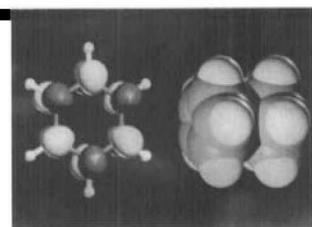# COMPUTATIONAL CHEMISTRY COLUMN

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Combined Quantum Mechanical and Molecular Mechanical Approaches

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Abstract. The embedding of a quantum mechanical region in a molecular mechanical environment allows a theoretical treatment of very large systems. This article reviews recent methodological developments for such hybrid methods and surveys selected applications including solvation effects, enzymatic reactions, and electronic excitations in condensed phase.

Quantum chemical calculations are usually applied to isolated molecules in the gas phase. Currently available quantum chemical methods provide reliable results for structures, stabilities, spectra, and reactions of isolated molecules (with computational effort and accuracy depending on molecular size). However, experimental work is mostly carried out not in the gas phase, but in the condensed phase. The quantitative calculation of such processes poses new challenges for theory: How can we best describe, *e.g.*, reactions in solution, in enzymes, or at heterogeneous catalysts? How can we model the effects of the environment on chemical reactions and electronic excitations? How can we efficiently treat systems with thousands of atoms in cases where the classical force field methods fail due to the nature of the problem?

Hybrid QM/MM methods represent a promising tool for answering such questions. The basic idea [1] is quite simple: the electronically important part of the

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system is described as accurately as needed using Quantum Mechanics (QM), whereas the rest of the system is handled by Molecular Mechanics (MM) with an appropriate force field. Such hybrid QM/MM procedures [1–5] allow a *tailored* treatment of very large systems. In this article, recent methodological advances are briefly outlined, and some typical applications are presented. The literature has been covered until the end of 1997.

Methods

The combination of QM and MM procedures requires the definition of coupling models [6] that describe the interactions between QM and MM regions. The accuracy of a QM/MM calculation depends not only on the chosen QM and MM methods, but also significantly on the coupling model. Therefore, a hierarchy of such coupling models has to be developed, and a suitable choice for each specific application has to be made.

The simplest coupling is based on a mechanical embedding of the QM region [6–8]. In this case, the energy of the total system X-Y (QM region Y, MM region X) is calculated from:

$$E(X\text{-}Y) = E_{MM}(X\text{-}Y) - E_{MM}(Y) + E_{QM}(Y) \quad (1)$$

Effectively, this amounts to an interpolation between independent QM and MM calculations where the QM/MM interactions are described by the force field. This model is simple and robust, and can be generalized easily: the IMOMM method [7] becomes IMOMO [9] or ONIOM [10], depending on whether two different QM procedures or several QM and MM procedures are combined together.

In the case of a mechanical embedding, the wave function in the QM region does not feel the influence of the environment. Such an approximation is more appropriate for apolar than for polar systems. To account for the electrostatic influence of a polar environment (*e.g.*, in aqueous solution or in proteins) an electronic embedding of the QM region is preferable: the QM wave function is calculated in the field of the MM partial charges and is therefore polarized relative to the gas phase [1–6]. Long-range electrostatic interactions can be taken into account with an appropriate *Ewald* summation [11].

This standard model of electronic embedding only contains the polarization of the QM region. For higher precision and for theoretical consistency, it would seem advisable to include also the polarization of the MM region [1][6][12–17]. This can be achieved using distributed atomic polarizabilities in the MM region, which interact with the electrical field of the QM region. The interaction energies can be obtained either from a single-point calculation using a given QM wave function [6], or by optimizing both the QM wave function and the MM polarization within a double iterative procedure [6][12–14]. The second possibility is computationally more expensive, but theoretically more consistent, and allows the derivation of analytical gradients [13]. The direct reaction field (DRF) method provides theoretical justification for describing the MM polarization through distributed charges and dipole polarizabilities [15][16]. Fluctuating partial charges in the MM region are an alternative for taking the MM polarization into account [17].

