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Theoretical Chemistry

QM/MM Methods for Biomolecular Systems

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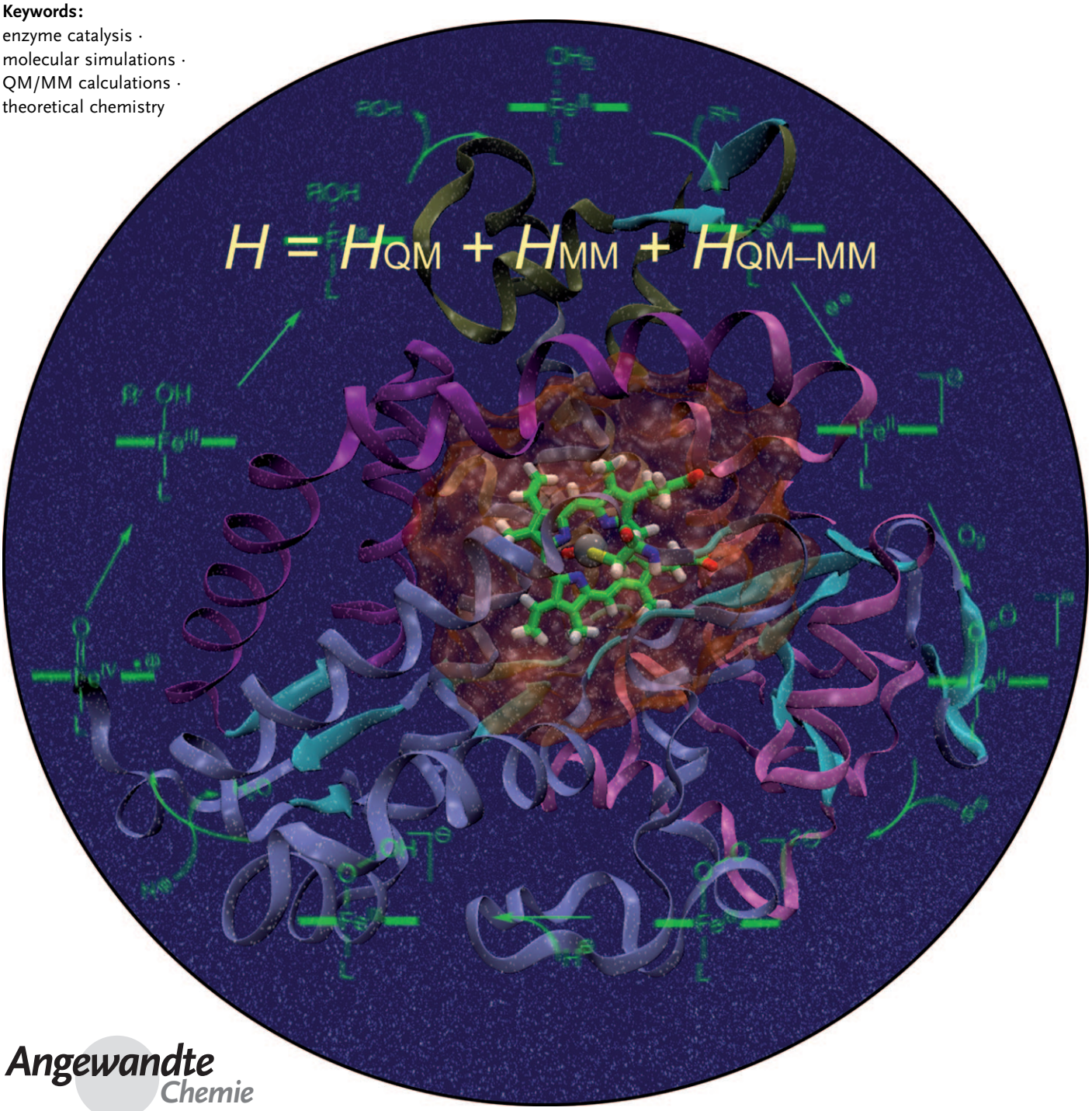

Combined quantum-mechanics/molecular-mechanics (QM/MM) approaches have become the method of choice for modeling reactions in biomolecular systems. Quantum-mechanical (QM) methods are required for describing chemical reactions and other electronic processes, such as charge transfer or electronic excitation. However, QM methods are restricted to systems of up to a few hundred atoms. However, the size and conformational complexity of biopolymers calls for methods capable of treating up to several 100 000 atoms and allowing for simulations over time scales of tens of nanoseconds. This is achieved by highly efficient, force-field-based molecular mechanics (MM) methods. Thus to model large biomolecules the logical approach is to combine the two techniques and to use a QM method for the chemically active region (e.g., substrates and co-factors in an enzymatic reaction) and an MM treatment for the surroundings (e.g., protein and solvent). The resulting schemes are commonly referred to as combined or hybrid QM/MM methods. They enable the modeling of reactive biomolecular systems at a reasonable computational effort while providing the necessary accuracy.

From the Contents

1. Introduction

The seminal contribution by Warshel and Levitt from 1976[1] marks the beginning of the QM/MM era. They introduced the QM/MM concept, presented a method with many of the features that are now considered essential in the field, and applied it to an enzymatic reaction. The QM/MM approach found widespread acceptance only much later, in the 1990s, beginning with the report by Field, Bash, and Karplus in 1990,[2] who described in detail the coupling of semi-empirical QM methods to the CHARMM force field and carefully evaluated the accuracy and effectiveness of the QM/MM treatment against ab initio and experimental data. Over the past decade, numerous Reviews have documented the development of the QM/MM approach as well as its application to biomolecular problems.[3–39] Among the more recent ones are the overview on current methodological aspects by Lin and Truhlar[36] and a comprehensive book chapter by ourselves.[38] A number of articles have combined, with varying accent, expositions of QM/MM and other computational methods for biomolecular systems with application surveys.[22,27,35,37,38] Recent reviews have also addressed the use of the QM/MM approach in combination with modern rate theory and techniques accounting for the quantum nature of atomic motion[25,40,41] and with free-energy and reaction-path methods,[39,42] in both cases with an emphasis on enzymatic reactions.

The QM/MM approach is by now established as a valuable tool not only for the modeling of biomolecular systems, but also for the investigation of inorganic/organometallic[43–60] and solid-state[61–68] systems and for studying processes in explicit solvent.[4,56,57,69–77] Herein we will focus entirely on the biomolecular area. We begin in Section 2 with an introduction into basic methodological features of the QM/MM approach, covering topics such as the QM–MM partitioning, the choice of suitable QM and MM methods, and the treatment of the QM–MM interactions and of the QM/MM boundary region. Section 3 highlights issues pertaining to QM/MM geometry optimization, molecular dynamics (MD), and free-energy simulation techniques. Section 4 covers different types of applications where the QM/MM approach has been particularly useful, including three case studies to illustrate the insights that can be gained from QM/MM calculations on enzymatic reactions. Section 5, provides an extensive tabular survey of QM/MM studies on biomolecular systems for the period 2006–2007, which updates the survey given in Ref. [38] We conclude with a summary and outlook in Section 6.

2. The QM/MM Method

2.1. General remarks

2.1.1. QM–MM partitioning

A general sketch of the division of the system into QM and MM parts is shown in Figure 1. The entire system ($\mathbb{S}$) is partitioned into the inner region ($\mathbb{I}$) that is treated quantum-mechanically and the outer region ($\mathbb{O}$) that is described by a force field. Inner and outer regions are therefore also often referred to as QM and MM regions, respectively. Owing to the (strong) QM–MM interactions, the total energy of the entire system cannot simply be written as the sum of the energies of the subsystems. Coupling terms have to be considered, and special precautions need to be taken at the boundary between

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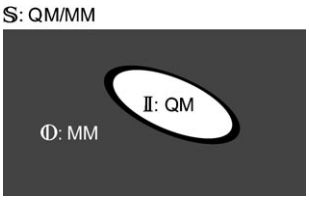

Figure 1. Partitioning of the entire system (𝕊) into inner (𝕀) and outer (𝕆) subsystems. The black ring around the inner system represents the boundary region.

the subsystems, especially if it cuts through covalent bonds. The term boundary region is used rather loosely to designate the region where the standard QM and MM procedures are modified or augmented in any way. Depending on the type of QM/MM scheme, this region may contain additional atoms (link atoms) that cap the QM subsystem and are not part of the entire system, or it may consist of atoms with special features that appear in both the QM and the MM calculation.

We will concern ourselves herein only with fixed QM–MM partitionings where the boundary between QM and MM regions in a calculation is defined once-and-for-all at the start. For QM/MM schemes that allow the boundary to change during the course of a simulation (adaptive partitioning, "hot spot" methods), suitable for processes with shifting active region(s), such as defect propagation in materials or solvated ions, see Ref. [78] and articles cited therein.

2.1.2. *Choice of QM and MM Methods*

The QM/MM formalism can accommodate almost any combination of QM and MM methods. The choice of the QM method follows the same criteria as in pure QM studies and is not further elaborated on herein. Essentially, the QM code must be able to perform the self-consistent-field (SCF) treatment in the presence of the external point-charge field that represents the MM charge model in the case of electronic or polarized embedding (see Section 2.2.2). In practice, many current biomolecular QM/MM applications use density-functional theory (DFT) as the QM method owing to its favorable computational-effort/accuracy ratio. Traditionally, semi-empirical QM methods have been most popular, and they remain important for QM/MM molecular dynamics. The semi-empirical, DFT-inspired SCC-DFTB (self-consistent-charge density-functional tight-binding)[79] method is increasingly being applied in biomolecular QM/MM studies.[80–83] At the high end in terms of accuracy and effort are post-Hartree–Fock ab initio electron-correlation methods, such as those based on Møller–Plesset perturbation theory (e.g., to second order, MP2) or coupled-cluster theory (e.g., CCSD including single and double excitations or CCSD(T), which adds a perturbative treatment of triple excitations). The recent development[84–91] of linear-scaling local correlation methods (e.g., LMP2, LCCSD) has significantly extended the size of systems that can be treated with such methods, up to several tens of atoms. The superior accuracy of high-level ab initio methods can now therefore also be exploited for biomolecular QM/MM studies,[92–94] certainly at the level of energy calculations at fixed geometry (i.e., single points).

Although not an electronic-structure QM method in the usual sense, we also mention the empirical valence-bond (EVB) method.[95–98] This approach employs a valence-bond description of the reactive part of the system. The energies of the interacting diabatic (resonance) states are represented by simple empirical potential terms which incorporate the interaction of the charges with the environment; the EVB energies are calibrated to reproduce experimental or ab initio data. The EVB method has been applied with much success, notably by Warshel and collaborators, to model the influence of the solvent and protein environment on reactions.

As far as the choice of MM method is concerned, there are a number of biomolecular force fields available. Popular examples include AMBER,[99–102] CHARMM,[103–107] GROMOS,[108,109] and OPLS-AA.[110–112] "Biomolecular" typically includes proteins[113,114] and in most cases also nucleic acids,[115,116] but less frequently carbohydrates[117] or lipids. Surveys of force fields are available in the literature.[118–120]

2.1.3. *The MM Energy Expression*

Unless stated otherwise, for the remainder of this Review the classical potential-energy function (the "force field") of the MM region contains bonded terms (typically bond stretching, angle bending, torsions, and out-of-plane deformations or improper torsions); Lennard–Jones-type van der Waals terms; and Coulomb interaction terms between rigid

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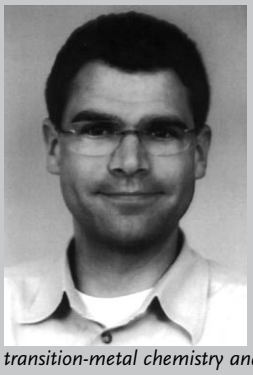

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point charges. A simple, prototypical MM energy expression of this type is shown in Equation (1).

$$E_{\mathrm{MM}} = \sum_{\text{bonds}} k_d (d-d_0)^2 + \sum_{\text{angles}} k_\theta (\theta-\theta_0)^2 + \sum_{\text{dihedrals}} k_\phi [1+\cos(n\phi+\delta)] + \sum_{\substack{\text{nonbonded}\\ \text{pairs AB}}} \left\{ \varepsilon_{\mathrm{AB}} \left[\left(\frac{\sigma_{\mathrm{AB}}}{r_{\mathrm{AB}}} \right)^{12} - \left(\frac{\sigma_{\mathrm{AB}}}{r_{\mathrm{AB}}} \right)^{6} \right] + \frac{1}{4\pi\varepsilon_0} \frac{q_{\mathrm{A}} q_{\mathrm{B}}}{r_{\mathrm{AB}}} \right\} \quad (1)$$

The symbols d, θ, and ϕ designate bond lengths, angles, and torsions, respectively; d_0 and θ_0 are the corresponding equilibrium values; n and δ are the torsional multiplicity and phase, respectively. The bonded force constants are k_d, k_θ, and k_ϕ; r_{AB} is the nonbonded distance between atoms A and B, and $\varepsilon_{\mathrm{AB}}$ and σ_{AB} are the Lennard–Jones parameters; q_{A}, q_{B} are atomic partial charges; and ε_0 is the vacuum permittivity (dielectric constant). We refer to the literature[107,118,119,121] for detailed information on more elaborate force fields.

2.2. The QM/MM Energy Expression

2.2.1. Subtractive and Additive QM/MM Schemes

Subtractive QM/MM schemes require 1) an MM calculation on the entire system; 2) a QM calculation on the inner subsystem; and 3) an MM calculation on the inner subsystem. The QM/MM energy of the entire system is then obtained by summing (1) and (2) and subtracting (3) to avoid double counting, which gives Equation (2).

$$E^{\mathrm{sub}}_{\mathrm{QM/MM}}(\mathbb{S}) = E_{\mathrm{MM}}(\mathbb{S}) + E_{\mathrm{QM}}(\mathbb{I}+\mathbb{L}) - E_{\mathrm{MM}}(\mathbb{I}+\mathbb{L}) \quad (2)$$

In this case and later, the subscript indicates the type of calculation while the system on which it is performed is given in parentheses. As formulated, Equation (2) holds for a scheme with link atoms ($\mathbb{L}$), in which the calculations are performed on a capped inner subsystem ($\mathbb{I}+\mathbb{L}$).

Conceptually, the subtractive QM/MM scheme can be seen as an MM approach where a certain region of space has been cut out and is treated at the QM level. Its main advantage is simplicity. No explicit QM–MM coupling terms are needed; the standard QM and MM procedures can be used without any modifications; and the implementation is thus straightforward. The subtraction corrects for artifacts caused by the link atoms, as long as the MM force terms involving the link atoms reproduce the QM potential reasonably well. On the downside, a subtractive scheme requires a complete set of MM parameters for the inner subsystem, which may be difficult or cumbersome to obtain. Moreover, and more severely, the coupling between the subsystems is handled entirely at the MM level. This is particularly problematic for the electrostatic interaction, which will then typically be represented by the Coulomb interaction between fixed atomic charges in the QM and MM regions.

As an example of a subtractive QM/MM scheme, we mention the IMOMM (integrated molecular orbital/molecular mechanics) method by Morokuma and co-workers.[45] It has subsequently been extended to allow for the combination of two QM methods (IMOMO[122]) and further generalized to n layers (typically, $n=3$), each of which can be treated at an arbitrary QM or MM level (ONIOM, our n-layered integrated molecular orbital and molecular mechanics[123–125]). Recent improvements of the ONIOM approach[126–128] enable the inclusion of MM charges into the QM Hamiltonian (electrostatic embedding, see Section 2.2.2) and thus take it beyond a strictly subtractive scheme. Another subtractive approach with electrostatic embedding has been introduced by Ryde.[129,130]

The basic energy expression for an additive QM/MM scheme is given in Equation (3).

$$E^{\mathrm{add}}_{\mathrm{QM/MM}}(\mathbb{S}) = E_{\mathrm{MM}}(\mathbb{O}) + E_{\mathrm{QM}}(\mathbb{I}+\mathbb{L}) + E_{\mathrm{QM\text{-}MM}}(\mathbb{I},\mathbb{O}) \quad (3)$$

In contrast to Equation (2), the MM calculation is now performed on the outer subsystem only. In addition, there appears an explicit coupling term, $E_{\mathrm{QM\text{-}MM}}(\mathbb{I},\mathbb{O})$, which collects the interaction terms between the two subsystems. The capped inner subsystem, $\mathbb{I}+\mathbb{L}$, is treated at the QM level as in the subtractive scheme. The majority of QM/MM schemes presently in use are of the additive type [Eq. (3)].

The exact form of the QM–MM coupling term $E_{\mathrm{QM\text{-}MM}}$ defines a particular QM/MM method. In accordance with the interactions considered in the force field [Eq. (1)], it includes bonded, van der Waals, and electrostatic interactions between QM and MM atoms [Eq. (4)]

$$E_{\mathrm{QM\text{-}MM}}(\mathbb{I},\mathbb{O}) = E^{\mathrm{b}}_{\mathrm{QM\text{-}MM}} + E^{\mathrm{vdW}}_{\mathrm{QM\text{-}MM}} + E^{\mathrm{el}}_{\mathrm{QM\text{-}MM}} \quad (4)$$

The following Sections deal in more detail with the individual contributions to $E_{\mathrm{QM\text{-}MM}}$. We begin with the electrostatic coupling term, which is normally the most important and also the most technically involved one. The van der Waals interaction and the bonded terms are discussed together thereafter. Finally, we present various ways that have been devised to treat covalent bonds across the QM–MM boundary.

2.2.2. The Electrostatic QM–MM Interaction

The electrostatic coupling between the QM charge density and the charge model used in the MM region can be handled at different levels of sophistication, characterized essentially by the extent of mutual polarization and classified[131,132] accordingly as mechanical embedding (model A), electrostatic embedding (model B), and polarized embedding (models C and D).

In the case of mechanical embedding, the QM–MM electrostatic interaction is treated on the same footing as the MM–MM electrostatics. The charge model of the MM method (typically rigid atomic point charges, but other approaches, e.g., bond dipoles, are also conceivable) is simply applied to the QM region as well. This is conceptually straightforward and computationally efficient. However,

there are some major disadvantages and limitations: 1) The charges in the outer region do not interact with the QM density, which is thus not directly influenced (polarized) by the electrostatic environment. 2) When the charge distribution in the QM region changes, for instance during a reaction, it would seem chemically sensible to update the charges. However, this would cause discontinuities in the potential-energy surface. 3) The derivation of appropriate MM point charges for the inner region is not trivial and may require considerable effort. 4) These MM charges do not necessarily reproduce the true charge distribution in the inner region faithfully. Individual MM charges need not be physically meaningful, as long as the force field provides an overall balanced description.

The major shortcomings of mechanical embedding can be eliminated or avoided by performing the QM calculation in presence of the MM charge model. For instance, by incorporating the MM point charges as one-electron terms in the QM Hamiltonian, which is thus augmented by an additional term (using atomic units) [Eq. (5)].

$$\hat{H}^{\mathrm{el}}_{\mathrm{QM\text{-}MM}} = -\sum_{i}^{N}\sum_{J\in\mathbb{O}}^{L}\frac{q_J}{|\boldsymbol{r}_i-\boldsymbol{R}_J|}+\sum_{\alpha\in\mathbb{I}+\mathbb{L}}^{M}\sum_{J\in\mathbb{O}}^{L}\frac{q_J\,Q_\alpha}{|\boldsymbol{R}_\alpha-\boldsymbol{R}_J|} \tag{5}$$

The symbols q_J are the MM point charges located at $\boldsymbol{R}_J$; Q_α are the nuclear charges of the QM atoms at $\boldsymbol{R}_\alpha$; and $\boldsymbol{r}_i$ designate electron positions. The indices i, J, and α run over the N electrons, L point charges, and M QM nuclei, respectively.

