}_{qm/mm} = \sum_{s=1}^{s}\sum_{m=1}^{m} 4\varepsilon_{sm}[(\sigma_{sm}/R_{sm})^{12} - (\sigma_{sm}/R_{sm})^{6}], \quad (3)$$

where s the number of atoms in the MM part, m is the number of atoms in QM the part, and σ and ε are experimental parameters;

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

where q_s is the atomic charge on the MM atom, Z_m is the atomic charge on the QM atom, and R_{sm} are the distances between particles; and

$$E_{qm/mm} = \langle\Psi|H_{qm/mm}|\Psi\rangle + E^{\text{vdw}}_{qm/mm}. \quad (5)$$

In the MM region, we use the total strain energy in the form

$$E_{\text{total}} = E_{\text{b}} + E_{\theta} + E_{\varphi} + E_{\text{nb}} + E_{\varepsilon} + E_{\text{hb}} + E_{\delta} + \ldots. \quad (6)$$

Computational Details

The Gaussian 98 software package [18] is used to perform Hartree-Fock HF, MP3, B3LYP, and LSDA calculations on vitamins. The semiempirical calculation is based on the AM1 method, and, because we are using the Gaussian 98 program, we must take a UFF force field for the molecular mechanics part.

Hybrid QM–MM runs were performed as implemented before by 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 techniques present in either the QM or MM packages. However, it is worth giving brief consideration to a couple implementation issues. If the starting point is working in QM and MM codes, QM–MM implementations can fall into three groups:

(1) those based on classical modeling packages, with a QM code integrated as a force field extension;

(2) those based on QM packages, incorporating the MM environment as a perturbation;

(3) modular schemes in which a central control program is provided and a choice of both QM and MM methods is left open.

Methodology

In a frame of the ONIOM method, we divided every molecule into three parts (L, M, and H) and then optimized each part. Some vitamins cannot be optimized by this method, because they have 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 recognize that the link part should always be in the form of C_α–C_β for two QM–MM subsystems since, the relation between the link part and the MM or QM subsystems must be through one atom.

The separation of the partial atomic driving force is as follows [19]: in the ONIOM calculation of the total energy, $E^{\text{REAL}}_{\text{ONIOM}}(R_1, \ldots, R_N; r_{m+1}, r_{m+2})$, is approximated by $E^{\text{REAL}}_{\text{ONIOM}}(R_1, \ldots, R_N; r_{m+1}, r_{m+2}) = E^{\text{REAL}}_{\text{MM}}(R_1, \ldots, R_N) + E^{\text{MODEL}}_{\text{QM}}(r_1, \ldots, r_m, r_{m+1}, r_{m+2}) - E^{\text{MODEL}}_{\text{MM}}(r_1, \ldots, r_m, r_{m+1}, r_{m+2})$ where the REAL system consists of N atoms at R_i ($i = 1, 2, \ldots, N$) and the MODEL system consists of $(m + 2)$ atoms at r_j ($j = 1, 2, \ldots, m + 1, m + 2$). The expression for the derivatives is given by the following equation:

$$\begin{aligned}\partial E^{\text{REAL}}_{\text{ONIOM}}/\partial R_i &= \partial E^{\text{REAL}}_{\text{MM}}/\partial R_i \\ &+ \sum_{j=1}^{m+2} \partial E^{\text{MODEL}}_{\text{QM}}/\partial r_j(\partial r_j/\partial R_i) \\ &- \sum_{j=1}^{m+2} (\partial E^{\text{MODEL}}_{\text{MM}}/\partial r_j)(\partial r_j/\partial R_i). \quad (i = 1, 2, \ldots, N).\end{aligned} \quad (7)$$

The unbonded interactions between the QM region and the MM region can be evaluated by the third term on the right hand side of the above equation. The partial atomic driving force can also be calculated using the above equation.

RESULTS AND DISCUSSION

In the present work, we compare the results of a test of a pure quantum mechanics (ab initio) calculation of a molecule and QM–MM results. The calculations were performed with the use of the Gaussian 98 software package [18]. We conclude that these two data groups are in good agreement. Then, we can use the QM–MM method for vitamins and identify the active site of these molecules and the mechanism of their reactions in the body. In all test examples, the