Most of the usual force fields are static and do not contain terms for polarization. If such a force field is used in a QM/MM procedure with MM polarization, the polarization should only be included for the calculation of the QM/MM interaction energy. The effects of polarization inside the MM region are covered through the parametrization of the force field, in an average sense. A better approach for such QM/MM studies would involve the development of new polarizable force fields. For simulations in the liquid phase, such intermolecular force fields have already been derived [17–20].

For an electronic embedding of the QM region, the total energy can schematically be written as:

$$E(X\text{-}Y) = E_{MM}(X) + E_{QM}(Y) + E_{QM/MM}(X\text{-}Y) \qquad (2)$$

The first two terms are usually calculated exactly as in the underlying QM and MM procedures. The QM/MM interaction energy is determined by the chosen coupling model and usually contains electrostatic and *van der Waals* contributions that can be parametrized in order to reproduce experimental results or data from accurate theoretical calculations. For electrostatic QM/MM interactions, such special parametrizations are particularly appropriate in the case of semiempirical QM methods [3], *e.g.*, through a parametrization of the electrostatic potentials and fields based on *ab initio* results [21]. For the *van der Waals* QM/MM interactions, optimized *van der Waals* parameters of QM atoms have been published for different types of QM procedures [22–26].

It seems to be generally accepted that some parametrization of the QM/MM interactions is necessary for reliable quantitative results. Using semiempirical QM methods, one can even go one step further by optimizing the semiempirical QM parameters for the desired system. This approach is central to the empirical valence-bond (EVB) method [4] and has recently also been tested successfully for AM1 [27]. Such specific parameterizations for particular systems are quite attractive, since they allow to carry out extensive simulations with relatively high accuracy and relatively low effort.

The preceding discussion has not yet addressed the problem of how the total system can be divided into QM and MM regions. Sometimes, there exists a natural separation, *e.g.*, in the study of solutions with a QM solute and MM solvent molecules. However, for other applications, the separation can be less obvious, as in enzy-

matic reactions where covalent bonds have to be cut in order to define the active site (QM) and the protein environment (MM). In this case, one can either satisfy the free valencies with link atoms (usually hydrogen) [2][3], or freeze the electron density at the broken bond in orthogonal hybrid orbitals [1][28–30]. Both methods have advantages and disadvantages, and it is not *a priori* obvious which one is preferable. The link-atom concept is more popular, and will therefore be discussed in the following paragraph.

Intuitively it is reasonable to require that the link atoms do not contribute to the total energy of the real system [3]. A corresponding link-atom correction can be defined for each coupling model [6]. In the simple mechanical embedding of the QM region, the link atoms then do not present any further problems. In the electronic embedding scheme, one has to decide whether the link atoms can electrostatically feel the MM atoms (if yes, which ones), and whether they can contribute to the electrostatic potential and field of the QM region (if yes, in which form). These details influence the QM polarization, the balance of the electrostatic QM/MM interactions, and therefore also the quality of the results. Semiempirical QM procedures are less sensitive to such link-atom problems than *ab initio* or density functional methods. It is generally recommended to define the QM region as large as possible, so that the link atoms are located far away from the electronically important region, in order to minimize any problems due to the link atoms. Clearly, the same is also valid if frozen hybrid orbitals are used.

QM/MM procedures are employed for the study of large systems, where geometry optimizations are no longer trivial. Recently, the transition state for a solvated enzyme-substrate complex with 1900 atoms has been successfully optimized and verified using gradient methods [31]. Usually, however, such systems are studied with Molecular Dynamics (MD) and Monte Carlo (MC) simulations. There is an obvious demand for techniques that can reduce the number of QM calculations in such QM/MM simulations, *e.g.*, through energy estimates based on perturbation theory [32] or through systematic interpolations [33]. Other practical questions are discussed in the literature [34].