In such an electrostatic or electronic embedding scheme, the electronic structure of the inner region can adapt to changes in the charge distribution of the environment and is automatically polarized by it. No charge model needs to be derived for the inner region. The QM–MM electrostatic interaction is treated at the QM level, which provides a more advanced and more accurate description than a mechanical-embedding scheme. Naturally, electrostatic embedding also increases the computational demands, especially for the calculation of the Coulomb forces as a result of the QM density acting on the (many) MM point charges. Special care is required at the QM–MM boundary, where the MM charges are placed in immediate proximity to the QM electron density and can thus cause overpolarization. This problem is especially pronounced when the boundary runs through a covalent bond.

There remains the general issue of compatibility between the MM charge model and the QM electron density. As mentioned above, the electrostatic MM parameters are not primarily designed to provide a faithful representation of the real charge distribution. It is thus in principle not legitimate to stitch a true charge distribution from a QM calculation into the carefully parameterized MM charge model. Nevertheless, this has become common practice, and experience shows that the results are generally reasonable, at least for the combination of a QM density with one of the widely used biomolecular force fields. The obvious appeal of this approach is that the MM atomic partial charges are readily available and that their inclusion in the QM Hamiltonian is efficient. Electrostatic embedding is the most popular embedding scheme in use today, certainly for biomolecular applications.

As electrostatic embedding accounts for the interaction of the polarizable QM density with rigid MM charges, the next logical step is to introduce a flexible MM charge model that is polarized by the QM charge distribution. These polarized-embedding schemes can be further divided into approaches where the polarizable charge model in the MM region is polarized by the QM electric field but does not itself act back on the QM density (model C); and fully self-consistent formulations that include the polarizable MM model into the QM Hamiltonian and therefore allow for mutual polarization (model D). There are various models for treating polarization in classical simulations,[118,133–142] but there are as yet no generally established polarizable biomolecular force fields. The development of polarizable protein force fields is in progress.[101,143–154] Although the very first QM/MM approaches[1,155] and other early semi-empirical QM/MM implementations[131,156–158] already used polarized-embedding schemes, biomolecular applications have remained scarce; a notable exception is a QM/MM study of excited states in the photosynthetic reaction center in which the MM polarization was included self-consistently.[156] Otherwise, polarized-embedding QM/MM calculations have essentially been restricted to explicit solvation (in particular, hydration), where the solute is treated at the QM level and the solvent by a polarizable force field.[16,157–165] In a recent implementation of polarized QM/MM, the induced dipoles in the MM region were represented by a charge-on-spring model.[164] Another scheme treats MM polarization in QM/MM calculations through induced charges that are determined by a QM-based distributed multipole analysis.[166] Finally, there is an interesting approach recently proposed by Zhang et al.,[167,168] which should be efficient because in it only the MM atoms at the boundary are polarized.

An accurate description of the electrostatic forces on the QM subsystem arising from the environment is essential for a realistic modeling of biomolecules. Including all the electrostatic interactions explicitly is computationally challenging. However, simple QM/MM electrostatic cutoffs are problematic because of the long-range nature of the Coulomb interaction.[169–171] The reliable and efficient treatment of these long-range electrostatic interactions is well-established in classical molecular dynamics (MD) simulations, but has only recently gained increased attention in the context of QM/MM methods. We mention a linear-scaling particle–mesh Ewald scheme for QM/MM simulations under periodic boundary conditions;[171] a charge-scaling procedure using continuum electrostatics, in which only a limited number of explicit solvent molecules is considered and the charges are scaled to mimic the shielding effect of the solvent;[172] the variational electrostatic projection method,[173,174] which aims at reducing the effort of calculating the electrostatic forces arising from the fixed external environment on the moving atoms in the inner regions by employing the framework of the stochastic-boundary approach;[175–178] and the adaptation of the generalized solvent boundary potential (GSBP)[179] for QM/MM.[169,180,181]

2.2.3. Other Nonbonded and Bonded QM–MM Interactions

In addition to the electrostatic interactions discussed in the previous section, there are also van der Waals and bonded contributions to the QM–MM coupling term [Eq. (4)]. Their treatment is considerably simpler as they are handled purely at the MM level, irrespective of the class (subtractive or additive) of QM/MM scheme.

The van der Waals interaction is typically described by a Lennard–Jones potential [Eq. (1)] so that suitable parameters are needed for the QM atoms in the inner region. They can often be adopted from similar atom types, but it is not uncommon that certain QM atoms are not covered by any of the atom types and assignment rules of the force field. Even if suitable Lennard–Jones parameters exist for a given configuration, QM atoms can change their character, for example, during a reaction. This then raises the question of whether the parameter set should be switched, say, from a "reactant description" to a "product description" somewhere along the reaction path. In practice, however, these complications are very much alleviated by the short-range nature of the van der Waals interaction. While every atom of the QM region is involved in van der Waals interactions with all the atoms of the MM region, only those closest to the boundary contribute significantly. Concerns about possible errors due to non-optimum Lennard–Jones parameters, may be minimized by moving the QM–MM boundary further away from the incriminated QM atoms.

Friesner and co-workers[182] have re-optimized the QM Lennard–Jones parameters against QM data for hydrogen-bonded pairs of small amino acid models. The Lennard–Jones radii thus obtained are 5–10% larger than those of the underlying force field (OPLS-AA); the Lennard–Jones well depths were left unchanged. The resulting increased repulsion compensates for the too strong QM–MM electrostatic attraction which arises from overpolarization at the boundary. Recently, a set of Lennard–Jones parameters optimized for B3LYP/AMBER was presented by a another group.[183] However, Cui and co-workers[184] showed that thermodynamic quantities in the condensed phase (e.g., free energies), calculated from QM/MM simulations, are rather insensitive towards the QM–MM van der Waals parameters, whereas there is some influence on the detailed structure around the QM region.

With regard to QM–MM van der Waals coupling, subtractive and additive schemes are identical. In an additive scheme, only pairs consisting of one atom from the inner and one atom from the outer subsystem are considered in $E^{\mathrm{vdW}}_{\mathrm{QM\text{-}MM}}$. This approach yields exactly the same van der Waals terms as a subtractive scheme, where the QM–QM van der Waals pairs are subtracted out.

The formal reservations against using standard MM parameters to describe QM–MM interactions apply of course also to the bonded (bond stretching, angle bending, torsional, etc.) interactions. And again, the solution is entirely pragmatic: usually the standard MM parameter set is retained and is complemented as necessary with additional bonded terms not covered by the default assignment rules of the force field.

2.3. Covalent Bonds that Cross the QM–MM Boundary

2.3.1. Overview of Boundary Schemes

This section is concerned with the various approaches that have been devised to treat covalent bonds cut by the QM–MM boundary. To facilitate the discussion, we introduce first some labeling conventions, illustrated in Figure 2, which

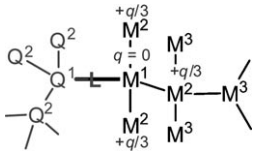


Figure 2. Labeling of atoms at the boundary between inner and outer regions. The partial charges illustrate a charge-shift scheme: The original MM charge q of M^1 is removed and evenly distributed onto the M^2 atoms. Additional pairs of charges are placed near the M^2 atoms to restore the original M^1–M^2 dipoles (not shown).

apply to covalent bonds that cross the QM–MM boundary. The QM and MM atoms directly connected are designated Q^1 and M^1, respectively, and are sometimes called boundary, frontier, or junction atoms. The first shell of MM atoms, that is, those directly bonded to M^1, is labeled M^2. The next shell, separated from M^1 by two bonds, is labeled M^3, and so on, following the molecular graph outwards from M^1. The corresponding naming convention applies to the QM side: atoms Q^2 are one bond away from Q^1; Q^3 are two bonds away, and so on. If a link-atom scheme is applied, the dangling bond of Q^1 is saturated by the link atom L. As a caveat, note that terms such as link, capping, boundary, junction, or frontier atom are not uniquely defined in the literature; their usage varies between authors.

The simplest solution to the problem of cutting covalent bonds is of course to circumvent it altogether by defining the subsystems such that the boundary does not pass through a covalent bond. This is trivially fulfilled for explicit-solvation studies, where the solute is normally described at the QM level, surrounded by MM solvent molecules. Such a favorable situation is sometimes encountered also for biomolecular systems; for instance, if an enzymatic reaction involves only partners (substrates, co-factors) that are not covalently bound to the enzyme. In many cases, however, it is unavoidable that the QM–MM boundary cuts through a covalent bond. Then three issues have to be dealt with: 1) The dangling bond of the QM atom Q^1 must be capped; since it would be entirely unrealistic to simply truncate the QM region (that is, treating the bond as being homolytically or heterolytically cleaved). 2) For electrostatic or polarized embedding, overpolarization of the QM density by the MM charges close to the cut has to be prevented, especially when using link atoms. 3) The bonded MM terms involving atoms from both subsystems have to be selected such that double-counting of interactions is avoided. Overall, the target is to achieve a well-balanced description of the QM–MM interactions at the border between the two subsystems. In the literature, there are essentially three different classes of boundary schemes:

- Link-atom schemes introduce an additional atomic center L (usually a hydrogen atom) that is not part of the real system. It is covalently bound to Q^1 and saturates its free valency.
- In boundary-atom schemes, the MM atom M^1 is replaced by a special boundary atom that appears in both the QM and the MM calculation. On the QM side, it mimics the cut bond and possibly also the electronic character of the MM moiety attached to Q^1; in the MM calculation, it behaves as a normal MM atom.
- Localized-orbital schemes place hybrid orbitals at the boundary and keep some of them frozen. They serve to cap the QM region, replacing the cut bond.

Generally speaking, possible artifacts can be minimized by an appropriate choice of the boundary. Clearly the QM–MM frontier should be as distant from the chemically active region as is feasible in terms of computational effort (which is controlled by the size of the QM part). Moreover, QM atoms participating in bond making or breaking should not be involved in any bonded coupling term.[128] Since the dihedral terms extend at most two bonds into the inner region (depending on the details of the boundary scheme used), such atoms should be at least three bonds away from the boundary. The bond being cut should be unpolar and not involved in conjugative interactions. A good place to cut is thus an aliphatic, "innocent" C–C bond, whereas, for example, an amide bond with partial double-bond character is less suitable. Cutting through an MM charge group is to be avoided because it creates an artificial net charge in the immediate vicinity of the QM density. Finally, the total charge of the MM atoms being replaced by the QM part should be zero.

2.3.2. Link Atoms

The link-atom method, adopted already in early QM/MM studies,[2,155] is conceptually simple: The free valency at Q^1 created by the QM–MM division is capped by an additional atom that is covalently bonded to Q^1 (see Figure 2). This link atom L; is in most cases a hydrogen atom, but any monovalent atom or group might be used. QM calculations are then performed on an electronically saturated system consisting of the inner subsystem and the link atom(s), $\mathbb{I}+\mathbb{L}$. The bond Q^1–M^1 is described at the MM level. The introduction of an additional atomic center, which is not part of the real system, creates some problems that need to be addressed: 1) Each link atom generates three artificial structural degrees of freedom not present in the real system. 2) The link atom, and with it the QM electron density, is spatially very close to the MM frontier atom M^1 so that the point charge on M^1 will tend to overpolarize the QM density in the case of electrostatic or polarized embedding. 3) The link atom is generally chemically and electronically different from the group which it replaces. Attempts to overcome these problems give rise to the more elaborate boundary schemes discussed in Section 2.3.3.

Despite these problems, link atoms are widely used. Correspondingly, a large variety of link-atom schemes has evolved.[2,45,50,62,124,125,129,155,185–191] In some of them,[2,155,187] the link atoms are treated as independent atomic centers, thus introducing three additional structural degrees of freedom per link atom. These can be eliminated by the use of constraints.[45] The procedure was subsequently refined to define the position of the link atom as a function of the positions of Q^1 and M^1. The link atom L is placed along Q^1–M^1, and the distance Q^1–L is related to the distance Q^1–M^1 by a scaling factor. [50,62,125,129,186,188–190] Exactly three degrees of freedom are thus removed. Most currently used link-atom schemes follow this general approach.

If the position of the link atom is determined by some rule and expressed as a function of other atomic positions, its coordinates can be eliminated from the set of independent variables. The link atoms will then appear only in the internal description of the QM/MM coupling scheme, and they are transparent to geometry-optimization or molecular-dynamics algorithms, which only handle the set of independent variables. In the QM calculation, there are forces acting on the link atoms, which must be relayed onto the atoms that define the link atom coordinates.[62] The link atoms are then effectively force-free; their coordinates in the next geometry or time step are fully determined by the positioning rule, rather than being propagated according to forces acting on them.

As noted above, the QM density will tend to be overpolarized by the rigid point charges of the MM charge model in the case of electrostatic or polarized embedding. While this artifact is always present to some extent when a point charge interacts with a polarizable charge distribution, it becomes more severe the closer the point charge approaches the QM density and the more spatially flexible the density is. The problem is therefore especially critical at the QM–MM boundary in the presence of link atoms, which are positioned in immediate proximity of the frontier MM atom, typically at a distance of about 0.5 Å. Overpolarization is less severe when small, atom-centered basis sets are used in the QM calculation, for example, in a semi-empirical method with a minimal basis. Larger basis sets, which include polarization and possibly diffuse functions, are more flexible and hence more prone to overpolarization. Especially affected are methods using plane waves.

Different approaches have been put forward to reduce overpolarization within link-atom schemes: 1) Deletion of the one-electron integrals associated with the link atoms.[2,131,132,189,192,193] 2) Deletion of MM point charges in the link region from the Hamiltonian.[129,132,155,185,187,194–198] 3) Shifting/redistribution of the point charges in the link region (Figure 2).[19,64,82,188,198,199] By preserving the charge and often also the dipole in the boundary region, while still removing the overpolarizing partial charge from M^1, these schemes cure[82,198,200] the major deficiencies of deleted-charge schemes. Widely used is the charge-shift scheme introduced by Sherwood and co-workers.[19,64,188,199] 4) "Smearing" the charges close to the QM region[186,191,200] by replacing them by (e.g., Gaussian) charge distributions.

2.3.3. Boundary Atoms

Boundary-atom schemes replace the MM frontier atom M^1 by a special boundary atom of Janus-like character that participates as an ordinary MM atom in the MM calculation but also carries QM features to saturate the free valency of Q^1. They avoid the complications associated with the introduction of additional atoms and aim at mimicking the electronic properties of the MM moiety at the link. Most of the boundary-atom schemes proposed are based on a type of monovalent pseudopotential (or effective potential) that is located at the position of M^1 and parameterized to reproduce certain desired properties. A typical choice is, for example, to mimic a methyl group at a cut C–C single bond. Of the different schemes proposed, we mention herein the adjusted connection atoms for semi-empirical QM methods;[201] the pseudobond approach for ab initio and DFT methods;[202–204] and the use of tailored pseudopotentials within plane-wave QM methods.[205] There are several other recent developments in this area,[206–212] which, however, have not yet been more widely used.

2.3.4. Frozen Localized Orbitals

The approach of using a frozen hybrid orbital to saturate the dangling bond at the QM–MM boundary dates back to Warshel and Levitt.[1] Different schemes have been elaborated that share the idea of placing a set of suitably oriented localized orbitals on one of the frontier atoms and keeping some of these orbitals frozen such that they do not participate in the SCF iterations.

- Local Self-Consistent Field (LSCF):[213–217] The LSCF method, developed by Rivail and co-workers, starts out with a QM calculation on a model system that contains the frontier bond to be described. Applying a localization scheme, a strictly localized bond orbital (SLBO) for this bond is constructed, which has contributions from the frontier atoms only and is assumed to be transferable. In the QM/MM calculation, it is excluded from the SCF optimization and does therefore not mix with other orbitals. It is oriented along the Q^1–M^1 vector and can be described as a kind of frozen lone pair on Q^1 pointing towards M^1 (Figure 3a). Recent modifications of the LSCF method include the use of extremely localized molecular orbitals (ELMOs)[218–220] or frozen core orbitals[221] at the frontier atom, and the optimized-LSCF method,[222] in which the SLBOs are allowed to mix with their antibonding counterparts.

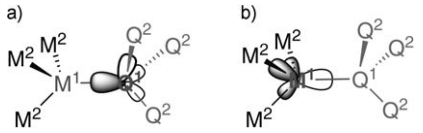


Figure 3. The frozen-orbital boundary methods. a) LSCF method: A set of localized orbitals is placed on Q^1, one of which (shaded) is kept frozen and points towards M^1. b) GHO method: A set of localized orbitals is placed on M^1, one of which (open) is active and points towards Q^1.

- Frozen Orbitals:[182,223,224] Friesner and co-workers have presented a variant of the LSCF procedure that differs in some technical details from the original one. Furthermore, contrary to most other QM/MM schemes, the QM–MM interactions at the boundary are heavily parameterized.
- Generalized Hybrid Orbitals (GHO):[225–230] The GHO method by Gao and co-workers is related to the LSCF and frozen-orbital approaches in that it constructs localized hybrid orbitals and freezes some of them. However, it places the set of localized hybrid orbitals on M^1 rather than Q^1 (Figure 3b). M^1 thus becomes a boundary atom, blurring the classification of boundary methods into boundary-atom and frozen-orbital schemes. The orbital pointing towards Q^1 is active and participates in the SCF iterations, while the remaining "auxiliary" hybrids are kept frozen and are not allowed to mix with the other orbitals. The GHO method was recently extended by Jung et al.[231]
- Effective Fragment Potentials (EFP):[232–235] We also mention the EFP approach at this point, although it differs conceptually from the other frozen-orbital methods. Separate calculations on model systems are used to derive a set of one-electron terms (the EFP) that account for the electrostatic, inductive, and repulsive interactions of a moiety. The EFP is then incorporated into the Hamiltonian of a QM calculation, where it describes the effects of the environment on the QM part. Originally designed to model the solvent environment in QM calculations, the scope of the EFP method was subsequently extended to biomolecular systems, using an LSCF-type procedure to treat covalent bonds across the boundary.[234,235] Later developments have lifted the limitation that the fragments be fixed in space.[236–238]

2.3.5. Summary

Several studies have evaluated the different boundary methods. As link atoms are most widely used, most of these assessments[82,132,192,198,200,239–241] compare link-atom approaches, which differ particularly in the way the charges at the boundary are handled. There are some comparisons between link-atom and localized-orbital schemes.[192,239,240,242] Approaches based on hybrid orbitals are more fundamental from the theoretical point of view since they provide a boundary description essentially at the QM level. However, they are also technically considerably more complicated, not least because of the orthogonality constraints required to prevent the mixing of frozen and active orbitals in the SCF treatment. In addition, the localized orbitals themselves, and/or specific parameter sets related to them, must be determined beforehand by calculations on model compounds. These parameters are usually not transferable and may need to be modified upon changing the MM force field, the QM method, or basis set. Overall the performance of link-atom schemes is generally on a par with localized-orbital approaches. They both provide reasonable accuracy when used with care.

3. Optimization and Simulation Techniques for QM/MM

3.1. General Comments

The QM/MM method as presented so far is a potential-energy scheme yielding the energy and the forces for a given structure. As such it can be combined with any approach that makes use of this information to update the structure, that is, with any optimization, molecular-dynamics, or Monte Carlo technique. QM/MM calculations are often performed for biomolecules containing thousands of atoms, but compared with pure MM treatments, the computational demands of a QM/MM energy and gradient evaluation is much higher. For the exploration of potential-energy surfaces, methods that can handle thousands of degrees of freedom are needed and these methods must still be efficient. Ideally, the algorithms for manipulating coordinates (e.g., in optimization schemes) should scale as $\mathcal{O}(N)$, where N is the number of degrees of freedom, and search algorithms should require a minimum number of steps to achieve convergence. Some of the techniques outlined below have been designed to scale as $\mathcal{O}(N)$. Others are efficient because they take specific advantage of the partitioning of the system into a QM region, in which evaluating energy and gradients is computationally demanding, and a MM region, in which these calculations are almost for free.