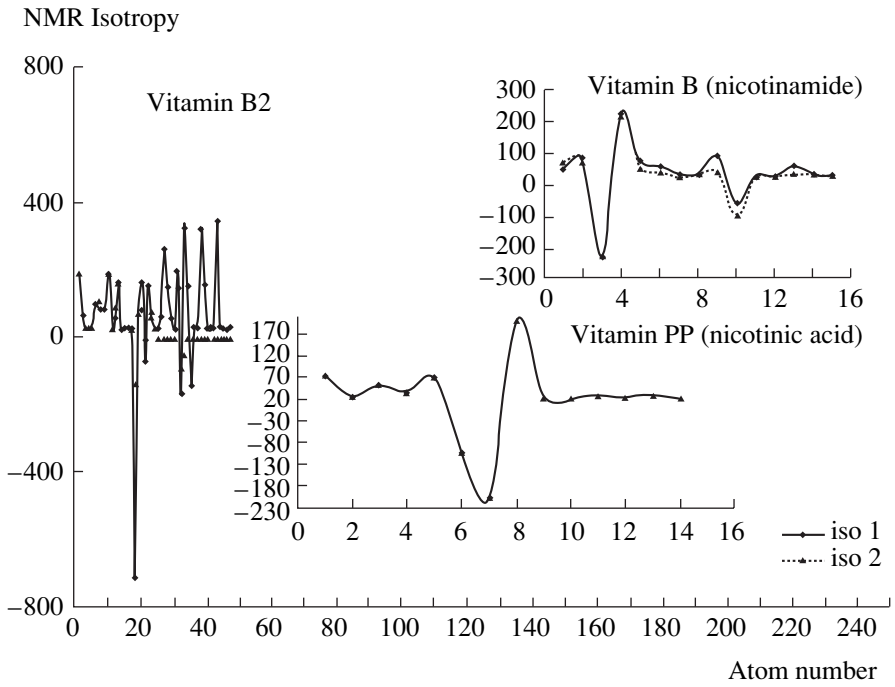

Fig. 1. NMR isotropy diagrams of vitamins for the QM method (iso 1) and QM–MM method (iso 2).

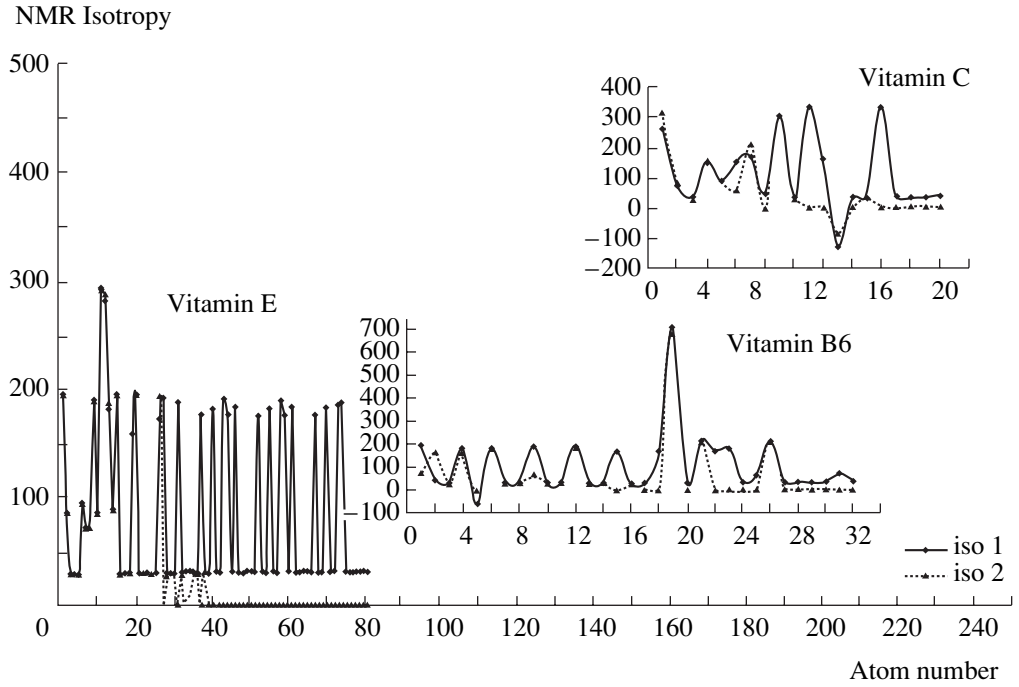

Fig. 2. NMR isotropy diagrams of vitamins for the QM method (iso 1) and QM–MM method (iso 2).

results of QM–MM calculations were compared to the corresponding results of a full quantum chemical study. The optimized geometries are summarized in Table 1.