The preceding discussion indicates that QM/MM calculations are not a 'black box' automatic procedure. For each specific application, it is necessary to make a series of critical choices with regard to practicality and accuracy. This includes the selec-

tion of QM method, force field and coupling model, the calibration of QM/MM interactions, the definition of QM and MM regions, the treatment of the link atoms, and the employed simulation technique. On the other hand, these choices offer the freedom to use a specifically tailored theoretical approach for modeling the electronic effects in large systems which were previously not accessible to theoretical investigation.

Applications

QM/MM calculations have become increasingly popular since 1990. For the QM component, semiempirical methods (*e.g.*, MNDO, AM1, PM3) are mostly used due to efficiency reasons, whereas the MM component is normally described by standard force fields without polarization terms (*e.g.*, AMBER, CHARMM, GROMOS, MM2, MM3, OPLS, SPC, TIP3P). The most widely used coupling models are mechanical embedding and the simplest form of electronic embedding. It is only recently that more complex QM procedures (*ab initio*, density functional) are employed more often and that polarization effects in the MM region are being considered.

Many of the early successful applications of QM/MM methodology have dealt with solvation effects [5]. After a suitable parametrization of the QM/MM interactions [22][24][25], it is possible to reproduce the experimental hydration energies for a large number of molecules, with errors significantly below 1 kcal/mol. The contribution of the QM polarization to the hydration energy is typically *ca.* 10–20%. More recent studies on solvation have compared the performance of different methods, *e.g.*, MC simulations of *N*-methylacetamide in water [35] (*ab initio* RHF/TIP3P *vs.* AM1/TIP3P *vs.* OPLS) and MD simulations of alanine dipeptide in water [36] (AM1/TIP3P compared to *ab initio* RHF continuum models).

In the 1980s, a three-step procedure has been developed for modeling organic reactions in solution [37]: first, the reaction profile in the gas phase is calculated with *ab initio* methods, then along this reaction path a special force field is derived for the interactions with the solvent molecules, and finally, classical MC calculations for points on the reaction path are carried out in order to calculate the solvent effects. Using a QM/MM procedure, the last two steps can be replaced by a QM/MM MC simulation that is conceptually simpler and that allows for a QM

polarization of the reacting system. Based on this strategy, there have been AM1/TIP3P studies of the *Claisen* rearrangement in water [38] and of hydrophobic and hydrogen-bonding effects on the rate of a *Diels-Alder* reaction in water [39]. QM/MM investigations of reactions in solution can also be carried out without previous gas-phase calculations, provided that the chosen QM method yields realistic intrinsic reaction barriers. Examples of such studies in aqueous solution are QM/TIP3P calculations for proton transfer in complexes with strong hydrogen bonds (double minimum potential with low barrier) [40] and for electrophilic attack of bromine on ethylene producing a bromonium ion [41] (using gradient-corrected density functional theory as QM component). The acid-catalyzed hydrolysis of glycoside in water has been studied at the AM1/TIP3P level, suggesting a stepwise mechanism based on the calculated kinetic isotope effects [42].

Organic reactions in solution can also be described with continuum models like SCRF (self-consistent reaction field) [43] [44]. These models incorporate the mutual polarization of solute and solvent without considering any special interactions. Whenever such explicit interactions are not particularly relevant, SCRF and QM/MM calculations often yield qualitative similar results. However, continuum models are not appropriate for studying enzymatic reactions, so that at present QM/MM methods are almost unrivalled in this research field [4]. The following section outlines some recent examples of QM/MM studies on the mechanism of enzymatic reactions:

- Catalysis by HIV protease (PM3/GRO-MOS): one protonated (Asp-25') and one unprotonated (Asp-25) aspartate, one water molecule, and one amide unit are involved in the reaction at the active site; after the formation of a tetrahedral intermediate, the nucleophilic attack and proton transfer occur in a concerted way [45].
- Catalysis by human carbonic anhydrase HCA II (PM3/AMBER): the initially formed *Lindskog* intermediate is unstable and rearranges to the more stable *Lipscomb* intermediate with a more favorable zinc-bicarbonate coordination [46].
- Catalysis by chorismate mutase (AM1/CHARMM): the reaction barrier of the *Claisen* rearrangement in the enzyme is lowered by 24 kcal/mol due to a combination of strain in the substrate and stabilization of the transition state [47].