Connected with the determination of stationary points (i.e., minima, saddle points) on potential-energy surfaces of biomolecular reactions, there is a problem that goes beyond purely algorithmic issues. The vast size of the available configuration space, as compared to a "small-molecule" reaction, drastically reduces the significance of single stationary points. Contrary to typical QM studies on smaller molecular systems, knowledge of the optimized reactant, transition state, and product is not "everything", even if a reaction path connecting them has been determined and even if finite-temperature effects are disregarded. As emphasized by Warshel and co-workers,[243] in QM/MM optimization studies at least several "representative" transition states should be considered along with their corresponding minima. While this approach provides only a very limited configurational sampling, it will at least partly reflect the influence of the conformational diversity of the environment on the reaction. An expedient way to generate a selection of configurations is, for instance, to take snapshots from a classical MD trajectory and use them as starting structures in subsequent QM/MM optimizations, as demonstrated, for example, in Ref. [244].

3.2. Stationary Points and Reaction Paths

Among the most efficient algorithms to locate stationary points on the PES are quasi-Newton methods using some form of internal coordinates (see the Refs. [26, 245–249] for general reviews on optimization algorithms). These methods require information on the curvature of the surface, that is, second derivatives, commonly referred to as the Hesse matrix or Hessean. The Hessean may be approximate and can be updated while the algorithm is exploring the PES, for example, according to the Broyden–Fletcher–Goldfarb–Shanno (BFGS) formula for minima. However, the computational demand (in terms of memory and central processor unit (CPU) usage) of quasi-Newton schemes scales as $\mathcal{O}(N^2)$ or $\mathcal{O}(N^3)$, which becomes impractical for large systems. A popular algorithm that scales linearly, that is, $\mathcal{O}(N)$, in both CPU and memory usage is the limited-memory BFGS (L-BFGS), which stores only the diagonal of the Hessean and uses information only from a limited number of previous steps.

A second scaling-bottleneck is associated with the conversion between internal and Cartesian coordinates. A number of methods have been proposed that reduce the associated scaling to $\mathcal{O}(N^2)$ or even $\mathcal{O}(N)$ by various algorithmic enhancements.[250–259] The scheme by Billeter et al.[260] divides the system into fragments and performs the computationally demanding coordinate manipulations only within these fragments ("divide-and-conquer" approach). It uses hybrid delocalized coordinates (HDLCs) that supplement the delocalized internal coordinates with a certain amount of Cartesian information, which is necessary to describe the relative position of the fragments.

For the optimization of transition states, the idea of microiterations[45,261,262] has been combined with HDLCs.[260] A core fragment is defined that contains the atoms immediately involved in the reaction. For these core degrees of freedom, the Hessean is calculated, and a traditional second-order algorithm takes an optimization step towards the saddle point. With the core kept frozen, the environment fragments are then fully relaxed using the L-BFGS algorithm in HDLCs; the next step is taken in the core; and the procedure is iterated to convergence. This scheme thus searches for a first-order saddle point controlled by the (low-dimensional) core Hessean, while minimizing the energy with respect to the degrees of freedom of the environment. The environment adiabatically follows the core degrees of freedom.

We now turn to QM/MM-specific optimization techniques. Their principal idea is to exploit, in the optimization, the division of the system into QM and MM regions in the spirit of the microiterative scheme.[45,261,262] The core contains (at least) the QM atoms, while the (remaining) MM atoms form the environment. The core optimization is referred to as "macroiterations", the optimization of the environment as "microiterations". Different coordinates and algorithms can be applied in the two regions; for instance, plain Cartesians with a conjugate-gradient or truncated-Newton algorithm for the environment degrees of freedom (which avoids demanding coordinate or Hessean manipulations) and an efficient quasi-Newton algorithm in internal coordinates for the core degrees of freedom. Mutual convergence of the optimizations can be achieved in essentially two ways: 1) The adiabatic approach, in which the environment is fully relaxed in each macrostep.[45,129,182,239,263,264] 2) The alternating scheme, in which the core and environment optimizations are alternately iterated to convergence,[155,265,266] with the core atoms being kept fixed during the microiterations and vice versa. Different options within the microiterative scheme, concerning the frequency of

environment minimizations, the size of the core, and approximations to the electrostatic QM–MM interaction, have been assessed for an enzymatic reaction.[267]

Separating the core (QM) and environment (MM) optimizations is straightforward for mechanical embedding and was used early on with the IMOMM scheme.[45] The case of electrostatic embedding is more difficult: The electrostatic QM–MM interaction is evaluated at the QM level, and a QM calculation is thus in principle required in each MM microiteration to let the density adapt to the new MM configuration and to obtain the forces on the MM atoms arising from the QM density. To restore the decoupling of QM and MM calculations, the QM density can be represented during the MM microiterations by a point-charge model. Schemes based on atomic charges fitted to the electrostatic potential (ESP charges) have been proposed,[182,266,268] the basic assumptions being that the QM charge distribution is described accurately enough by the charges and that its relaxation during the MM optimization can be neglected. The use of a lower-level QM scheme, rather than a point-charge model, to calculate the QM–MM electrostatic interaction during the MM optimization has also been suggested.[269–271] This approach leads to smoother convergence behavior, because the QM density can adapt to changes in the MM environment, and is still computationally practical.

The application of reaction-path techniques within QM/MM requires special care regarding the selection of the relevant coordinates to be included in the path definition and the smoothness of the path. Among others, the Yang group has been active in this area:[39,272–274] They extended the nudged-elastic-band (NEB) method to large systems;[272] adapted the path-optimization procedure by Ayala and Schlegel[275] for the use within QM/MM;[273] and combined the two schemes into a two-step procedure.[274]

3.3. Molecular Dynamics and Simulation Techniques

The QM/MM energy and forces can in principle be used within any molecular-dynamics (MD) or Monte Carlo (MC) scheme. In most cases, the objective of such simulations is the sampling of configuration space to calculate statistical-thermodynamical ensemble averages. Typical examples include free-energy differences, such as reaction, activation, or solvation free energies. As the amount of sampling necessary to obtain converged averages is considerable, the computational demands of these simulations are extremely high. Approximate treatments have therefore been developed that reduce the computational effort, again by taking advantage of the QM–MM partitioning; in particular, by trying to avoid the demanding direct sampling of the QM contribution. Herein we highlight some of the simulation techniques that have been applied in QM/MM calculations on biomolecular systems.

3.3.1. QM/MM Molecular-Dynamics and Monte Carlo Simulations

Historically, full QM/MM simulations (i.e., with freely moving QM atoms) were first employed in explicit-solvent studies to calculate solvation free energies or reaction free energies in solution.[3,4,276–282] They used both molecular dynamics and Monte Carlo methods for sampling, along with free-energy treatments such as free-energy perturbation, umbrella sampling, and thermodynamic integration. In most cases, semi-empirical QM methods were applied, but there are also examples[279–282] for QM/MM MD with a first-principles QM method, such as density-functional theory (DFT) or Hartree–Fock (HF). Simulations at the semi-empirical level are now routinely practical (see, e.g., Ref. [283]), but first-principles QM/MM MD remains computationally demanding even by today's standards.

In the MD studies mentioned above, the QM energy and forces come from a converged SCF calculation in each step (Born–Oppenheimer MD). An alternative is Car–Parrinello MD (CP-MD),[284,285] in which the wave functions are treated as fictitious dynamic variables within a Lagrangean scheme and follow the motion of the nuclei "on the fly". QM/MM approaches based on CP-MD have been developed by several groups.[49–51,186,205,209,286–291] Notably the groups of Röthlisberger and Carloni and their collaborators have been active in this area of biomolecular simulations.[205,209,288–294]

3.3.2. QM/MM Free-Energy Perturbation

A QM/MM free-energy perturbation (FEP) scheme to calculate free-energy differences along a predefined reaction path was introduced by Yang and co-workers.[39,266] Rod and Ryde presented a more general formulation,[130,295] named QTCP (quantum-mechanical thermodynamic-cycle perturbation), and Valiev et al.[296,297] proposed a three-level (coupled-cluster/DFT/MM) FEP treatment. The basic idea is to sample only the MM degrees of freedom while the QM atoms are kept fixed, thus significantly reducing the computational effort compared to full QM/MM sampling. QM/MM FEP (sometimes also referred to as QM/MM-FE) is related to previous techniques[298–301] which also avoid sampling of the QM degrees of freedom. However, in those QM free-energy (QM-FE) approaches, the reaction path is determined in the gas phase and the QM and MM potentials are not coupled. That approach amounts to assuming that the influence of the environment on the reaction path as well as polarization effects are negligible; both approximations are absent in QM/MM FEP.

The QM/MM FEP schemes use an ESP charge model of the QM density, in analogy to some of the QM/MM optimization schemes (see Section 3.2). This avoids the demanding evaluation of the electrostatic QM–MM interactions at the QM level, but approximates the continuous density by point charges and implies a frozen density that cannot adapt to the changing MM environment. We have recently shown that such an approximate QM/MM FEP approach yields results comparable to full thermodynamic integration or umbrella sampling in a fraction of the computa-

tional time[302] and is thus highly justified for treating enzymatic reactions. QTCP[130,295] in its most general formulation calculates also the free-energy differences associated with changing from a QM density to a point-charge model by additional FEP steps.

To efficiently calculate reaction and activation free energies in enzymes, Warshel and co-workers[303–306] developed a scheme in which the sampling is performed on an empirical valence bond reference (EVB) potential fitted to ab initio data. A linear-response approximation is then applied to evaluate the free energy of transfer from the EVB to the ab initio surface. Different formulations have also been proposed to solve the problems that arise when performing "alchemical" FEP simulations with a QM/MM potential.[307–311]

3.3.3. Other Free-Energy Techniques

Jarzynski discovered a remarkable equality[312–318] that connects the equilibrium free-energy difference to the irreversible work expended for switching between two states using a constraint or a guiding potential.[316,319–321] Applications of free-energy methods based on the Jarzynski equality in the context of enzymatic QM(DFT)/MM simulations have been reported.[322,323]

Transition-path sampling (TPS) uses Monte Carlo importance sampling in the space of trajectories connecting the reactant with the product basin, yielding an ensemble of reactive trajectories.[324–334] It does not involve any preconceived knowledge about the reaction path or the transition state. All that is required are low-dimensional order parameters (e.g., combinations of bond lengths) that are able to unambiguously separate reactant from product configurations. TPS has been applied to an enzymatic reaction, with trajectories being generated by semi-empirical QM/MM MD.[335]

The metadynamics approach[336–345] is capable of exploring the free-energy surface without prior information about the location of minima or transition states; it is related to earlier techniques.[346–351] It describes the dynamics in the space of a set of collective coordinates that characterize the process of interest. The metadynamics is coupled to the real dynamics of the system by a history-dependent bias potential, which drives the system away from regions of the free-energy surface it has already visited by "filling them up". This technique has also been applied to enzyme reactions.[352,353]

Phase-space sampling can be enhanced in constant-temperature MD by coupling selected degrees of freedom to a separate thermostat and keeping them at a higher temperature than the remainder of the system. To minimize the heat flow from the hot degrees of freedom into the cooler surroundings, the masses of the hot atoms are scaled up, thus creating an adiabatic separation between the hot, slow and the cool, fast degrees of freedom. The dynamics of the slow degrees of freedom is then effectively performed on the free-energy surface generated by the environment. Such techniques are known as adiabatic free-energy dynamics[354,355] or canonical adiabatic free-energy sampling.[356] A biomolecular application using Car–Parrinello QM/MM MD is described in Ref. [357].

Lu and Yang[358] extended the concept of the reaction-path Hamiltonian[359] to large QM/MM systems. Using the energies, vibrational frequencies, and electronic response properties of the QM region along a QM/MM reaction path (e.g., the minimum-energy path), they construct a harmonic reaction-path potential. It provides an analytical expression for the QM/MM potential energy along the path, accounting for the coupled dynamics of QM and MM parts. This potential can subsequently be used for sampling, for instance, to perform thermodynamic integration with constrained MD.

Also from the Yang group stems the QM/MM minimum free-energy path (MFEP) scheme, which evaluates free-energy gradients to optimize the minimum-energy path on the free-energy surface.[360] It combines QM/MM FEP with a chain-of-replicas optimization method (e.g., NEB or the Ayala–Schlegel MEP).

4. Survey of QM/MM Applications

4.1. QM/MM Implementations

QM/MM applications require efficient programs with wide-ranging functionality. There are essentially three strategies that have been followed in the development of QM/MM codes: 1) Adding QM capabilities to an MM package; 2) adding MM functionality to a QM package; or 3) coupling existing QM and MM programs in a modular manner to a central QM/MM engine. Approaches (1) and (2) take advantage of the inherent strengths of the respective base program. MM packages are designed to handle large complex systems and offer the corresponding simulation and analysis tools, whereas QM programs traditionally provide efficient algorithms to locate stationary points on potential-energy surfaces.

The modular approach (3) offers more flexibility. The external QM and MM packages are linked by interfaces to a central core that supplies the QM/MM coupling as well as routines for standard tasks, such as structure optimization, and molecular dynamics (Figure 4). The core also provides a common user interface to the external programs, at least for their most common options. Extensions and updates are relatively easy since they only require interfacing to additional or updated QM or MM programs. The ChemShell[199,361] is an example for such a modular QM/MM implementation.

4.2. QM/MM Application Areas

For quite some time, biomolecular QM/MM applications were entirely dominated by, if not synonymous with, the study of enzymatic reactivity. Indeed, questions of structure and energetics of enzyme reactions remain a prime area where QM/MM methods can fully show their potential; the discussion of optimization and simulation techniques in the previous Section should be viewed in this context. It is also reflected in the application survey in Section 5. However, not

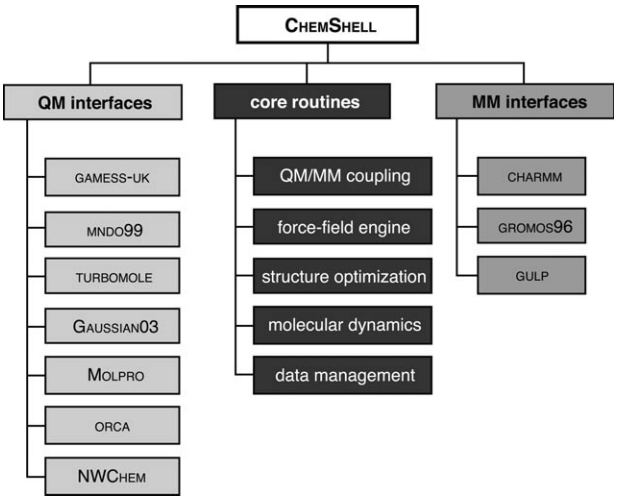


Figure 4. Overview of the modular QM/MM package ChemShell.

only the forming and breaking of chemical bonds requires a QM/MM description but also other processes associated with a reorganization of the electronic structure. Examples include spectroscopic properties depending on the electronic ground or excited states, excited-state dynamics, and charge-transfer processes. Recent years have seen an increasing number of studies that apply QM/MM methods to questions from these areas as well; some examples are presented below (Section 4.3) before we address QM/MM studies of enzyme reactivity (Section 4.4).

A particular application of the QM/MM method is its combination with experimental structural data. QM/MM structure refinement was pioneered by Ryde and co-workers.[362–364] They introduced an approach that integrates QM calculations into the refinement of experimental structural data of biological macromolecules, in particular proteins. The basic idea is to use a QM/MM, rather than a pure MM, model that is refined against the experimental data. This approach largely alleviates the problem that the quality of experimental structures is less reliable in and around the active site, since the commonly applied MM models are carefully tuned to describe the protein but less so for substrates and cofactors (generally, the non-protein parts of the structure). The method has been used for the refinement of single-crystal X-ray diffraction,[362–370] NMR,[371] and EXAFS[372–374] data. Merz and co-workers have presented a similar approach.[375]

4.3. QM/MM Calculations of Spectroscopic and Excited-States Properties

Herein we highlight a few selected applications where QM/MM methods have been used to calculate spectroscopic properties and to investigate electronically excited states.

- Vertical electronic excitation energies (UV/Vis absorption, emission, or fluorescence spectra): The general approach is to perform a QM/MM optimization, for example, at the DFT/MM level, or to extract snapshots from a QM/MM MD simulation run, for example, at the semi-empirical QM/MM level. The excited-states calculations, which provide the vertical excitation energies, are then performed on the individual structures using, for example, time-dependent DFT (TD-DFT), multiconfiguration ab initio methods (e.g., CASSCF or CASPT2), or multireference ab initio methods (e.g., MRCI). The environment normally enters the excited-state calculations by way of the atomic point charges (electrostatic embedding). A number of applications of this type can be found in Section 5, mainly in the group of photoactive proteins; for instance, the mechanism of color tuning in rhodopsins.[376]
- Magnetic-resonance spectroscopic properties: In a similar strategy as for optical spectra, magnetic-resonance spectroscopic parameters can be obtained. Examples include NMR chemical shifts of retinal in rhodopsins;[377,378] ^{51}V NMR anisotropic shifts in vanadium chloroperoxidase;[379] and EPR g and hyperfine-coupling tensors of the heme in cytochrome P450[380] and plastocyanin.[381]
- Mössbauer spectroscopic parameters: ^{57}Fe Mössbauer spectroscopy has been proven to be a very powerful technique to elucidate the high-oxidation-state intermediates of iron-dependent enzymes. As these intermediates are normally highly reactive and correspondingly elusive and difficult to characterize, the computation of Mössbauer spectroscopic properties can greatly contribute to the interpretation and analysis of their spectra, for example, in cytochrome P450[380] and a nonheme-iron/2-oxoglutarate dependent dioxygenase.[382]
- Excited-state reactivity: A step beyond the calculation of properties that depend on electronically excited states is the simulation of the reactivity and the dynamics of the excited states themselves. Examples are the simulations performed on the photoactivated *trans*-to-*cis* isomerization of the *p*-coumaric acid chromophore in the photoactive yellow protein[383] or of the dynamics of a photoactivated C–G base pair in DNA.[384]

4.4. QM/MM Studies of Enzymatic Reactions

Performing a QM/MM study of an enzymatic reaction is a nontrivial task. It should be emphasized that a considerable amount of work has to be invested into the setup and preparation of the system prior to the actual QM/MM calculations. Errors and wrong choices in this initial phase cannot normally be recovered at a later stage. The practical issues that need to be addressed in QM/MM work have been discussed thoroughly in Ref. [38], which should be consulted for more detailed information. Further practical guidance can be found in original papers that deal with such issues, for example Refs. [385,386].

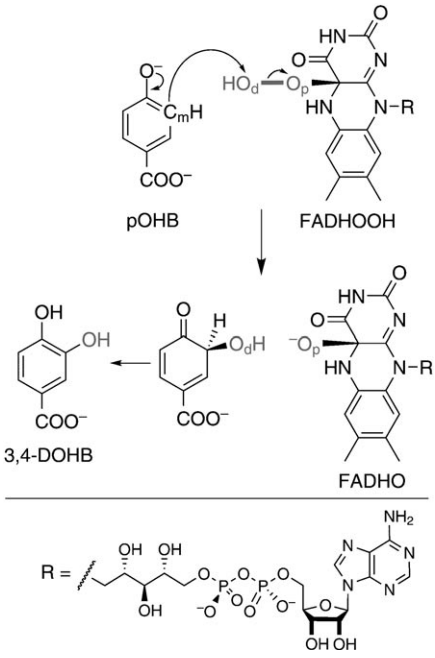
A comprehensive overview of QM/MM studies of enzymatic reactions is beyond the scope of this article. Early applications up to 2001 are summarized in Ref. [25]. We have previously covered the period 2000 to early 2006,[38] and we extend this tabular survey in Section 5 to the full period 2006–2007. Herein we first illustrate the use of QM/MM methods for the investigation of enzyme reactivity by three examples. For the selected enzymatic reactions, a sizeable body of work

both from others and ourselves is available, and the studies showcase a broad variety of methodologies and features. The reactions chosen also involve different chemistry and reaction types.