In the 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

Table 1. Comparison of geometrical data

QM (HF/3-21G)						QM/MM (ONIOM/AM1)		
R		*A*		*D*		*R*	*A*	*D*
Vitamin 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)	179.9114	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
Vitamin PP (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, 6)	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
Vitamin B (Nicotinic amid)								
R(6, 11)	1.3317	*A*(1, 4, 3)	118.1458	*D*(15, 11, 6, 4)	−179.8392	1.3307(H)	118.1459	−179.7854
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)	−179.2764	1.4088(M)	120.2057	−179.5231
R(8, 14)	0.9976	*A*(14, 13, 8)	118.1665	*D*(13, 8, 2, 7)	168.9234	1.0443(L)	118.5687	177.7076
R(8, 13)	0.993	*A*(2, 7, 8)	112.2829			1.0443(L)	119.7286	
Vitamin B6								
R(6, 14)	1.2126	*A*(9, 8, 3)	104.4162	*D*(3, 1, 2, 10)	173.2984	1.212(H)	106.8842	176.0137
R(4, 9)	1.8864	*A*(7, 6, 14)	126.8767	*D*(8, 9, 4, 13)	153.5011	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
Vitamin B2								
R(7, 2)	1.3762	*A*(1, 2, 7)	119.4352	*D*(1, 2, 7, 10)	−179.8536	1.3765(H)	119.5124	−179.9244
R(19, 22)	1.2815	*A*(10, 18, 12)	120.3268	*D*(33, 27, 22, 19)	−179.9708	1.2752(H)	120.5583	−179.8956
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(25, 35)	1.5253	*A*(29, 34, 35)	107.5426	*D*(20, 23, 28, 36)	178.7476	1.5586(L)	110.68	178.9318
R(23, 28)	1.4397	*A*(45, 39, 35)	109.3799			1.4033(L)	108.8044	
Vitamin E								
R(1, 30)	1.3814	*A*(26, 28, 30)	119.4697	*D*(5, 4, 26, 6)	164.2559	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)	−176.2977	1.5033(M)	107.9848	−171.7505
R(26, 19)		*A*(26, 31, 32)		*D*(26, 31, 37, 40)				
R(8, 9)	1.5421	*A*(10, 11, 12)	111.0577	*D*(18, 19, 20, 22)	171.5713	1.5379(L)	111.1261	169.3888
R(31, 37)		*A*(40, 43, 44)		*D*(6, 67, 70, 74)				
R(21, 20)	1.541	*A*(20, 21, 22)	109.5977	*D*(22, 20, 21, 62)	−56.4022	1.5344(L)	109.772	−52.7193
R(74, 70)		*A*(73, 70, 74)		*D*(74, 70, 73, 76)				

Note: Bond lengths in Ångstroms and angles in degrees; calculations in QM were performed for 3–21 G basis set those except for Vitamin PP (nicotinic acid), which were done for 6–31 G basis set; H, M, and L are related to the level of calculations. D—torsion angles. After optimization, the atom number is different in each method; therefore, for Vitamin E we wrote equal positions, the upper being the nomenclature in QM and the lower in QM–MM.

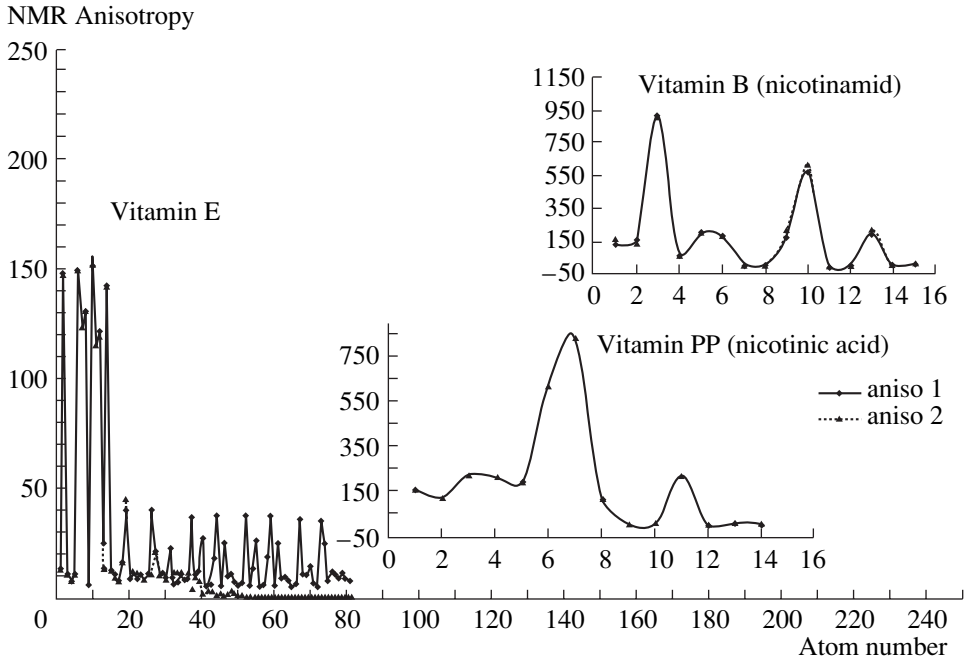

Fig. 3. NMR anisotropy diagrams of vitamins for the QM method (aniso 1) and QM–MM method (aniso 2).