- Catalysis by malate dehydrogenase (AM1/CHARMM): during the interconversion of malate to oxaloacetate, the proton transfer precedes the hydride transfer; the role of the protein environment is analyzed in detail [48]. The energy profile of the reaction in the enzyme and in aqueous solution is similar [23][48].
- Catalysis by papain (AM1/AMBER): the amide hydrolysis in the enzyme follows a concerted rather than a stepwise mechanism [49].
- Catalysis by tyrosine phosphatase (PM3/AMBER): the hydrolysis of the phosphate ester in the enzyme proceeds by a dissociative mechanism; the transition state does not show bonds to the attacking nucleophile (cysteine) [50].
- Catalysis by citrate synthase (AM1/CHARMM): the enolization of acetyl-CoA starts with a deprotonation and is followed by nucleophilic attack and subsequent hydrolysis; the enolate intermediate is stabilized in the enzyme by hydrogen bonds [51].
- Catalysis by lactate dehydrogenase: in this case, two independent QM/MM studies for the conversion of pyruvate into lactate lead to different results. Using AM1/AMBER, two transition states are found, where the slower hydride transfer precedes the faster proton transfer [52]; on the other hand, AM1/CHARMM predicts the existence of just one concerted transition state, where the proton transfer is more advanced than the hydride transfer [31].

QM/MM methods have also been applied to the theoretical study of reactions on zeolites [53] and in organometallic chemistry [54–57]. In these investigations [53–57], *ab initio* and DFT methods are employed for the calculation of the QM region which is mechanically embedded. The zeolites work concerns the initial adsorption of ammonia on H-faujasite and the specific acidity of different binding sites on the catalyst [53], whereas the organometallic studies concentrate on steric effects. Using the IMOMM method, it has been shown how the structure of the transition state for the oxidative addition of H_2 to $Pt(PR_3)_2$ (R = H, Me, *t*-Bu, Ph) changes due to increasing steric effects (RHF/MM3) [54] and how the isotacticity in the propylene polymerization by silylene-bridged metallocenes is sterically controlled by substituents (RHF/MM2) [55]. Similarly, steric effects due to bulky substituents significantly influence the barriers for chain propagation, chain branching, and chain termination in the

catalytic *Brookhart*-type Ni^{II} olefin polymerization; the QM/MM barriers (DFT-BP86/AMBER) are in much better agreement with experiment than the QM values for smaller model systems without substituents [56][57].

Electronic excitations in condensed phase are another important application for QM/MM methods. The solvatochromism of n $\rightarrow$ π^* transitions has been investigated by several authors [13][58–60], mostly employing semiempirical QM methods [13][58][59] and MM polarization [13][59][60]. Other recent work addresses the ground- and excited-state pK_a difference of phenol in water [61], the solvent effects on the geometry of conjugated chromophores and their solvatochromic shift for $\pi \rightarrow \pi^*$ excited states [62], and the photophysics of uracil and 1,3-dimethyluracil [63]. Especially impressive is a QM/MM study of the photosynthetic reaction center reporting the excited states of the bacteriochlorophyll *b* (325 QM atoms, 20158 MM atoms; QM = MNDO, AM1, PM3, INDO/S and MM = AMBER, CVFF) [12].

Outlook

The examples discussed show that QM/MM methods, if applied in a critical and careful manner, can successfully model electronic effects in large systems. Alternatively, it may become feasible to treat such systems using pure QM calculations with linear scaling (for selected references see [64–79]). These calculations are much more expensive from a computational point of view, but are theoretically more consistent and less affected by approximations. They account for long-range charge transfers and charge fluctuations in proteins, which cannot be described by the usual QM/MM methods. However, the QM/MM methods have the advantage that they are more efficient and offer the possibility of a specifically *tailored* description of the system, where the computational effort is concentrated on the chemically important part of the system. We believe that both theoretical methods will be successfully applied in future studies, since they complement each other.

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