4.4.1. para-*Hydroxybenzoate Hydroxylase*

The enzyme *para*-hydroxybenzoate hydroxylase[387] (PHBH) catalyzes the transformation of *p*-hydroxybenzoate (pOHB) into 3,4-dihydroxybenzoate (3,4-DOHB). It is active, for example, in soil bacteria, where it plays a crucial role in the oxidative degradation of aromatic compounds, such as lignin; the resulting 3,4-DOHB is the substrate for subsequent catechol ring-cleavage reactions. PHBH was also proposed as a biocatalyst for the hydroxylation of fluorinated and chlorinated pOHB derivatives.[388,389] The enzyme contains flavin-adenine dinucleotide (FAD) as a cofactor. Since the oxygen of the transferred hydroxy group stems from O_2, PHBH is classified as a monooxygenase; the second oxygen atom is not utilized for product formation but is ultimately reduced to H_2O.

The catalytic cycle of PHBH may be divided into a reductive and an oxidative branch, as assessed by the oxidation state of the cofactor. In the reductive half-reaction, the flavin cofactor is reduced to $FADH_2$. In the subsequent oxidative half-reaction, $FADH_2$ reacts with molecular oxygen to form a flavin hydroperoxide (FADHOOH) that acts as the active hydroxylation agent. FADHOOH hydroxylates pOHB in the *meta* position, yielding $FADHO^-$ (FADHOH after protonation) and a hydroxycyclohexadienone intermediate that tautomerizes rapidly into the aromatic 3,4-DOHB (Scheme 1). To close the cycle, FADHOH loses water, regenerating the oxidized form of FAD, and 3,4-DOHB is liberated.



Scheme 1. Hydroxylation step in PHBH. O_p and O_d designate, respectively, the proximal and distal peroxide oxygen of the hydroperoxyflavin; C_m is the *meta* carbon atom of pOHB.

PHBH has been the subject of numerous experimental investigations over the last three decades and has become a classic example for flavoprotein monooxygenases.[387] The hydroxylation reaction follows the aromatic electrophilic substitution (S_EAr) mechanism, that is, FADHOOH acts formally as an "OH^+" donor. The substrate reacts in its dianionic (phenolate) form, the oxido substituent being strongly activating and *ortho* directing in S_EAr reactions.

The hydroxylation step of the PHBH catalytic cycle has received considerable attention from the theoretical perspective and has become one of the prototype systems for computational studies on enzyme reactions. An early QM study found a good correlation of experimental turnover rates of fluoro-substituted pOHB derivatives with the energy of the highest occupied molecular orbital (HOMO) calculated for the free substrates in the gas phase at the semi-empirical AM1 level.[390] This observation supported the notion that the hydroxylation is rate-determining under the conditions of the measurements. It also provided evidence for the dianionic state of the active substrate as well as for the S_EAr mechanism. QM/MM calculations were reported in a series of contributions by Ridder et al.[391–394] Applying AM1 to the substrate and the isoalloxazine part of FADHOOH (50 atoms) and the CHARMM force field to the remaining part of the cofactor as well as for the whole protein including crystal water (4840 atoms), they computed reaction profiles along a predefined reaction coordinate describing the attack of the hydroperoxy "OH^+" on the *meta* position of the substrate, optimizing at each point along the reaction coordinate the atoms within a given distance of the active region. The activation barriers thus obtained correlated well with the experimental turnover rates of fluoro-substituted pOHB derivatives and with experimental rate constants for the hydroxylation step for a series of modified flavins and substrates, corroborating the S_EAr mechanism and the dianionic state of the substrate. These conclusions were strengthened by analyzing in detail[392] the structural and electronic changes as well as the interactions of the substrate and cofactor with specific residues along the reaction path. The overall effect of the surrounding protein on the energetics of the reaction was found to be relatively small and the dominant contributions to stem from the QM part. The role of the enzyme in this case thus appears to consist mainly in activating the substrate by deprotonation, preparing the "OH^+" donor FADHOOH and protecting it from reaction with water, and keeping the two reactants in a position favorable for reacting. A later contribution[394] improved upon the computational level, employing HF/6-31G(d) instead of AM1 for the QM part in the reaction-profile calculations. In addition, single-point calculations were performed on the isolated QM part in the gas phase with B3LYP/6-311 + G(d,p) and LMP2/6-31 + G(d). The results largely confirmed the conclusions obtained before with regard to the mechanism and the role of the protein.

The barrier calculated for the hydroxylation of pOHB is 17.6 kcal mol^{-1} using AM1/CHARMM.[391] HF/CHARMM provides a considerably higher value (about 30 kcal mol^{-1}),

and single-point calculations at HF/CHARMM geometries yield 12.1 and 11.2 kcal mol^{-1} with B3LYP and LMP2, respectively.[394] The reaction energy is about −55 kcal mol^{-1} at this level. The comparison of different methods against gas-phase calculations up to MP2/6-31++G(d,p)//HF/6-31++G(d,p) on model reactions for the PHBH hydroxylation showed that HF drastically overestimates the barrier height, whereas B3LYP underestimates it; AM1 also overestimates, by about the same amount as B3LYP is too low.[395]

Starting with work by Billeter et al.,[395] our group has used the OH-transfer in PHBH to investigate a number of methodological and procedural issues in the context of QM/MM simulations. In collaboration with Werner and co-workers, we pushed the limits of static QM/MM calculations with respect to the QM level employed.[92,94] Using an enlarged model with a fully hydrated protein and a shell of water molecules around it (about 23000 atoms, including approximately 50 QM atoms), the GROMOS force field was combined with QM methods ranging from Hartree–Fock over DFT (B3LYP) to LMP2 and LCCSD(T0); the largest coupled-cluster calculations involved 284 electrons and 1294 basis functions. The structures at the stationary points and the reaction profiles were obtained at the DFT/MM level and used for the correlated single-point calculations. To sample the influence of structural changes in the environment, the optimizations were started from ten snapshots taken from MD simulations. As shown in Table 1, the high-level ab initio methods afford near-quantitative activation enthalpies.

Table 1: Activation enthalpy of the OH-transfer in PHBH using successively higher QM levels.[a]

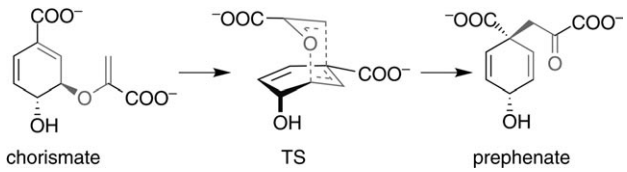
Method[b]	$\Delta^{\ddagger}H°$(300 K) [kcal mol^{-1}][c]
HF	36.7 ± 2.6
B3LYP	8.4 ± 1.4
LMP2	10.7 ± 1.2
LCCSD(T0)	13.3 ± 1.5
Experiment	12.0

[a] Data from Ref. [92]. [b] Structures optimized at B3LYP/GROMOS. [c] QM/MM barrier plus zero-point and finite-temperature corrections obtained from QM-only calculations on cluster models. The error interval indicated is the RMS deviation over ten snapshots.

We also applied free-energy techniques based on QM/MM MD to PHBH. These simulations used the semi-empirical AM1 method for the QM part. Using point-wise thermodynamic integration, we obtained the average activation free-energy starting from ten classical-MD snapshots.[283] These simulations also provided insights into the dynamic reorganization of the hydrogen-bonding network in the active site along the reaction coordinate. In particular, the amide carbonyl of Pro293 was found to stabilize the transferring OH in the transition-state region. The thermodynamic-integration results served as a reference in a subsequent study that described the implementation and validation of the QM/MM free-energy perturbation (FEP) technique (see Section 3.3.2).[302] A new method for analyzing the data from umbrella-sampling simulations, dubbed "umbrella integration", was tested and validated using PHBH.[302,396]

4.4.2. *Chorismate Mutase*

Chorismate mutase catalyses the Claisen rearrangement of chorismate to prephenate (Scheme 2), a key step of the shikimate pathway for the synthesis of aromatic amino acids



Scheme 2. Claisen rearrangement of chorismate to prephenate in chorismate mutase. The allyl vinyl ether unit which rearranges into a 4,5-unsaturated ketone is highlighted in gray.

in plants, fungi, and bacteria. The reaction, a rare example of a pericyclic reaction in biochemistry, has been the subject of numerous theoretical studies dealing with the structure of the enzyme–substrate complex, reaction pathways, and the role of specific residues in transition-state stabilization. It has also served as an important case for testing and developing theories on the origin of enzymatic catalysis.

Lyne, Mulholland, and Richards reported in 1995 the first QM/MM (AM1/CHARMM) study on chorismate mutase.[397] They optimized the reactant complex and reaction profile and identified key residues in the active site. They found that the structure of enzyme-bound chorismate is distorted compared to the gas phase, resembling more the transition state, such that the stabilizing interactions with Arg90 and Glu78 are maximized. These two residues also contribute the most to the stabilization of the transition state. Later studies used improved models, such as a larger number of atoms, higher QM levels, and more rigorous optimization methods.[398,399] The conformation of the enzyme-bound reactant was the focus of several investigations[400–403] that used optimization and QM/MM MD techniques to compare conformational preferences in the enzyme, in solution, and in the gas phase. Guo et al.[402] concluded that the enzyme does not bind the reactive reactant conformer preferentially, but rather promotes the rapid conversion of nonreactive conformers, which prevail in solution, into the reactive form once they are bound.

The importance and validity of the near-attack conformations (NAC) concept of enzymatic catalysis was extensively discussed based on the example of chorismate mutase.[403–414] Whereas Bruice and co-workers[403–407,414] have advanced NAC as the dominant catalytic effect in chorismate mutase (and other enzymes), Warshel and co-workers,[408] Mulholland and collaborators,[412,413,415–417] and others[411] have concluded that electrostatic transition-state stabilization is the dominant contribution. Evidence in support of this conclusion was derived from AM1/MM and HF/MM reaction-path optimizations, corrected by DFT and MP2 single-point calculations, comparing the reaction in the enzyme and in continuum

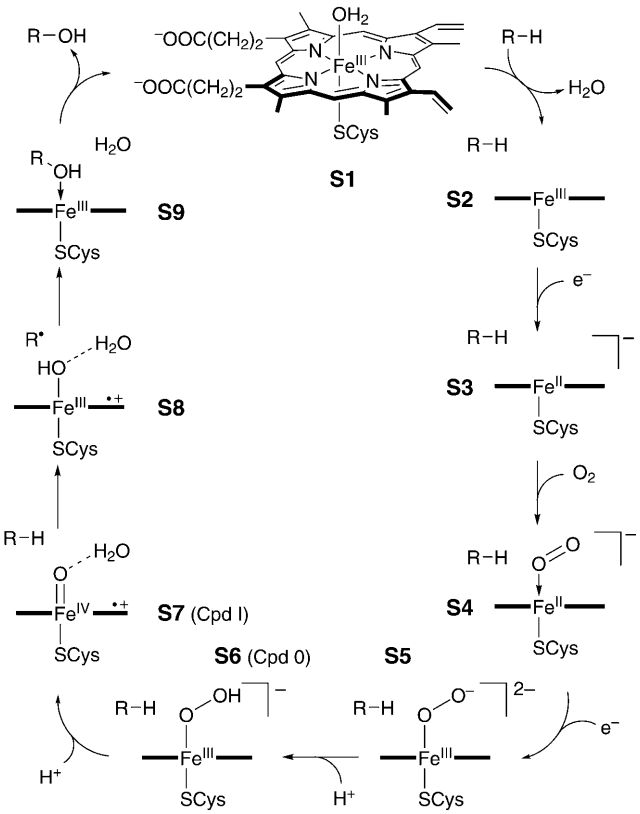
solvent,[412,415] and from a comparative study between Claisen and Cope rearrangements in the enzyme.[411] Moreover, the free energy required to generate NACs[412] suggests that these cannot account for catalysis by themselves. Using the differential transition-state stabilization approach, the contributions of specific residues to transition-state stabilization was analyzed.[417,418] To assess the influence of variations in the environment on the reaction barrier, the Mulholland group calculated reaction paths starting from 16 snapshots taken from QM/MM MD simulations.[413] They explained the overall catalytic effect by the almost equal cost of forming a NAC in the enzyme and transition-state stabilization. It was proposed that the enzyme binds to NACs because of their similarity to the transition state; the enzyme is adapted to bind to the transition state, so it also binds to the NACs closely resembling it. The NAC effect is thus explained as a consequence of electrostatic transition-state stabilization. Still, Bruice and co-workers attributed only about 10% of the catalytic effect to transition-state stabilization.[414] The different views have also been analyzed from the kinetic perspective.[419]

The role of the Arg 90 residue in stabilizing the reactant and transition state in the active site was studied in detail by QM/MM MD[420] and QM/MM Monte Carlo[421] simulations in combination with different free-energy techniques. Additionally, calculations of kinetic isotope effects based on a semiclassical model (primary ^{13}C- and ^{18}O-, secondary ^{3}H-kinetic isotope effects) were reported.[269,422] Like PHBH, chorismate mutase has served as a case study in more method-oriented work on, for example, a replica-path method for optimizing reaction paths,[423] DFT-corrections to semi-empirical energies,[269,424,425] free-energy simulations based on Jarzynski's equality,[323] new QM/MM implementations,[426–428] or a full ab initio QM description of the enzyme.[429] It was also included in the high-level ab initio QM/MM study discussed above for PHBH,[92] and excellent agreement was again found between the experimental and the best theoretical barrier computed at the coupled-cluster level.

4.4.3. *Cytochrome P450*

The cytochrome P450 enzymes constitute a superfamily of monooxygenases that perform a variety of essential functions, such as biosynthesis and detoxification, in nearly all life forms.[430–432] These heme proteins catalyze many types of oxidation reactions, often with high regio- and stereoselectivity, including hydroxylation, epoxidation, and heteroatom oxidation. A comprehensive Review[433] covers the extensive theoretical work on these enzymes until 2004, in particular DFT model studies and early QM/MM studies. In this Section we focus on recent QM/MM investigations of cytochrome P450cam, the prototypical bacterial enzyme that catalyzes the stereospecific hydroxylation of the non-activated C^5–H^{exo} bond in camphor under physiological conditions.[380,385,386,434–449]

The key steps of the catalytic cycle of cytochrome P450cam are shown in Scheme 3. The cycle[430–432] starts with the resting state (**S1**), a hexacoordinate Fe^{III} complex with a water ligand in the distal coordination site. The entrance of the camphor substrate displaces the water molecule and leads to a pentacoordinate Fe^{III} species (**S2**), which is then reduced to a Fe^{II} complex (**S3**). The binding of molecular oxygen yields the Fe^{II} dioxygen complex (**S4**), which is then reduced again to the Fe^{III} peroxo species (**S5**). Subsequent protonation gives the Fe^{III} hydroperoxo complex (**S6**), called Compound 0, and uptake of another proton causes heterolytic O–O cleavage to form Compound I (**S7**) and water. Owing to its Fe^{IV} oxo moiety, Compound I is very reactive and can thus transfer an oxygen atom to the camphor substrate, via a rebound mechanism which first generates a radical pair (**S8**) by hydrogen abstraction and then the product complex (**S9**) by recombination. The catalytic cycle is closed by dissociation of the alcohol product and binding of a water molecule.



Scheme 3. Catalytic cycle for the hydroxylation of an aliphatic hydrocarbon substrate R–H in cytochrome P450.

All the intermediates in the catalytic cycle of cytochrome P450cam have now been characterized through DFT/MM calculations. An important issue is the correct assignment of the spin states of these intermediates. Their relative energies are strongly dependent on the admixture of Hartree–Fock exchange in the chosen density functional; in addition, they are tuned by the interactions with the protein environment. The B3LYP hybrid functional in combination with any of the established protein force fields (CHARMM, OPLS, etc.) is found to provide realistic spin-state energies that are compatible with the available experimental evidence. More specifically, B3LYP/CHARMM calculations correctly give a low-spin doublet ground state for **S1**,[438] a high-spin sextet ground state for **S2** only slightly below the doublet and

quartet,[440] a high-spin quintet ground state for **S3** well separated from the triplet and singlet,[440] and an open-shell singlet ground state for **S4** with a small energy gap to the other spin states.[449] These calculations predict a doublet ground state both for **S5**[449] and **S6**,[448] a doublet ground state for **S7** that is almost degenerate with the quartet,[380,434] several close-lying doublet and quartet states for **S8**,[436] and a doublet for **S9** with a short Fe–O bond slightly below the quartet and sextet states with a longer Fe–O bond.[439] The relative energies for the spin states of **S6**, **S7**, and **S8** from B3LYP/CHARMM agree quite well with correlated ab initio QM/MM results, with the QM region being treated at the CASSCF/MRCI level.[380,448]

Apart from the spin-state ordering, the DFT/MM calculations also yield realistic results for other properties of the intermediates. In addition, they allow an assessment of the effects of the protein environment. In the case of the resting state (**S1**), the computed geometry and spectroscopic parameters of the doublet ground state are in good agreement with the available experimental data, and comparison with gas-phase model calculations shows that the protein environment favors an upright conformation of the axial water ligand as a result of hydrogen-bond interactions in the binding pocket.[438] The camphor substrate is held in the active site of cytochrome P450cam by a hydrogen bond to Tyr 96, whose strength is estimated to be around 6 kcal mol^{-1} at the BP86/AMBER level.[441] In the case of the pentacoordinate Fe^{III} complex (**S3**), the inclusion of the protein environment changes the orbital occupation in the quintet ground state compared to the gas phase: the d_{xz} orbital is doubly occupied in the enzyme as confirmed by the good agreement between computed and observed Mössbauer parameters.[440] B3LYP/CHARMM calculations for the Fe^{II} dioxygen complex (**S4**) indicate that the protein environment reduces the open-shell singlet–quintet energy gap which should facilitate the required spin inversion.[449] The Fe^{III} peroxo complex (**S5**) only remains intact upon B3LYP/CHARMM geometry optimization when in the doublet ground state while the quartet and sextet states dissociate (uncoupling).[449]

Compound I (**S7**) is generally considered to be the crucial reactive intermediate of cytochrome P450cam. It is an iron(IV) oxo species with three unpaired electrons, two of which are located in π^* orbitals of the FeO moiety while the third one is delocalized over the ligands. B3LYP/CHARMM calculations have established that the protein environment controls and tunes the spin density distribution in the porphyrin and sulfur ligands through hydrogen bonding to sulfur, giving rise to a porphyrin radical cation and an essentially closed-shell situation at sulfur in the enzyme.[434] This prediction for the experimentally yet unknown P450cam Compound I was later confirmed by an ENDOR study of chloroperoxidase Compound I,[450] which yields a spin density of only about 0.2 *e* at sulfur, in agreement with the computed value. Correlated ab initio QM/MM calculations predict a small antiferromagnetic coupling and thus support a doublet ground state for P450cam Compound I.[380] However, the doublet–quartet splitting is so small that the zero-field splitting from spin–orbit coupling is sufficient to generate three Kramers doublets of mixed multiplicity, which are all populated at room temperature.[380] B3LYP/CHARMM calculations indicate that there is a rather low-lying sextet/quartet manifold with a different orbital occupation pattern (ca. 12 kcal mol^{-1} above the ground state),[380] whereas electron configurations with an Fe^{V} oxo moiety are much higher in energy.[445]