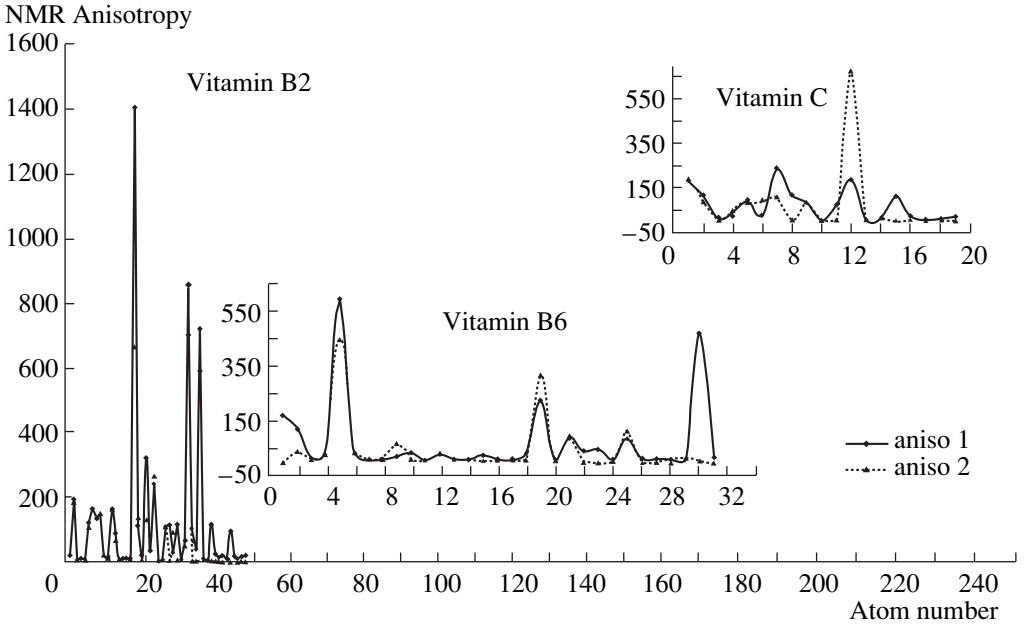

Fig. 4. NMR anisotropy diagrams of vitamins for the QM method (aniso 1) and QM–MM method (aniso 2).

either for an excellent agreement (possibly 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- and low-level subsystems do not disturb the statistical ensemble.

NMR shielding tensors have been computed with a continuous set of the gauge invariant atomic orbital (GIAO) method [20–23]. The δ values for isotropy and anisotropy are shown in Figs. 1–4.

As we see using NMR isotropy and anisotropy for all of the molecules, at the high level of calculations a similar trend was obtained for the QM and QM-MM methods [24]. In the medium and low regions (the semiempirical and molecular mechanics parts), some perturbations were observed; this is in

Table 2. Energy values (–*E*, Hartree)

Methods / Vitamins	QM(HF)	QM/MM	QM(MP3)	QM/MM
C	677.199766	667.199760	713.6287257	677.1997662
PP (Nicotinic acid)	434.1213417	434.1151957	434.1213418	434.1152216
B (Nicotinamide)	412.1578258	412.1578153	412.1578258	431.8748814
E	1269.996881	1269.977009	–	–
B6	1113.662355	1113.073894	–	–
B2	1315.034385	1314.995636	–	–
Methods / Vitamins	**DFT(B3LYP)**	**QM/MM**	**DFT(LSDA)**	**QM/MM**
C	717.51221	680.9442525	713.948978	677.5082932
PP (Nicotinic acid)	436.716137	436.7155297	434.3644688	434.3644309
B (Nicotinamide)	414.6767787	434.4321184	412.4300262	432.1087647
E	1278.717119	1278.710773	1271.736894	1271.74198
B6	1118.156323	1118.148479	1113.328608	1113.325304
B2	1322.838881	1322.873542	1315.9028	1315.940476

Note: The MP3 calculations were possible only for three vitamins.

agreement with Eq. (5). In this part of the calculations, two dummy atoms (H) are entered into the molecule and the chemical environment of the atoms differs from the primary structure. With the full ab initio method, the hydrogen and carbon atoms resemble a chemical environment and their chemical shifts are approximately uniform. Therefore, we can see the effect of isolation of parts in the NMR spectra. Usually, the heavy atoms that contain electron pairs have high δ values and display peaks. In small molecules such as nicotinic acid, in which there is no important difference between the QM and QM–MM methods, the NMR shifts completely overlap (Fig. 1).