Concerning P450cam reactions, DFT/MM studies have been reported for the protonation steps (**S5**→**S6**→**S7**)[437,443,447] and the hydroxylation steps (**S7**→**S8**→**S9**).[385,386,435–437,442,444,445] Among the proton sources that have been considered in P450cam, the Asp 251 channel appears to be most favorable, which connects the heme by a hydrogen-bond network (involving Thr 252–water–Asp 251–Arg 186) to the bulk solvent. The first proton transfer (**S5**→**S6**) is extremely facile in the wild-type enzyme, with a computed barrier of about 1 kcal mol^{-1}, so that the reduced oxyheme complex (**S5**) can barely be detected at liquid-helium temperatures of 4–7 K.[447] In the D251N mutant, where Asp 251 is replaced by Asn 251, the Asn 251 side chain flips and disrupts the hydrogen-bond network, which leads to a larger barrier and hence to a longer lifetime of **S5** (as observed experimentally).[447] The transformation of Compound 0 to Compound I (**S6**→**S7**) is usually regarded as a heterolytic process, with the addition of a proton to the hydroperoxo ligand being followed by dissociation of water. B3LYP/CHARMM calculations indicate, however, that a mixed homolytic–heterolytic pathway is more favorable: The initially homolytic O–O cleavage in Compound 0 is followed by a concomitant proton and electron transfer to yield Compound I and water in an overall heterolytic fashion.[443] The alternative traditional mechanism via protonated Compound 0 seemed viable in a DFT model study with unconstrained geometry optimizations,[451] but is energetically disfavored in the enzyme owing to the structural constraints imposed by the protein environment.[443]

B3LYP/CHARMM studies on camphor hydroxylation by Compound I (Scheme 3) support the two-state rebound mechanism (**S7**→**S8**→**S9**) previously proposed on the basis of QM model calculations: The initial hydrogen abstraction encounters similar barriers in both spin states (slightly lower in the doublet), whereas the subsequent recombination step is essentially barrierless in the doublet but has to overcome a non-negligible barrier in the quartet.[436] This latter barrier is of electronic origin: To generate a quartet state during rebound, one electron must occupy the iron d_{z^2} orbital, which is antibonding in axial direction and thus destabilizing.[436] B3LYP/OPLS studies have led to the suggestion that the quartet transition state for hydrogen abstraction in P450cam is stabilized by remote effects, specifically by electrostatic interactions between the porphyrin A-propionate side chain and the neighboring Arg 299 residue.[435,437] This unusual transition-state stabilization mechanism was, however, not supported by subsequent DFT/MM calculations with a properly screened A-propionate and a protonated Asp 297 residue (consistent with the available X-ray structures).[385,442,444] In the course of that work, it was discovered that a single water molecule (e.g., the one liberated during the formation of Compound I from Compound 0) can cause a significant lowering of the barrier for hydrogen abstraction,

by about 4 kcal mol^{-1} because its hydrogen bond to the oxo atom becomes stronger in the transition state for simple electrostatic reasons.[385,442] Hydrogen abstraction by the low-lying sextet/quartet excited-state manifold of Compound I[380] has been considered as an alternative pathway for camphor hydroxylation: The B3LYP/CHARMM barriers are quite low in the excited states, but the corresponding pentaradicaloid transition states still lie somewhat above their usual triradicaloid counterparts and should thus normally not be relevant.[445] According to DFT model calculations, the pentaradicaloid species become further stabilized during the rebound step (**S8**→**S9**), which might give rise to multi-state reactivity.[452] Active species for camphor hydroxylation other than Compound I have been discussed repeatedly in the literature. However, according to recent B3LYP/CHARMM work, Fe^{V} oxo compounds are too high in energy to be of importance; and one-electron reduced species (Compound II) show only sluggish reactivity compared with Compound I.[445] The available QM/MM evidence thus confirms the central role of Compound I in the two-state rebound mechanism for camphor hydroxylation.

As stated at the outset, we have primarily addressed in this Section the mechanistic insights that have been gained from QM/MM studies on the prototypical P450cam enzyme. Of course, there have also been many QM/MM investigations on related enzymes. To quote only a few selected examples, we mention the DFT/MM studies on Compound I in human isoforms of cytochrome P450,[453,454] in peroxidases,[455–458] in nitric oxide synthase,[459] and in a designed mutant of cytochrome P450 containing selenocystein,[460] as well as mechanistic DFT/MM studies on horseradish peroxidase[461,462] and other heme proteins.[463]

5. Recent Biomolecular QM/MM Studies

In Ref. [38], we tabulated biomolecular QM/MM studies having appeared between 2000 and early 2006. Herein we provide an update of this survey for the full period 2006–2007 (Table 2). The table is organized in the same way as before: Entries are grouped by the type of biomolecule investigated; enzymes are further sorted according to enzyme class (EC number). Note that the classification is determined by the enzyme's main function, which need not be identical to the process actually investigated in the cited study. To make the Table more readable, identical entries in the columns "Biomolecule", "Process studied", "QM level", "MM level", and "Calculation type" are not repeated in successive rows for the same biomolecule; "Comments", however, apply to the specific row only.

The same provisos as before[38] apply also to the Table herein: If a contribution does not contain any of the pertinent keywords (such as QM/MM, combined quantum mechanics/molecular mechanics, hybrid quantum mechanics/molecular mechanics, etc.) in the title or the abstract, it is likely to have been missed by our literature search. We thus cannot claim to provide a comprehensive listing and apologize for any oversights and omissions.

6. Summary and Outlook

QM/MM methods are by now established as the state-of-the-art computational technique to treat reactive and other "electronic" processes in biomolecular systems. The rapidly growing number of publications using QM/MM techniques gives impressive testimony that they have come of age since the pioneering beginnings some thirty years ago.[1] In this Review, we have summarized general methodological aspects of the QM/MM approach, its use within optimization and simulation techniques, and its areas of application, always with a focus on biomolecular systems. We have also discussed some illustrative case studies and provided a tabular survey of recent applications.

As documented in many of these publications, QM/MM calculations provide detailed mechanistic insight into enzymatic reactions. The QM/MM formalism allows a partitioning of the total energy, and particularly of the QM–MM interaction energy, into various components, and thus offers the opportunity to analyze the effects of the protein environment (down to individual residues) on the species in the catalytic cycle. An alternative approach towards this goal makes use of comparisons between the QM/MM results for the complete enzyme and QM results for suitably chosen model systems. Understanding the origin of the catalytic power of enzymes, with their sometimes spectacular rate enhancements, requires simulations for the given reaction in the enzyme and in aqueous solution. QM/MM methods are in principle well suited for this task, and a number of QM/MM studies have addressed this question for different enzymes. A variety of concepts and ideas have been advanced to explain the origin of enzymatic catalysis, many of which have been subject to critical and often controversial discussion in the literature (for Reviews see Refs. [25, 40–42, 97, 98, 618–625]). Without going into any details, we note that transition-state stabilization, based on electrostatic effects,[621] is mostly considered to be the dominant factor in the actual chemical step of enzymatically catalyzed transformations, consistent with Linus Pauling's original proposal[626] that enzymes work by binding the transition state more strongly than the substrate and thus lowering the activation barrier.

While this Review has focused on biomolecular systems, it is clear that QM/MM methods are suitable for treating many other complex systems in all branches of chemistry. They can be applied whenever it is necessary to model a localized electronic event in an active site (typically of the order of 100 atoms) that is influenced by an interacting larger environment. There is an obvious need to improve the available QM/MM tools further, particularly by pushing for higher accuracy and better sampling, but the existing QM/MM methods are already good enough to allow for realistic modeling of real-world chemical problems. We anticipate a growing number of such applications in the future.

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Table 2: Survey of biomolecular QM/MM applications for 2006–2007.

Biomolecule	Process studied	QM level	MM level	Calculation type[a]	Comments	Refs
Oxidoreductases (EC 1); O_2- and electron-transport proteins						
Flavin-dependent oxidoreductases						
p-Hydroxybenzoate hydroxylase	OH transfer	AM1	GROMOS	Opt, QM/MM FEP, US(MD)	Comparison of free-energy methods	[302]
Flavin reductase	Flavin fluorescence	INDO/S-CIS	CHARMM	MD		[464]
Flavodoxin reductase	Flavin fluorescence	INDO/S-CIS	CHARMM	MD		[464]
Medium-chain acyl-CoA dehydrogenase (MCAD)	FAD redox potential	SCC-DFTB	CHARMM	US(MD)		[465]
Cholesterol oxidase	FAD redox potential	SCC-DFTB	CHARMM	US(MD)		[465]
NAD(P)-dependent oxidoreductases						
Liver alcohol dehydrogenase (LADH)	Electronic excitations of bound NADH	TD-DFT, TD-HF, CIS	CHARMM	Single points		[466]
Aldehyde dehydrogenase	Thioacetal formation, H^+ transfer	PM3	OPLS-AA	Opt, US(MD)		[467]
Dihydrofolate reductase	H^- transfer	PM3, HF, DFT	AMBER	Opt, TI(MD)		[468]
		AM1	CHARMM	US(MD), KIE	VTST with tunneling	[469]
		PM3, DFT	AMBER	TI(MD)	2D-MFEP	[470]
TTQ-dependent oxidoreductases						
Methylamine dehydrogenase	H^+ transfer	PM3	CHARMM	US(MD), KIE	VTST with tunneling	[471]
Aromatic amine dehydrogenase	H^+ transfer	PM3	CHARMM	US(MD), KIE	VTST with tunneling	[472–474]
Nonheme-iron oxidoreductases						
HIF-1α asparaginyl hydroxylase	O_2 activation	CASSCF	EFP (AMBER)	Opt	Electronic structure	[475]
Isopenicillin N synthase	O_2 binding	DFT	AMBER	Opt		[476]
Soybean lipoxygenase-1	H abstraction	PM3/d, DFT	CHARMM	Opt	PM3/d parameters	[477]
Heme-dependent oxidoreductases						
Cytochrome C peroxidase	Characterization of Fe^{IV} oxo species (Cpd I)	DFT	CHARMM	Opt		[457]
Cytochrome P450	Characterization of Fe^{IV} oxo species (Cpd I)	DFT	CHARMM	Opt	Influence of mutation	[457, 460]
	Formation of Fe^{IV} oxo (Cpd I)		CHARMM			[443]
	H abstraction		CHARMM, OPLS-AA			[442]
			CHARMM			[385]
					Substrate selectivity	[478]
					Spin density on propionates	[444]
					Effect of electronic configurations	[445]
	Structure preparation	DFT	CHARMM	Opt	Hydration schemes, protonation states	[386]
Cytochrome P450 3 A4	Characterization of Fe^{IV} oxo species (Cpd I)	DFT	CHARMM	Opt		[454]
Ascorbate peroxidase	Characterization of Fe^{IV} oxo species (Cpd I)	DFT	CHARMM	Opt		[457]
Horseradish peroxidase	Characterization of Fe-OH species (Cpd II)	DFT	CHARMM	Opt		[462]
	Formation of Fe^{IV} oxo species (Cpd I)					[461]
	Formation of Fe-OOH species (Cpd 0)					[479]

Table 2: (Continued)

Biomolecule	Process studied	QM level	MM level	Calculation type[a]	Comments	Refs
NO synthase	Formation of Fe^{IV} oxo species (Cpd I)				Mössbauer parameters	[459]
Catalase	Active-site structure	DFT	AMBER	Opt	Rigid protein	[458]
	Active-site structure, electronic configuration			Opt, CP-MD		[480]
Catalase-peroxidase (KatG)	Characterization of Fe^{IV} oxo (Cpd I) and Fe-OH (Cpd II) species	DFT	AMBER	Opt, CP-MD		[481]
Other heme proteins						
Truncated hemoglobin (PcHb)	O_2 binding	DFT	AMBER	Opt	Effect of protein conformations	[482]
Various heme proteins	O_2 binding	DFT	AMBER	Opt		[483]
Myoglobin	Vibrational analysis with bound CO	DFT	AMBER	Opt		[484]
	Vibrational spectrum of dissociated CO		CHARMM			[485]
	CO dissociation		OPLS-AA		Protein structural changes	[486]
			CHARMM			[487]
	O_2 binding		AMBER		Mutants	[488]
	Characterization of Fe-OOH species		CHARMM			[489]
Leghemoglobin	O_2 binding	DFT	AMBER	Opt	Mutants	[488]
					Effect of protein conformations	[482]
Other Fe-dependent oxidoreductases						
Fe-only hydrogenase	Active-site structure	DFT	AMBER	Opt, QM/MM-FEP	IR, EPR parameters,	[490]
	H_2 formation			Opt		[491]
Soluble methane monooxygenase (MMO)	O_2 activation	DFT	OPLS-AA	Opt		[492]
V-, Cu-dependent oxidoreductases						
V haloperoxidases	Active-site protonation state, formation of OOH intermediate	DFT	AMBER	CP-MD, metadynamics		[352]
V chloroperoxidase	Active-site protonation state, ^{51}V NMR	DFT	CHARMM	Opt		[379]
Dopamine β-monooxygenase	H abstraction	DFT	AMBER	Opt		[493]
Peptidylglycine α-hydroxylating monooxygenase	O_2 binding, activation	DFT	AMBER	Opt		[494]
Particulate methane monooxygenase (pMMO)	$CH_4 \rightarrow CH_3OH$ conversion	DFT	AMBER	Opt	Cu and Cu_2 sites considered	[495]
Cu nitrite reductase	Nitrite reduction	DFT	AMBER	Opt	Comparison to model compounds	[496]
Other metalloproteins						
Rubredoxin	Active-site structure, redox potentials	DFT	AMBER	Opt	Influence of mutations	[497]
Blue copper proteins (azurin, plastocyanin, stellacyanin)	Active-site structure, redox potentials	DFT	AMBER	Opt		[498]
Azurin	Electronic excitations	DFT, TDDFT	AMBER	CP-MD		[499]
Other oxidoreductases						
Glutathione peroxidase	H_2O_2 reduction	DFT	AMBER	Opt		[500]
DsbA	Cys pK_a	PM3, DFT	AMBER	Opt	Comparison to thioredoxin	[501]
Quinoprotein methanol dehydrogenase	Dehydrogenation	SCC-DFTB	CHARMM	Opt		[502]
Luciferase	Structure of bound excited oxyluciferin, fluorescence energies	SAC/SAC-CI	AMBER	Opt		[503]

Table 2: (Continued)

Biomolecule	Process studied	QM level	MM level	Calculation type[a]	Comments	Refs
Other redox proteins						
Thioredoxin	Disulfide reduction	HF, DFT, MP2	UFF	Opt		[504]
	Cys pK_a	PM3, DFT	AMBER	Opt	Comparison to DsbA	[501]
Transferases (EC 2)						
Glutathione-*S*-transferase	Thiolate addition	AM1	CHARMM	US(MD)	Mutants	[505]
Catechol *O*-methyltransferase	Methyl transfer	AM1	CHARMM	Opt, US(MD)	Corrections to PMF	[506]
		DFT	AMBER	QM/MM FEP	Comparison of solvation models	[507]
		AM1, DFT	OPLS	Opt, US(MD)	2D-interpolation to higher QM	[425]
Histone Lys methyltransferase SET7/9	Methyl transfer	DFT, MP2	AMBER	Opt, QM/MM FEP		[508]
		SCC-DFTB	CHARMM	US(MD)		[509]
		HF	AMBER	US(MD)		[510]
		SCC-DFTB	CHARMM	Opt		[511]
Viral histone Lys methyltransferase (vSET)	Methyl transfer	SCC-DFTB, MP2	CHARMM	Opt		[512]
Gly *N*-methyltransferase	Methyl transfer	AM1	OPLS	Opt, US(MD)		[513]
DNA C5 cytosine Methyltransferase M.HhaI	Methylation	SCC-DFTB	CHARMM	Opt		[514]
Rubisco large subunit methyltransferase (LSMT)	Methyl transfers	SCC-DFTB, MP2	CHARMM	Opt		[515]
Pyrimidine nucleoside phosphorylase	Active-site structure	DFT	CHARMM	Opt		[516]
cAMP-dependent protein kinase (cAPK)	Serine phosphorylation	DFT	AMBER	Opt	Effect of enzyme phosphorylation	[517]
				Opt, NEB, QM/MM FEP		[518]
Cyclin-dependent kinase 2 (CDK2)	Inhibitor binding	AM1	OPLS-AA	MD		[519]
Phosphoryl transfer	DFT	AMBER	CP-MD			[520]
HIV-1 reverse transcriptase	Active-site structure	AM1, PM3	CHARMM	Opt	Protonation states	[521]
HIV-1 integrase	Inhibitor binding	AM1	OPLS-AA	MD	Different inhibitors	[522]
		AM1, DFT				[523]
		PM3	CHARMM	Opt, MD		[524]
DNA polymerase β	Phosphoryl transfer	HF, DFT, MP2	CHARMM	Opt		[525]
Polymerase IV (Dpo4)	Nucleotidyl transfer	DFT	AMBER	Opt, QM/MM FEP		[526]
Hypoxanthine guanine phosphoribosyl transferase (HGPRTase)	Phosphoribosyl transfer	AM1, HF, DFT	OPLS-AA	Opt, US(MD)	Comparison to HGXPRTase	[527]
Hypoxanthine guanine xanthine phosphoribosyl transferase (HGXPRTase)	Phosphoribosyl transfer	AM1, HF, DFT	OPLS-AA	Opt, US(MD)	Comparison to HGPRTase	[527]
Farnesyltransferase	Active-site structure with bound product	DFT	UFF	Single points		[528]
Golgi glycosyltransferase (*N*-acetylglucosaminyltransferase)	Glycosyl transfer	DFT	AMBER	Opt		[529]
Estrogen sulfotransferase	Sulfuryl transfer	HF, DFT	AMBER	Opt		[530]
Thymidylate synthase	Folate-dependent methylation	AM1, DFT	OPLS-AA	Opt, US(MD), KIE		[531]
Hydrolases (EC 3)						
Peptidases and other amidases						
Subtilisin	Structure of tetrahedral intermediate	PM3	AMBER	Single point		[532]
Thermolysin	Peptide hydrolysis	DFT	AMBER	TI(CP-MD)		[533]
Trypsin	H^+ transfer	HF	AMBER	Opt, QM/MM FEP, NMR parameters		[534]

Table 2: (Continued)

Biomolecule	Process studied	QM level	MM level	Calculation type[a]	Comments	Refs
Kumamolisin-As (sedolisin, Ser-carboxyl peptidase)	Peptide hydrolysis	SCC-DFTB	CHARMM	US(MD)		[535, 536]
		DFT	EFP(AMBER)	Opt		[537]
	Acylation step	SCC-DFTB	CHARMM	US(MD)		[538]
Hepatitis C virus protease NS3	Peptide hydrolysis	AM1	CHARMM	Opt, MD		[539]
	Formation of tetrahedral intermediate			Opt, US(MD)	Comparison of boundary methods	[242]
HIV-1 Asp protease	Active-site structure with bound substrates	DFT	AMBER	CP-MD	H-bonding patterns	[540]
	Inhibitor binding	DFT:PM3	UFF	Single points	3-layer ONIOM; effect of mutations	[541]
Histone-deacetylase-like protein	Amide hydrolysis	DFT	AMBER	Opt		[542]
Cathepsin K	Peptide hydrolysis	AM1	CHARMM	2D-US(MD), EA-VTST		[543]
Cathepsin B	Thiolate attack on 3-ring of inhibitor	DFT	CHARMM	Opt		[544]
Class A β-lactamase	Deacylation	AM1, DFT	CHARMM	Opt		[545]
Class B2 metallo-β-lactamase	Hydrolysis	SCC-DFTB, DFT	CHARMM	US(MD)		[546]
Metallo-β-lactamase IMP-1	Inhibitor binding	SCC-DFTB	CHARMM	MD		[547]
Dizinc L1 β-lactamase	Formation of tetrahedral intermediate	SCC-DFTB, DFT	CHARMM	Opt, US(MD)		[548]
	Substrate binding	SCC-DFTB		MD		[549]
Gelatinase A (MMP-2)	Active-site structure	DFT	OPLS-AA	Opt		[550]
Peptide deformylase	Deformylation	DFT	AMBER	Opt		[551]
Esterases						
Acetylcholinesterase	1,3-dipolar cycloaddition	DFT	AMBER	Opt	In situ inhibitor synthesis	[552]
	Acylation of inhibitors			Opt, QM/MM FEP	Mutants	[553]
Butyrylcholinesterase	Cocaine hydrolysis	HF	AMBER	Opt		[554]
Glycosylases						
Bacillus 1,3–1,4-β-glucanase	Structure of bound substrate	DFT	CHARMM	CP-MD		[555]
Phosphatases, phosphoesterases						
PcrA Helicase	ATP hydrolysis	DFT	AMBER			[556]
Phosphotriesterase	Phosphotriester hydrolysis	AM1(DFT, MP2)	CHARMM	US(MD)	Dual-level QM	[557]
Cyclic nucleotide phosphodiesterases PDE4, PDE5	Active-site structure	DFT	AMBER	Opt	Identity of metals, ligands	[558]
Other hydrolases						
4-Chlorobenzoyl-CoA dehalogenase	S_NAr displacement	PM3	CHARMM	US(MD)		[559]
Yeast cytosine deaminase	Zn-O(uracil) cleavage	PM3:DFT	AMBER	US(MD)	2-QM-layer ONIOM + MM-MD scheme	[560]
	Attack of OH^- to form TS analogue	SCC-DFTB	CHARMM	Opt, US(MD)		[561]
Guanine deaminase bGD	Deamination	PM3:DFT	AMBER	Opt	2-QM-layer ONIOM	[562]
Soluble epoxide hydrolase (sEH)	Phosphoryl transfer	DFT	AMBER	TI(CP-MD)		[563]
Lyases (EC 4)						
Orotidine-5′-monophosphate decarboxylase	Direct decarboxylation	DFT	CHARMM	Metadynamics		[353]
Carbonic anhydrase II	H^+ transport	SCC-DFTB	CHARMM	US(MD)		[564]
	pK_a			MD	Comparison of GSBP and PBC	[180]

Table 2: (Continued)

Biomolecule	Process studied	QM level	MM level	Calculation type[a]	Comments	Refs
Diol dehydratase	H abstraction, OH migration	DFT	AMBER	Opt	Effect of mutations	[565]
Citrate synthase	H^+ transfer/enolization	AM1	CHARMM	Opt, US(MD)		[566]
		AM1, HF, MP2		Opt		[567]
Isomerases (EC 5)						
4-Oxalocrotonate tautomerase	H^+ transfers	HF, DFT	AMBER	Reaction path opt, QM/MM FEP	Different substrates	[568]
		AM1, DFT	CHARMM	Opt	Effect of Mutations	[569]
		DFT				[570]
Glu racemase	H^+ transfers	AM1	CHARMM	Opt, MD		[571]
Ala racemase	H^+ transfer	AM1	CHARMM	US(MD)		[572]
				US(MD), KIE	VTST with tunneling, path integrals	[573]
Triosephosphate isomerase	Active-site Pro pucker	DFT	GROMOS, OPLS-AA	Opt		[574]
Chorismate mutase	Claisen rearrangement	HF	AMBER	Opt	Comparison to FMO all-QM	[429]
		AM1, DFT	OPLS-AA	Opt, US(MD)	2D-interpolation to higher QM	[425]
		AM1, HF	CHARMM	MD	DTSS analysis	[418]
Methylmalonyl-CoA mutase	H transfer	AM1	CHARMM	US(MD), KIE	VTST with tunneling	[575]
Chalcone isomerase	Michael addition	AM1, MP2	OPLS-AA	Opt, US(MD)		[576]
					Pre-reaction equilibrium	[577]
Photoactive proteins						
Bacterial reaction center	EPR parameters of reduced ubiquinone	DFT	UFF	Opt		[578]
Bovine rhodopsin	Active-site structure	DFT	AMBER	Opt	Review	[378]
	Electronic excitations	SCC-DFTB, CASSCF, CASPT2	CHARMM	MD	Different retinal derivatives	[579]
		DFT, CASSCF, MCQDPT2	EFP(AMBER)	Opt		[580]
		DFT, SAC-CI	AMBER	Opt		[581]
Bacteriorhodopsin	H^+ transfer	SCC-DFTB	CHARMM	Opt	Review	[582]
		HF	AMBER		Mechanical embedding only	[583]
	Electronic excitations	SCC-DFTB, MRCI (OM2, SORCI)	CHARMM	Opt, MD		[376]
		DFT, SAC-CI	AMBER	Opt		[581]
Sensory rhodopsin II	Electronic excitations	SCC-DFTB, MRCI (OM2, SORCI)	CHARMM	Opt, MD		[376]
		DFT, SAC-CI	AMBER	Opt		[581]
Human blue pigment	Electronic excitations	DFT, SAC-CI	AMBER	Opt		[584]
Human opsins	Electronic excitations	HF	Dreiding	Single points	Relative spectral shifts	[585]
Green fluorescent protein	Electronic excitations	DFT, TDDFT	UFF	Opt	Mutants	[586]
Photoactive yellow protein	H^+ transfer	DFT	AMBER	QM/MM-FEP		[587]
Kindling fluorescent protein asFP595	Electronic excitations	HF, (TD)DFT, CASSCF	EFP(AMBER)	Opt		[588]
		HF, (TD)DFT				[589]
Photosystem II	Structures of O_2-evolving complex	DFT	AMBER	Opt		[590, 591]
α-C-phycocyanin	Raman parameters of bound phycocyanobilin	DFT	CHARMM	Opt		[592]
Other proteins and protein–ligand complexes						
Hsc70 ATPase	ATP hydrolysis	DFT	AMBER	CP-MD, metadynamics		[593]

Table 2: (Continued)

Biomolecule	Process studied	QM level	MM level	Calculation type[a]	Comments	Refs
Yeast metallochaperone Atx1	Structure of Cu binding site	DFT	AMBER	Opt	EXAFS parameters	[594]
G-actin	Binding of latrunculins	MNDO/H	CHARMM	Opt	Synthetic analogues	[595]
Myosin	ATP hydrolysis	HF, DFT	CHARMM	Opt		[596]
		HF	EFP(AMBER)	Opt	Partial model	[597]
Ras p21	GTP hydrolysis	HF	EFP(AMBER)	Opt	Partial model	[598]
		DFT	CHARMM	Opt, CP-MD		[599]
Ras-RasGAP	GTP hydrolysis	DFT	CHARMM	Opt, CP-MD		[599]
KcsA K^+ channel	Electronic structure	DFT	AMBER	CP-MD		[600]
	Protonation states					[601]
NR_4^+ transporter AmtB	Structure of binding pocket	HF	AMBER	Opt		[602]
	NH_4^+ deprotonation	DFT	CHARMM	Opt, MD		[603]
Human serum albumin (HSA)	Bilirubin binding	PM3	GROMOS	Opt		[604]
γD-Crystallin	Trp fluorescence	INDO/S-CIS	CHARMM	MD		[605]
Various proteins	Trp fluorescence	INDO/S-CIS	CHARMM	MD		[606]
Oligonucleotides and adducts						
DNA	Structure	DFT	AMBER	Opt	Bonding analysis	[607]
		PM3, DFT	UFF		Influence of Mg^{2+}, Ca^{2+}	[608]
		DFT	AMBER		Effect of phosphate modifications	[609]
	Deactivaton of excited CG pair	CASSCF		MD		[384]
	Charge transport	DFT		MD	SIC-DFT	[610]
	Electronic excitations in C	EOM-CCSD(T)		Single points	Snapshots from MM MD	[611]
	Electronic excitations in G	DFT,TD-DFT, EOM-CCSD(T)		Opt		[612]
DNA–cisplatin	Structure	DFT	AMBER	Opt	Bonding analysis	[613]
DNA–Pt_2 complex	Structure	DFT	AMBER	CP-MD		[614]
DNA–duocarmycin	S_N2 attack	DFT	AMBER	CP-MD		[615]
DNA–anthramycin	Structure	DFT	AMBER	CP-MD		[616]
DNA–dynemicin A	Bergman cyclization	DFT	CHARMM	Opt		[617]

[a] CP-MD: Car-Parrinello MD, EA-VTST: Ensemble-averaged variational transition-state theory, EFP: Effective fragment potential, FEP: Free-energy perturbation, Opt: Optimization, TI: Thermodynamic integration, US: Umbrella sampling.

[1] A. Warshel, M. Levitt, *J. Mol. Biol.* **1976**, *103*, 227–249.
[2] M. J. Field, P. A. Bash, M. Karplus, *J. Comput. Chem.* **1990**, *11*, 700–733.
[3] J. Gao, *Acc. Chem. Res.* **1996**, *29*, 298–305.
[4] J. Gao, *Reviews in Computational Chemistry*, *Vol. 7* (Eds.: K. B. Lipkowitz, D. B. Boyd), VCH, New York, **1996**, pp. 119–185.
[5] M. A. Cunningham, P. A. Bash, *Biochimie* **1997**, *79*, 687–689.
[6] *Combined Quantum Mechanical and Molecular Mechanical Methods* (*ACS Symp. Ser.*, *Vol. 712*) (Eds.:J. Gao, M. A. Thompson), American Chemical Society, Washington, **1998**.
[7] K. M. Merz, Jr. in *Combined Quantum Mechanical and Molecular Mechanical Methods (ACS Symp. Ser.*, *Vol. 712*) (Eds.: J. Gao, M. A. Thompson), American Chemical Society, Washington, **1998**, pp. 2–15.
[8] J. Gao in *Encyclopedia of Computational Chemistry*, *Vol. 2* (Ed.: P. v. R. Schleyer), Wiley, Chichester, **1998**, pp. 1257–1263.
[9] P. Amara, M. J. Field in *Encyclopedia of Computational Chemistry*, *Vol. 1* (Ed.: P. v. R. Schleyer), Wiley, Chichester, **1998**, pp. 431–437.
[10] M. F. Ruiz-López, J.-L. Rivail in *Encyclopedia of Computational Chemistry*, *Vol. 1* (Ed.: P. v. R. Schleyer), Wiley, Chichester, **1998**, pp. 437–448.
[11] K. M. Merz, Jr., R. V. Stanton in *Encyclopedia of Computational Chemistry*, *Vol. 4* (Ed.: P. v. R. Schleyer), Wiley, Chichester, **1998**, pp. 2330–2343.
[12] R. A. Friesner, M. D. Beachy, *Curr. Opin. Struct. Biol.* **1998**, *8*, 257–262.
[13] B. Beck, T. Clark, *Perspect. Drug Discovery Des.* **1998**, *9–11*, 131–159.
[14] T. Mordasini, W. Thiel, *Chimia* **1998**, *52*, 288–291.
[15] G. Monard, K. M. Merz, Jr., *Acc. Chem. Res.* **1999**, *32*, 904–911.
[16] I. H. Hillier, *THEOCHEM* **1999**, *463*, 45–52.
[17] P. Amara, M. J. Field in *Computational Molecular Biology*, *Vol. 8* (Ed.: J. Leszczynski), Elsevier, Amsterdam, **1999**.
[18] T. C. Bruice, K. Kahn, *Curr. Opin. Chem. Biol.* **2000**, *4*, 540–544.
[19] P. Sherwood in *Modern Methods and Algorithms of Quantum Chemistry* (*NIC Ser.*, *Vol. 1*) (Ed.: J. Grotendorst), John von Neumann Institute of Computing, Jülich, **2000**, pp. 257–277.
[20] P. D. Lyne, O. A. Walsh in *Computational Biochemistry and Biophysics* (Eds.: O. M. Becker, M. Watanabe), Dekker, New York, **2001**, pp. 221–236.
[21] A. J. Mulholland in *Theoretical Biochemistry: Processes and Properties of Biological Systems* (*Theor. Comput. Chem.*, *Vol. 9*) (Ed.: L. A. Eriksson), Elsevier, Amsterdam, **2001**, pp. 597–653.
[22] M. J. Field, *J. Comput. Chem.* **2002**, *23*, 48–58.
[23] V. Gogonea, *Internet Electron. J. Mol. Des.* **2002**, 1, 173–184.
[24] R. Castillo, M. Oliva, S. Martí, V. Moliner, I. Tuñón, J. Andrés, *Recent Res. Dev. Quantum Chem.* **2002**, *3*, 51–74.

[25] J. L. Gao, D. G. Truhlar, *Annu. Rev. Phys. Chem.* **2002**, *53*, 467 – 505.
[26] G. Monard, X. Prat-Resina, A. González-Lafont, J. M. Lluch, *Int. J. Quantum Chem.* **2003**, *93*, 229 – 244.
[27] L. Ridder, A. J. Mulholland, *Curr. Top. Med. Chem.* **2003**, *3*, 1241 – 1256.
[28] G. Náray-Szabó, I. Berente, *THEOCHEM* **2003**, *666–667*, 637 – 644.
[29] U. Ryde, *Curr. Opin. Chem. Biol.* **2003**, *7*, 136 – 142.
[30] M. Peräkylä in *Quantum Medicinal Chemistry* (*Methods Princ. Med. Chem.*, *Vol. 17*) (Eds.: P. Carloni, F. Alber), Wiley-VCH, Weinheim, **2003**, S. 157 – 176.
[31] F. Perruccio, L. Ridder, A. J. Mulholland in *Quantum Medicinal Chemistry* (*Methods Princ. Med. Chem.*, *Vol. 17*) (Eds.: P. Carloni, F. Alber), Wiley-VCH, Weinheim, **2003**, pp. 177 – 198.
[32] J.-L. Rivail in *Computational Medicinal Chemistry for Drug Discovery* (Eds.: P. Bultinck, H. De Winter, L. Wilfried, J. P. Tollenaere), Dekker, New York, **2004**, pp. 119 – 131.
[33] R. A. Friesner, *Drug Discovery Today Technol.* **2004**, *1*, 253 – 260.
[34] A. J. Mulholland, *Drug Discovery Today* **2005**, *10*, 1393 – 1402.
[35] R. A. Friesner, V. Guallar, *Annu. Rev. Phys. Chem.* **2005**, *56*, 389 – 427.
[36] H. Lin, D. G. Truhlar, *Theor. Chem. Acc.* **2007**, *117*, 185 – 199.
[37] H. M. Senn, W. Thiel, *Curr. Opin. Chem. Biol.* **2007**, *11*, 182 – 187.
[38] H. M. Senn, W. Thiel in *Atomistic Approaches in Modern Biology* (*Top. Curr. Chem.*, *Vol. 268*) (Ed.: M. Reiher), Springer, Berlin, **2007**, pp. 173 – 290.
[39] H. Hu, W. Yang, *Annu. Rev. Phys. Chem.* **2008**, *59*, 573 – 601.
[40] M. Garcia-Viloca, J. Gao, M. Karplus, D. G. Truhlar, *Science* **2004**, *303*, 186 – 195.
[41] J. Pu, J. Gao, D. G. Truhlar, *Chem. Rev.* **2006**, *106*, 3140 – 3169.
[42] J. Gao, S. Ma, D. T. Major, K. Nam, J. Pu, D. G. Truhlar, *Chem. Rev.* **2006**, *106*, 3188 – 3209.
[43] F. Maseras in *Organometallic Bonding and Reactivity: Fundamental Studies* (*Top. Organomet. Chem.*, *Vol. 4*) (Eds.: J. M. Brown, P. Hofmann), Springer, Berlin, **1999**, pp. 165 – 191.
[44] I. B. Bersuker in *Computational Chemistry: Reviews of Current Trends*, *Vol. 6* (Ed.: J. Leszczynski), World Scientific, Singapore, **2001**, pp. 69 – 135.
[45] F. Maseras, K. Morokuma, *J. Comput. Chem.* **1995**, *16*, 1170 – 1179.
[46] T. Matsubara, F. Maseras, N. Koga, K. Morokuma, *J. Phys. Chem.* **1996**, *100*, 2573 – 2580.
[47] F. Maseras, *Chem. Commun.* **2000**, 1821 – 1827.
[48] D. Balcells, G. Drudis-Solé, M. Besora, N. Dölker, G. Ujaque, F. Maseras, A. Lledós, *Faraday Discuss.* **2003**, *124*, 429 – 441.
[49] T. K. Woo, P. M. Margl, P. E. Blöchl, T. Ziegler, *J. Phys. Chem. B* **1997**, *101*, 7877 – 7880.
[50] T. K. Woo, L. Cavallo, T. Ziegler, *Theor. Chem. Acc.* **1998**, *100*, 307 – 313.
[51] T. K. Woo, P. M. Margl, L. Deng, L. Cavallo, T. Ziegler, *Catal. Today* **1999**, *50*, 479 – 500.
[52] S.-Y. Yang, T. Ziegler, *Organometallics* **2006**, *25*, 887 – 900.
[53] L. Guidoni, P. Maurer, S. Piana, U. Rothlisberger, *Quant. Struct.-Act. Relat.* **2002**, *21*, 119 – 127.
[54] A. Magistrato, A. Togni, U. Röthlisberger, T. K. Woo in *Computational Modeling of Homogeneous Catalysis* (*Catalysis by Metal Complexes*, *Vol. 25*) (Eds.: F. Maseras, A. Lledos), Springer, Dordrecht, **2002**, pp. 213 – 252.
[55] A. Magistrato, A. Togni, U. Rothlisberger, *Organometallics* **2006**, *25*, 1151 – 1157.
[56] B. M. Rode, C. F. Schwenk, T. S. Hofer, B. R. Randolf, *Coord. Chem. Rev.* **2005**, *249*, 2993 – 3006.
[57] M. Bühl, S. Grigoleit, H. Kabrede, F. T. Mauschick, *Chem. Eur. J.* **2006**, *12*, 477 – 488.
[58] S. Tsushima, U. Wahlgren, I. Grenthe, *J. Phys. Chem. A* **2006**, *110*, 9175 – 9182.
[59] S. L. Chatwin, M. G. Davidson, C. Doherty, S. M. Donald, R. F. R. Jazzar, S. A. Macgregor, G. J. McIntyre, M. F. Mahon, M. K. Whittlesey, *Organometallics* **2006**, *25*, 99 – 110.
[60] A. Genest, A. Woiterski, S. Krüger, A. M. Shor, N. Rösch, *J. Chem. Theory Comput.* **2006**, *2*, 47 – 58.
[61] M. Sierka, J. Sauer in *Handbook of Materials Modeling*, *Vol. A* (Ed.: S. Yip), Springer, Dordrecht, **2005**, pp. 241 – 258.
[62] U. Eichler, C. M. Kölmel, J. Sauer, *J. Comput. Chem.* **1997**, *18*, 463 – 477.
[63] J. Sauer, M. Sierka, *J. Comput. Chem.* **2000**, *21*, 1470 – 1493.
[64] P. Sherwood, A. H. de Vries, S. J. Collins, S. P. Greatbanks, N. A. Burton, M. A. Vincent, I. H. Hillier, *Faraday Discuss.* **1997**, *106*, 79 – 92.
[65] S. A. French, A. A. Sokol, S. T. Bromley, C. R. A. Catlow, P. Sherwood, *Top. Catal.* **2003**, *24*, 161 – 172.
[66] C. R. A. Catlow, S. A. French, A. A. Sokol, J. M. Thomas, *Philos. Trans. R. Soc. London Ser. A* **2005**, *363*, 913 – 936.
[67] J. To, P. Sherwood, A. A. Sokol, I. J. Bush, C. R. A. Catlow, H. J. J. van Dam, S. A. French, M. F. Guest, *J. Mater. Chem.* **2006**, *16*, 1919 – 1926.
[68] Y. Shiota, K. Suzuki, K. Yoshizawa, *Organometallics* **2006**, *25*, 3118 – 3123.
[69] A. Cembran, J. Gao, *Mol. Phys.* **2006**, *104*, 943 – 955.
[70] A. Tongraar, T. Kerdcharoen, S. Hannongbua, *J. Phys. Chem. A* **2006**, *110*, 4924 – 4929.
[71] I. Tubert-Brohman, O. Acevedo, W. L. Jorgensen, *J. Am. Chem. Soc.* **2006**, *128*, 16904 – 16913.
[72] O. Acevedo, W. L. Jorgensen, *J. Org. Chem.* **2006**, *71*, 4896 – 4902.
[73] O. Acevedo, W. L. Jorgensen, *J. Am. Chem. Soc.* **2006**, *128*, 6141 – 6146.
[74] O. Acevedo, W. L. Jorgensen, *J. Chem. Theory Comput.* **2007**, *3*, 1412 – 1419.
[75] O. Acevedo, W. L. Jorgensen, J. D. Evanseck, *J. Chem. Theory Comput.* **2007**, *3*, 132 – 138.
[76] A. N. Alexandrova, W. L. Jorgensen, *J. Phys. Chem. B* **2007**, *111*, 720 – 730.
[77] H. Gunaydin, O. Acevedo, W. L. Jorgensen, K. N. Houk, *J. Chem. Theory Comput.* **2007**, *3*, 1028 – 1035.
[78] A. Heyden, H. Lin, D. G. Truhlar, *J. Phys. Chem. B* **2007**, *111*, 2231 – 2241.
[79] M. Elstner, D. Porezag, G. Jungnickel, J. Elsner, M. Haugk, T. Frauenheim, S. Suhai, G. Seifert, *Phys. Rev. B* **1998**, *58*, 7260 – 7268.
[80] Q. Cui, M. Elstner, E. Kaxiras, T. Frauenheim, M. Karplus, *J. Phys. Chem. B* **2001**, *105*, 569 – 585.
[81] M. Elstner, T. Frauenheim, S. Suhai, *THEOCHEM* **2003**, *632*, 29 – 41.
[82] P. H. König, M. Hoffmann, T. Frauenheim, Q. Cui, *J. Phys. Chem. B* **2005**, *109*, 9082 – 9095.
[83] N. Otte, M. Scholten, W. Thiel, *J. Phys. Chem. A* **2007**, *111*, 5751 – 5755.
[84] M. Schütz, G. Hetzer, H.-J. Werner, *J. Chem. Phys.* **1999**, *111*, 5691 – 5705.
[85] M. Schütz, H.-J. Werner, *Chem. Phys. Lett.* **2000**, *318*, 370 – 378.
[86] M. Schütz, *J. Chem. Phys.* **2000**, *113*, 9986 – 10001.
[87] M. Schütz, H.-J. Werner, *J. Chem. Phys.* **2001**, *114*, 661 – 681.
[88] M. Schütz, *J. Chem. Phys.* **2002**, *116*, 8772 – 8785.
[89] M. Schütz, F. R. Manby, *Phys. Chem. Chem. Phys.* **2003**, *5*, 3349 – 3358.
[90] H.-J. Werner, F. R. Manby, P. J. Knowles, *J. Chem. Phys.* **2003**, *118*, 8149 – 8160.
[91] H.-J. Werner, F. R. Manby, *J. Chem. Phys.* **2006**, *124*, 054114.
[92] F. Claeyssens, J. N. Harvey, F. R. Manby, R. A. Mata, A. J. Mulholland, K. E. Ranaghan, M. Schütz, S. Thiel, W. Thiel, H.-