The energy values for some ab initio and DFT methods and the comparison between the QM and QM–MM methods are given in Table 2. From the energy comparison table, we see that the MP3 method gives the closest values to the full ab initio (HF) one.

Table 3. The standard deviation for bond length (ΔR), angle (ΔA), and torsion angle (ΔD) for of vitamins

Vitamin	ΔR	ΔA	ΔD
C	0.0177	1.6828	4.5745
B (Nicotinamide)	0.0238	1.2707	3.8086
PP (Nicotinic acid)	0.0249	1.5079	0.0271
B2	0.0143	1.5946	0.7553
B6	0.0159	0.8815	1.8365
E	0.0118	0.5885	1.5947

Table 3 shows the standard deviation for bond length, angle, and torsion angle between the two methods, QM[1] and QM–MM.

As observed geometrical values and their standard deviations are very close in the two methods, so that, when the ab initio calculations are not possible, for example, in molecules that consist of 100 or more atoms, we can use the QM–MM results with complete confidence.

CONCLUSIONS

This brief review of the QM–MM approach has emphasized the variety of ways in which QM and MM calculations can be combined. As should be clear from the number of possible variations, it will probably be difficult to obtain exactly the same answer with two separate implementations and, like 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 methods 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

[1] In the structures of vitamins the QM part includes only rings and neighbouring atoms.

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 a specific group of biomolecules.

REFERENCES

1. X. Assfeld, N. Ferre, and J.-L. Rivail, ACS Symp. Ser. **712**, 234 (1998).
2. D. Vanderbitt, Phys. Rev. B: Condens. Matter **41**, 7892 (1990).
3. D. A. Estrin, C. J. Tsoo, and S. Singer, Chem. Phys. Lett **184**, 571 (1984).
4. A. Bergner, M. Dolg, W. Kuchle, et al., Mol. Phys. **80** (1998).
5. U. Röthlisberger, ACS Symp. Ser. **712**, 262 (1998).
6. *ACS Symposium Series*, Vol. 712: *Combined Quantum Mechanical and Molecular Mechanical Methods* Ed. by J. Gao and M. A. Thompson (American Chemical Society, Washington, DC, 1998).
7. U. Chandra Singh and P. A. Kollman, J. Comput. Chem. **7**, 718 (1986).
8. I. Antes and W. Thiel, ACS Symp. Ser. **712**, 50 (1998).
9. A. Warshel and M. Levitt, J. Mol. Biol. **103**, 227 (1978).
10. M. J. Field, P. A. Bash, and M. Karplus, J. Comput. Chem. **11**, 700 (1990).
11. T. Z. Mordasini and W. Thiel, Chimia **52** (6), 288 (1998).
12. S. Dapprich, I. Komaromi, K. S. Byun, et al., THEOCHEM **461–462**, 1 (1999).
13. M. Svensson, S. Humbel, R. D. J. Froese, et al., J. Phys. Chem. **100**, 19357 (1996).
14. T. Vreven and K. J. Morokuma, Chem. Phys. **113**, 2969 (2000).
15. J. H. Harding, A. H. Harker, P. B. Keegstra, et al., Physica B (Amsterdam) **131** (1–3), 151 (1985).
16. Z. Barandiaran and L. Seijo, J. Chem. Phys. **89** (9), 5739 (1988).
17. P. L. Cummins and J. E. Gready, Chem. Phys. Lett. **225**, 11 (1994).
18. M. J. Frisch, G. W. Trucks, H. B. Schlegel, et al., *Gaussian 98, Revision A.7* (Gaussian Inc., Pittsburgh PA, 1998).
19. A. Yamada, T. Ishikura, and T. Yamato, Proteins: Structure, Function, Bioinformatics **55**, 1070 (2004).
20. R. Ditchfield, Mol. Phys. **27**, 789 (1994).
21. J. R. Cheesman, M. J. Frisch, F. J. Devlin, and P. J. Stephens, Chem. Phys. Lett. **252**, 211 (1996).
22. R. Mac Weeny, Phys. Rev. **126**, 1028 (1962).
23. K. Wolinsky, J. F. Hilton, and P. Pulay, J. Am. Chem. Soc. **112**, 8251 (1990).
24. Q. Cui and M. Karplus, J. Phys. Chem. B **104**, 3721 (2000).