J. Werner, *Angew. Chem.* **2006**, *118*, 7010 – 7013; *Angew. Chem. Int. Ed.* **2006**, *45*, 6856 – 6859.
[93] A. J. Mulholland, *Chem. Cent. J.* **2007**, *1*(19), 1 – 5.
[94] R. A. Mata, H.-J. Werner, S. Thiel, W. Thiel, *J. Chem. Phys.* **2008**, *128*, 025104.
[95] A. Warshel, *Computer Modeling of Chemical Reactions in Enzymes and Solutions*, Wiley, New York, **1991**.
[96] J. Åqvist, A. Warshel, *Chem. Rev.* **1993**, *93*, 2523 – 2544.
[97] A. Shurki, A. Warshel in *Protein Simulations* (*Adv. Protein Chem.*, *Vol. 66*) (Ed.: V. Dagett), Academic Press, San Diego, **2003**, pp. 249 – 313.
[98] A. Warshel, *Annu. Rev. Biophys. Biomol. Struct.* **2003**, *32*, 425 – 443.
[99] W. D. Cornell, P. Cieplak, C. I. Bayly, I. R. Gould, K. M. Merz, D. M. Ferguson, D. C. Spellmeyer, T. Fox, J. W. Caldwell, P. A. Kollman, *J. Am. Chem. Soc.* **1995**, *117*, 5179 – 5197.
[100] P. Kollman, J. W. Caldwell, W. S. Ross, D. A. Pearlman, D. A. Case, S. DeBolt, T. E. Cheatham III, D. Ferguson, G. Seibel in *Encyclopedia of Computational Chemistry*, *Vol. 1* (Ed.: P. v. R. Schleyer), Wiley, Chichester, **1998**, pp. 11 – 13.
[101] J. Wang, P. Cieplak, P. A. Kollman, *J. Comput. Chem.* **2000**, *21*, 1049 – 1074.
[102] Y. Duan, C. Wu, S. Chowdhury, M. C. Lee, G. Xiong, W. Zhang, R. Yang, P. Cieplak, R. Luo, T. Lee, J. Caldwell, J. Wang, P. Kollman, *J. Comput. Chem.* **2003**, *24*, 1999 – 2012.
[103] A. D. MacKerell, Jr. et al., *J. Phys. Chem. B* **1998**, *102*, 3586 – 3616.
[104] A. D. MacKerell, Jr., B. Brooks, C. L. Brooks III, L. Nilsson, B. Roux, Y. Won, M. Karplus in *Encyclopedia of Computational Chemistry*, *Vol. 1* (Ed.: P. v. R. Schleyer), Wiley, Chichester, **1998**, pp. 271 – 277.
[105] N. Foloppe, A. D. MacKerell, Jr., *J. Comput. Chem.* **2000**, *21*, 86 – 104.
[106] A. D. MacKerell, Jr., N. K. Banavali, *J. Comput. Chem.* **2000**, *21*, 105 – 120.
[107] A. D. MacKerell, Jr. in *Computational Biochemistry and Biophysics* (Eds.: O. M. Becker, A. D. MacKerell, Jr., B. Roux, M. Watanabe), Dekker, New York, **2001**, pp. 7 – 38.
[108] W. F. van Gunsteren, X. Daura, A. E. Mark in *Encyclopedia of Computational Chemistry*, *Vol. 2* (Eds.: P. v. R. Schleyer), Wiley, Chichester, **1998**, pp. 1211 – 1216.
[109] W. R. P. Scott, P. H. Hünenberger, I. G. Tironi, A. E. Mark, S. R. Billeter, J. Fennen, A. E. Torda, T. Huber, P. Krüger, W. F. van Gunsteren, *J. Phys. Chem. A* **1999**, *103*, 3596 – 3607.
[110] W. L. Jorgensen, D. S. Maxwell, J. Tirado-Rives, *J. Am. Chem. Soc.* **1996**, *118*, 11225 – 11236.
[111] W. L. Jorgensen in *Encyclopedia of Computational Chemistry*, *Vol. 3* (Ed.: P. v. R. Schleyer), Wiley, Chichester, **1998**, pp. 1986 – 1989.
[112] G. A. Kaminski, R. A. Friesner, J. Tirado-Rives, W. L. Jorgensen, *J. Phys. Chem. B* **2001**, *105*, 6474 – 6487.
[113] A. D. MacKerell, Jr. in *Encyclopedia of Computational Chemistry*, *Vol. 3* (Ed.: P. v. R. Schleyer), Wiley, Chichester, **1998**, pp. 2191 – 2200.
[114] A. D. MacKerell, Jr. in *Annual Reports in Computational Chemistry*, *Vol. 1* (Ed.: D. C. Spellmeyer), Elsevier, Amsterdam, **2005**, pp. 91 – 102.
[115] P. Cieplak in *Encyclopedia of Computational Chemistry*, *Vol. 3* (Ed.: P. v. R. Schleyer), Wiley, Chichester, **1998**, pp. 1922 – 1930.
[116] T. E. Cheatham III in *Annual Reports in Computational Chemistry*, *Vol. 1* (Ed.: D. C. Spellmeyer), Elsevier, Amsterdam, **2005**, pp. 75 – 89.
[117] R. J. Woods in *Encyclopedia of Computational Chemistry*, *Vol. 1* (Ed.: P. v. R. Schleyer), Wiley, Chichester, **1998**, pp. 220 – 233.
[118] J. W. Ponder, D. A. Case in *Protein Simulations* (*Adv. Protein Chem.*, *Vol. 66*) (Ed.: V. Daggett), Academic Press, San Diego, **2003**, pp. 27 – 85.
[119] A. D. MacKerell, Jr., *J. Comput. Chem.* **2004**, *25*, 1584 – 1604.
[120] T. Liljefors, K. Gundertofte, P.-O. Norrby, I. Pettersson in *Computational Medicinal Chemistry for Drug Discovery* (Ed.: P. Bultinck, H. De Winter, L. Wilfried, J. P. Tollenaere), Dekker, New York, **2004**, pp. 1 – 28.
[121] J. R. Maple in *Encyclopedia of Computational Chemistry*, *Vol. 2* (Ed.: P. v. R. Schleyer), Wiley, Chichester, **1998**, pp. 1015 – 1024.
[122] S. Humbel, S. Sieber, K. Morokuma, *J. Chem. Phys.* **1996**, *105*, 1959 – 1967.
[123] M. Svensson, S. Humbel, R. D. J. Froese, T. Matsubara, S. Sieber, K. Morokuma, *J. Phys. Chem.* **1996**, *100*, 19357 – 19363.
[124] R. D. J. Froese, K. Morokuma in *Encyclopedia of Computational Chemistry*, *Vol. 2* (Ed.: P. v. R. Schleyer), Wiley, Chichester, **1998**, pp. 1244 – 1257.
[125] S. Dapprich, I. Komáromi, K. S. Byun, K. Morokuma, M. J. Frisch, *THEOCHEM* **1999**, *461–462*, 1 – 21.
[126] I. Komáromi, L. Muszbek in *Frontiers of Multifunctional Nanosystems* (*NATO Sci. Ser. II*, *Vol. 57*) (Eds.: E. V. Buzaneva, P. Scharff), Kluwer, Dordrecht, **2002**,, pp. 17 – 28.
[127] T. Vreven, K. Morokuma, *Theor. Chem. Acc.* **2003**, *109*, 125 – 132.
[128] T. Vreven, K. S. Byun, I. Komáromi, S. Dapprich, J. A. Montgomery, Jr., K. Morokuma, M. J. Frisch, *J. Chem. Theory Comput.* **2006**, *2*, 815 – 826.
[129] U. Ryde, *J. Comput.-Aided Mol. Des.* **1996**, *10*, 153 – 164.
[130] T. H. Rod, U. Ryde, *J. Chem. Theory Comput.* **2005**, *1*, 1240 – 1251.
[131] D. Bakowies, W. Thiel, *J. Phys. Chem.* **1996**, *100*, 10580 – 10594.
[132] I. Antes, W. Thiel in *Combined Quantum Mechanical and Molecular Mechanical Methods* (*ACS Symp. Ser.*, *Vol. 712*) (Eds.: J. Gao, M. A. Thompson), American Chemical Society, Washington, **1998**, pp. 50 – 65.
[133] A. Warshel, S. T. Russell, *Q. Rev. Biophys.* **1984**, *17*, 283 – 422.
[134] F. S. Lee, Z. T. Chu, A. Warshel, *J. Comput. Chem.* **1993**, *14*, 161 – 185.
[135] S. W. Rick, S. J. Stuart in *Reviews in Computational Chemistry*, *Vol. 18* (Eds.: K. B. Lipkowitz, D. B. Boyd), Wiley-VCH, Hoboken, **2002**, pp. 89 – 146.
[136] H. Yu, W. F. van Gunsteren, *Comput. Phys. Commun.* **2005**, *172*, 69 – 85.
[137] *J. Chem. Theory Comput.* **2007**, *3*, 1877 – 2145.
[138] A. Warshel, M. Kato, A. V. Pisliakov, *J. Chem. Theory Comput.* **2007**, *3*, 2034 – 2045.
[139] T. P. Straatsma, J. A. McCammon, *Mol. Simul.* **1990**, *5*, 181 – 192.
[140] S. W. Rick, S. J. Stuart, B. J. Berne, *J. Chem. Phys.* **1994**, *101*, 6141 – 6156.
[141] J. W. Caldwell, P. A. Kollman, *J. Phys. Chem.* **1995**, *99*, 6208 – 6219.
[142] H. Yu, T. Hansson, W. F. van Gunsteren, *J. Chem. Phys.* **2003**, *118*, 221 – 234.
[143] S. Patel, C. L. Brooks III, *J. Comput. Chem.* **2004**, *25*, 1 – 16.
[144] S. Patel, A. D. MacKerell, Jr., C. L. Brooks III, *J. Comput. Chem.* **2004**, *25*, 1504 – 1514.
[145] I. V. Vorobyov, V. M. Anisimov, A. D. MacKerell, Jr., *J. Phys. Chem. B* **2005**, *109*, 18988 – 18999.
[146] V. M. Anisimov, G. Lamoureux, I. V. Vorobyov, N. Huang, B. Roux, A. D. MacKerell, Jr., *J. Chem. Theory Comput.* **2005**, *1*, 153 – 168.
[147] P. Cieplak, J. Caldwell, P. Kollman, *J. Comput. Chem.* **2001**, *22*, 1048 – 1057.
[148] Z.-X. Wang, W. Zhang, C. Wu, H. Lei, P. Cieplak, Y. Duan, *J. Comput. Chem.* **2006**, *27*, 781 – 790.

[149] J. L. Banks, G. A. Kaminski, R. Zhou, D. T. Mainz, B. J. Berne, R. A. Friesner, *J. Chem. Phys.* **1999**, *110*, 741 – 754.
[150] H. A. Stern, G. A. Kaminski, J. L. Banks, R. Zhou, B. J. Berne, R. A. Friesner, *J. Phys. Chem. B* **1999**, *103*, 4730 – 4737.
[151] G. A. Kaminski, H. A. Stern, B. J. Berne, R. A. Friesner, *J. Phys. Chem. A* **2004**, *108*, 621 – 627.
[152] G. A. Kaminski, H. A. Stern, B. J. Berne, R. A. Friesner, Y. X. Cao, R. B. Murphy, R. Zhou, T. A. Halgren, *J. Comput. Chem.* **2002**, *23*, 1515 – 1531.
[153] P. Ren, J. W. Ponder, *J. Comput. Chem.* **2002**, *23*, 1497 – 1506.
[154] W. Xie, J. Gao, *J. Chem. Theory Comput.* **2007**, *3*, 1890 – 1900.
[155] U. C. Singh, P. A. Kollman, *J. Comput. Chem.* **1986**, *7*, 718 – 730.
[156] M. A. Thompson, G. K. Schenter, *J. Phys. Chem.* **1995**, *99*, 6374 – 6386.
[157] M. A. Thompson, *J. Phys. Chem.* **1996**, *100*, 14492 – 14507.
[158] J. Gao, *J. Comput. Chem.* **1997**, *18*, 1061 – 1071.
[159] J. L. Gao, K. Byun, *Theor. Chem. Acc.* **1997**, *96*, 151 – 156.
[160] J. L. Gao, C. Alhambra, *J. Am. Chem. Soc.* **1997**, *119*, 2962 – 2963.
[161] Y.-L. Lin, J. Gao, *J. Chem. Theory Comput.* **2007**, *3*, 1484 – 1493.
[162] R. A. Bryce, M. A. Vincent, N. O. J. Malcolm, I. H. Hillier, N. A. Burton, *J. Chem. Phys.* **1998**, *109*, 3077 – 3085.
[163] L. Jensen, P. T. van Duijnen, J. G. Snijders, *J. Chem. Phys.* **2003**, *118*, 514 – 521.
[164] D. P. Geerke, S. Thiel, W. Thiel, W. F. van Gunsteren, *J. Chem. Theory Comput.* **2007**, *3*, 1499 – 1509.
[165] D. P. Geerke, S. Thiel, W. Thiel, W. F. van Gunsteren, *Phys. Chem. Chem. Phys.* **2008**, *10*, 297 – 302.
[166] C. J. R. Illingworth, S. R. Gooding, P. J. Winn, G. A. Jones, G. G. Ferenczy, C. A. Reynolds, *J. Phys. Chem. A* **2006**, *110*, 6487 – 6497.
[167] Y. Zhang, H. Lin, D. G. Truhlar, *J. Chem. Theory Comput.* **2007**, *3*, 1378 – 1398.
[168] Y. Zhang, H. Lin, *J. Chem. Theory Comput.* **2008**, *4*, 414 – 425.
[169] P. Schaefer, D. Riccardi, Q. Cui, *J. Chem. Phys.* **2005**, *123*, 014905.
[170] D. Riccardi, P. Schaefer, Q. Cui, *J. Phys. Chem. B* **2005**, *109*, 17715 – 17733.
[171] K. Nam, J. Gao, D. M. York, *J. Chem. Theory Comput.* **2005**, *1*, 2 – 13.
[172] A. R. Dinner, X. Lopez, M. Karplus, *Theor. Chem. Acc.* **2003**, *109*, 118 – 124.
[173] B. A. Gregersen, D. M. York, *J. Phys. Chem. B* **2005**, *109*, 536 – 556.
[174] B. A. Gregersen, D. M. York, *J. Comput. Chem.* **2006**, *27*, 103 – 115.
[175] M. Berkowitz, J. A. McCammon, *Chem. Phys. Lett.* **1982**, *90*, 215 – 217.
[176] C. L. Brooks III, A. Brünger, M. Karplus, *Biopolymers* **1985**, *24*, 843 – 865.
[177] C. L. Brooks III, M. Karplus, *J. Mol. Biol.* **1989**, *208*, 159 – 181.
[178] A. Brünger, C. L. Brooks III, M. Karplus, *Chem. Phys. Lett.* **1984**, *105*, 495 – 500.
[179] W. Im, S. Bernèche, B. Roux, *J. Chem. Phys.* **2001**, *114*, 2924 – 2937.
[180] D. Riccardi, Q. Cui, *J. Phys. Chem. A* **2007**, *111*, 5703 – 5711.
[181] T. Benighaus, W. Thiel, *J. Chem. Theory Comput.* **2008**, *4*, 1600 – 1609.
[182] R. B. Murphy, D. M. Philipp, R. A. Friesner, *J. Comput. Chem.* **2000**, *21*, 1442 – 1457.
[183] M. Freindorf, Y. Shao, T. R. Furlani, J. Kong, *J. Comput. Chem.* **2005**, *26*, 1270 – 1278.
[184] D. Riccardi, G. Li, Q. Cui, *J. Phys. Chem. B* **2004**, *108*, 6467 – 6478.
[185] K. P. Eurenius, D. C. Chatfield, B. R. Brooks, M. Hodoscek, *Int. J. Quantum Chem.* **1996**, *60*, 1189 – 1200.
[186] M. Eichinger, P. Tavan, J. Hutter, M. Parrinello, *J. Chem. Phys.* **1999**, *110*, 10452 – 10467.
[187] P. D. Lyne, M. Hodoscek, M. Karplus, *J. Phys. Chem. A* **1999**, *103*, 3462 – 3471.
[188] A. H. de Vries, P. Sherwood, S. J. Collins, A. M. Rigby, M. Rigutto, G. J. Kramer, *J. Phys. Chem. B* **1999**, *103*, 6133 – 6141.
[189] M. J. Field, M. Albe, C. Bret, F. Proust-De Martin, A. Thomas, *J. Comput. Chem.* **2000**, *21*, 1088 – 1100.
[190] M. Swart, *Int. J. Quantum Chem.* **2003**, *91*, 177 – 183.
[191] D. Das, K. P. Eurenius, E. M. Billings, P. Sherwood, D. C. Chatfield, M. Hodošček, B. R. Brooks, *J. Chem. Phys.* **2002**, *117*, 10534 – 10547.
[192] N. Reuter, A. Dejaegere, B. Maigret, M. Karplus, *J. Phys. Chem. A* **2000**, *104*, 1720 – 1735.
[193] N. Ferré, M. Olivucci, *THEOCHEM* **2003**, *632*, 71 – 82.
[194] B. Waszkowycz, I. H. Hillier, N. Gensmantel, D. W. Payling, *J. Chem. Soc. Perkin Trans. 2* **1990**, 1259 – 1268.
[195] B. Waszkowycz, I. H. Hillier, N. Gensmantel, D. W. Payling, *J. Chem. Soc. Perkin Trans. 2* **1991**, 225 – 231.
[196] B. Waszkowycz, I. H. Hillier, N. Gensmantel, D. W. Payling, *J. Chem. Soc. Perkin Trans. 2* **1991**, 1819 – 1832.
[197] V. V. Vasilyev, *THEOCHEM* **1994**, *110*, 129 – 141.
[198] H. Lin, D. G. Truhlar, *J. Phys. Chem. A* **2005**, *109*, 3991 – 4004.
[199] P. Sherwood, et al., *THEOCHEM* **2003**, *632*, 1 – 28.
[200] P. Amara, M. J. Field, *Theor. Chem. Acc.* **2003**, *109*, 43 – 52.
[201] I. Antes, W. Thiel, *J. Phys. Chem. A* **1999**, *103*, 9290 – 9295.
[202] Y. Zhang, T.-S. Lee, W. Yang, *J. Chem. Phys.* **1999**, *110*, 46 – 54.
[203] Y. Zhang, *J. Chem. Phys.* **2005**, *122*, 024114.
[204] Y. Zhang, *Theor. Chem. Acc.* **2006**, *116*, 43 – 50.
[205] A. Laio, J. VandeVondele, U. Rothlisberger, *J. Chem. Phys.* **2002**, *116*, 6941 – 6947.
[206] G. A. DiLabio, M. M. Hurley, P. A. Christiansen, *J. Chem. Phys.* **2002**, *116*, 9578 – 9584.
[207] G. A. DiLabio, R. A. Wolkow, E. R. Johnson, *J. Chem. Phys.* **2005**, *122*, 044708.
[208] K. Yasuda, D. Yamaki, *J. Chem. Phys.* **2004**, *121*, 3964 – 3972.
[209] O. A. von Lilienfeld, I. Tavernelli, U. Rothlisberger, D. Sebastiani, *J. Chem. Phys.* **2005**, *122*, 014113.
[210] P. Slavíček, T. J. Martínez, *J. Chem. Phys.* **2006**, *124*, 084107.
[211] Y. Shao, J. Kong, *J. Phys. Chem. A* **2007**, *111*, 3661 – 3671.
[212] C. Xiao, Y. Zhang, *J. Chem. Phys.* **2007**, *127*, 124102.
[213] V. Théry, D. Rinaldi, J. L. Rivail, B. Maigret, G. G. Ferenczy, *J. Comput. Chem.* **1994**, *15*, 269 – 282.
[214] G. Monard, M. Loos, V. Théry, K. Baka, J. L. Rivail, *Int. J. Quantum Chem.* **1996**, *58*, 153 – 159.
[215] X. Assfeld, J. L. Rivail, *Chem. Phys. Lett.* **1996**, *263*, 100 – 106.
[216] X. Assfeld, N. Ferré, J.-L. Rivail in *Combined Quantum Mechanical and Molecular Mechanical Methods* (*ACS Symp. Ser.*, *Vol. 712*) (Eds.: J. Gao, M. A. Thompson), American Chemical Society, Washington, **1998**, pp. 234 – 249.
[217] N. Ferré, X. Assfeld, J. L. Rivail, *J. Comput. Chem.* **2002**, *23*, 610 – 624.
[218] A. Fornili, Y. Moreau, M. Sironi, X. Assfeld, *J. Comput. Chem.* **2006**, *27*, 515 – 523.
[219] A. Fornili, M. Sironi, M. Raimondi, *THEOCHEM* **2003**, *632*, 157 – 172.
[220] M. Sironi, A. Genoni, M. Civera, S. Pieraccini, M. Ghitti, *Theor. Chem. Acc.* **2007**, *117*, 685 – 698.
[221] A. Fornili, P.-F. Loos, M. Sironi, X. Assfeld, *Chem. Phys. Lett.* **2006**, *427*, 236 – 240.
[222] P.-F. Loos, X. Assfeld, *J. Chem. Theory Comput.* **2007**, *3*, 1047 – 1053.
[223] D. M. Philipp, R. A. Friesner, *J. Comput. Chem.* **1999**, *20*, 1468 – 1494.
[224] R. B. Murphy, D. M. Philipp, R. A. Friesner, *Chem. Phys. Lett.* **2000**, *321*, 113 – 120.

[225] J. Gao, P. Amara, C. Alhambra, M. J. Field, *J. Phys. Chem. A* **1998**, *102*, 4714 – 4721.
[226] P. Amara, M. J. Field, C. Alhambra, J. Gao, *Theor. Chem. Acc.* **2000**, *104*, 336 – 343.
[227] M. Garcia-Viloca, J. Gao, *Theor. Chem. Acc.* **2004**, *111*, 280 – 286.
[228] J. Pu, J. Gao, D. G. Truhlar, *J. Phys. Chem. A* **2004**, *108*, 5454 – 5463.
[229] J. Pu, J. Gao, D. G. Truhlar, *J. Phys. Chem. A* **2004**, *108*, 632 – 650.
[230] J. Pu, J. Gao, D. G. Truhlar, *ChemPhysChem* **2005**, *6*, 1853 – 1865.
[231] J. Jung, C. H. Choi, Y. Sugita, S. Ten-no, *J. Chem. Phys.* **2007**, *127*, 204102.
[232] J. H. Jensen, P. N. Day, M. S. Gordon, H. Basch, D. Cohen, D. R. Garmer, M. Krauss, W. J. Stevens in *Modeling the Hydrogen Bond* (*ACS Symp. Ser.*, *Vol. 569*) (Ed.: D. A. Smith), American Chemical Society, Washington, **1994**, pp. 139 – 151.
[233] P. N. Day, J. H. Jensen, M. S. Gordon, S. P. Webb, W. J. Stevens, M. Krauss, D. Garmer, H. Basch, D. Cohen, *J. Chem. Phys.* **1996**, *105*, 1968 – 1986.
[234] V. Kairys, J. H. Jensen, *J. Phys. Chem. A* **2000**, *104*, 6656 – 6665.
[235] M. S. Gordon, M. A. Freitag, P. Bandyopadhyay, J. H. Jensen, V. Kairys, W. J. Stevens, *J. Phys. Chem. A* **2001**, *105*, 293 – 307.
[236] A. V. Nemukhin, B. L. Grigorenko, A. V. Bochenkova, I. A. Topol, S. K. Burt, *THEOCHEM* **2002**, *581*, 167 – 175.
[237] B. L. Grigorenko, A. V. Nemukhin, I. A. Topol, S. K. Burt, *J. Phys. Chem. A* **2002**, *106*, 10663 – 10672.
[238] A. V. Nemukhin, B. L. Grigorenko, I. A. Topol, S. K. Burt, *J. Comput. Chem.* **2003**, *24*, 1410 – 1420.
[239] R. J. Hall, S. A. Hindle, N. A. Burton, I. H. Hillier, *J. Comput. Chem.* **2000**, *21*, 1433 – 1441.
[240] R. M. Nicoll, S. A. Hindle, G. MacKenzie, I. H. Hillier, N. A. Burton, *Theor. Chem. Acc.* **2001**, *106*, 105 – 112.
[241] C. Lennartz, A. Schäfer, F. Terstegen, W. Thiel, *J. Phys. Chem. B* **2002**, *106*, 1758 – 1767.
[242] A. Rodríguez, C. Oliva, M. González, M. van der Kamp, A. J. Mulholland, *J. Phys. Chem. B* **2007**, *111*, 12909 – 12915.
[243] M. Klähn, S. Braun-Sand, E. Rosta, A. Warshel, *J. Phys. Chem. B* **2005**, *109*, 15645 – 15650.
[244] Y. Zhang, J. Kua, J. A. McCammon, *J. Phys. Chem. B* **2003**, *107*, 4459 – 4463.
[245] H. B. Schlegel in *Modern Electronic Structure Theory* (*Adv. Ser. Phys. Chem.*, *Vol. 2/I*) (Ed.: D. R. Yarkony), World Scientific, Singapore, **1995**, pp. 459 – 500.
[246] H. B. Schlegel in *Encyclopedia of Computational Chemistry*, *Vol. 2* (Ed.: P. v. R. Schleyer), Wiley, Chichester, **1998**, pp. 1136 – 1142.
[247] T. Schlick in *Encyclopedia of Computational Chemistry*, *Vol. 2* (Ed.: P. v. R. Schleyer), Wiley, Chichester, **1998**, pp. 1142 – 1157.
[248] F. Jensen in *Encyclopedia of Computational Chemistry*, *Vol. 5* (Ed.: P. v. R. Schleyer), Wiley, Chichester, **1998**, pp. 3114 – 3123.
[249] H. B. Schlegel, *J. Comput. Chem.* **2003**, *24*, 1514 – 1527.
[250] Ö. Farkas, H. B. Schlegel, *J. Chem. Phys.* **1998**, *109*, 7100 – 7104.
[251] Ö. Farkas, H. B. Schlegel, *J. Chem. Phys.* **1999**, *111*, 10806 – 10814.
[252] Ö. Farkas, H. B. Schlegel, *Phys. Chem. Chem. Phys.* **2002**, *4*, 11 – 15.
[253] Ö. Farkas, H. B. Schlegel, *THEOCHEM* **2003**, *666*, 31 – 39.
[254] B. Paizs, G. Fogarasi, P. Pulay, *J. Chem. Phys.* **1998**, *109*, 6571 – 6576.
[255] B. Paizs, J. Baker, S. Suhai, P. Pulay, *J. Chem. Phys.* **2000**, *113*, 6566 – 6572.
[256] J. Baker, D. Kinghorn, P. Pulay, *J. Chem. Phys.* **1999**, *110*, 4986 – 4991.
[257] K. Németh, O. Coulaud, G. Monard, J. G. Ángyán, *J. Chem. Phys.* **2000**, *113*, 5598 – 5603.
[258] K. Németh, O. Coulaud, G. Monard, J. G. Ángyán, *J. Chem. Phys.* **2001**, *114*, 9747 – 9753.
[259] X. Prat-Resina, M. Garcia-Viloca, G. Monard, A. González-Lafont, J. M. Lluch, J. M. Bofill, J. M. Anglada, *Theor. Chem. Acc.* **2002**, *107*, 147 – 153.
[260] S. R. Billeter, A. J. Turner, W. Thiel, *Phys. Chem. Chem. Phys.* **2000**, *2*, 2177 – 2186.
[261] V. Moliner, A. J. Turner, I. H. Williams, *Chem. Commun.* **1997**, 1271 – 1272.
[262] A. J. Turner, V. Moliner, I. H. Williams, *Phys. Chem. Chem. Phys.* **1999**, *1*, 1323 – 1331.
[263] T. Vreven, K. Morokuma, Ö. Farkas, H. B. Schlegel, M. J. Frisch, *J. Comput. Chem.* **2003**, *24*, 760 – 769.
[264] T. Vreven, M. J. Frisch, K. N. Kudin, H. B. Schlegel, K. Morokuma, *Mol. Phys.* **2006**, *104*, 701 – 714.
[265] S. Hayashi, I. Ohmine, *J. Phys. Chem. B* **2000**, *104*, 10678 – 10691.
[266] Y. Zhang, H. Liu, W. Yang, *J. Chem. Phys.* **2000**, *112*, 3483 – 3492.
[267] X. Prat-Resina, J. M. Bofill, À. González-Lafont, J. M. Lluch, *Int. J. Quantum Chem.* **2004**, *98*, 367 – 377.
[268] J. Kästner, S. Thiel, H. M. Senn, P. Sherwood, W. Thiel, *J. Chem. Theory Comput.* **2007**, *3*, 1064 – 1072.
[269] S. Martí, V. Moliner, I. Tuñón, I. H. Williams, *J. Phys. Chem. B* **2005**, *109*, 3707 – 3710.
[270] S. Martí, V. Moliner, I. Tuñón, *J. Chem. Theory Comput.* **2005**, *1*, 1008 – 1016.
[271] S. Martí, V. Moliner, I. Tuñón, *J. Chem. Theory Comput.* **2006**, *2*, 216.
[272] L. Xie, H. Liu, W. Yang, *J. Chem. Phys.* **2004**, *120*, 8039 – 8052.
[273] H. Liu, Z. Lu, G. A. Cisneros, W. Yang, *J. Chem. Phys.* **2004**, *121*, 697 – 706.
[274] G. A. Cisneros, H. Liu, Z. Lu, W. Yang, *J. Chem. Phys.* **2005**, *122*, 114502.
[275] P. Y. Ayala, H. B. Schlegel, *J. Chem. Phys.* **1997**, *107*, 375 – 384.
[276] P. A. Bash, M. J. Field, M. Karplus, *J. Am. Chem. Soc.* **1987**, *109*, 8092 – 8094.
[277] J. Gao, X. Xia, *Science* **1992**, *258*, 631 – 635.
[278] J. Gao, *J. Phys. Chem.* **1992**, *96*, 537 – 540.
[279] R. V. Stanton, D. S. Hartsough, K. M. Merz, Jr., *J. Phys. Chem.* **1993**, *97*, 11868 – 11870.
[280] D. S. Hartsough, K. M. Merz, Jr., *J. Phys. Chem.* **1995**, *99*, 11266 – 11275.
[281] R. V. Stanton, L. R. Little, K. M. Merz, Jr., *J. Phys. Chem.* **1995**, *99*, 17344 – 17348.
[282] R. V. Stanton, D. S. Hartsough, K. M. Merz, Jr., *J. Comput. Chem.* **1995**, *16*, 113 – 128.
[283] H. M. Senn, S. Thiel, W. Thiel, *J. Chem. Theory Comput.* **2005**, *1*, 494 – 505.
[284] R. Car, M. Parrinello, *Phys. Rev. Lett.* **1985**, *55*, 2471 – 2474.
[285] D. Marx, J. Hutter in *Modern Methods and Algorithms of Quantum Chemistry* (*NIC Ser.*, *Vol. 1*) (Ed.: J. Grotendorst), John von Neumann Institute of Computing, Jülich, **2000**, pp. 301 – 449.
[286] T. K. Woo, P. M. Margl, L. Deng, T. Ziegler in *Combined Quantum Mechanical and Molecular Mechanical Methods* (*ACS Symp. Ser.*, *Vol. 712*) (Eds.: J. Gao, M. A. Thompson), American Chemical Society, Washington, **1998**, pp. 128 – 147.
[287] T. K. Woo, P. E. Blöchl, T. Ziegler, *THEOCHEM* **2000**, *506*, 313 – 334.
[288] M. C. Colombo et al., *Chimia* **2002**, *56*, 13 – 19.
[289] A. Laio, J. VandeVondele, U. Rothlisberger, *J. Phys. Chem. B* **2002**, *106*, 7300 – 7307.

[290] D. Sebastiani, U. Röthlisberger in *Quantum Medicinal Chemistry* (*Methods Princ. Med. Chem.*, *Vol. 17*) (Eds.: P. Carloni, F. Alber), Wiley-VCH, Weinheim, **2003**, pp. 5 – 39.
[291] A. Laio, F. L. Gervasio, J. VandeVondele, M. Sulpizi, U. Rothlisberger, *J. Phys. Chem. B* **2004**, *108*, 7963 – 7968.
[292] M. C. Colombo, C. Gossens, I. Tavernelli, U. Rothlisberger in *Modelling Molecular Structure and Reactivity in Biological Systems* (Eds.: K. J. Naidoo, J. Brady, M. J. Field, J. Gao, M. Hann), Royal Society of Chemistry, Cambridge, **2006**, pp. 85 – 100.
[293] U. Rothlisberger, P. Carloni in *Computer Simulations in Condensed Matter Systems: From Materials to Chemical Biology, Vol. 2* (Eds.: M. Ferrario, G. Ciccotti, K. Binder), Springer, Berlin, **2006**, pp. 449 – 479.
[294] K. Spiegel, A. Magistrato, *Org. Biomol. Chem.* **2006**, *4*, 2507 – 2517.
[295] T. H. Rod, U. Ryde, *Phys. Rev. Lett.* **2005**, *94*, 138302.
[296] M. Valiev, B. C. Garrett, M.-K. Tsai, K. Kowalski, S. M. Kathmann, G. K. Schenter, M. Dupuis, *J. Chem. Phys.* **2007**, *127*, 051102.
[297] M. Valiev, E. J. Bylaska, M. Dupuis, P. G. Tratnyek, *J. Phys. Chem. A* **2008**, *112*, 2713 – 2720.
[298] J. Chandrasekhar, S. F. Smith, W. L. Jorgensen, *J. Am. Chem. Soc.* **1984**, *106*, 3049 – 3050.
[299] J. Chandrasekhar, S. F. Smith, W. L. Jorgensen, *J. Am. Chem. Soc.* **1985**, *107*, 154 – 163.
[300] Y. J. Zheng, K. M. Merz, Jr., *J. Am. Chem. Soc.* **1992**, *114*, 10498 – 10507.
[301] R. V. Stanton, M. Peräkylä, D. Bakowies, P. A. Kollman, *J. Am. Chem. Soc.* **1998**, *120*, 3448 – 3457.
[302] J. Kästner, H. M. Senn, S. Thiel, N. Otte, W. Thiel, *J. Chem. Theory Comput.* **2006**, *2*, 452 – 461.
[303] J. Bentzien, R. P. Muller, J. Florián, A. Warshel, *J. Phys. Chem. B* **1998**, *102*, 2293 – 2301.
[304] J. Bentzien, J. Florián, T. M. Glennon, A. Warshel in *Combined Quantum Mechanical and Molecular Mechanical Methods* (*ACS Symp. Ser.*, *Vol. 712*) (Eds.: J. Gao, M. A. Thompson), American Chemical Society, Washington, **1998**, pp. 16 – 34.
[305] M. Štrajbl, G. Hong, A. Warshel, *J. Phys. Chem. B* **2002**, *106*, 13333 – 13343.
[306] E. Rosta, M. Klähn, A. Warshel, *J. Phys. Chem. B* **2006**, *110*, 2934 – 2941.
[307] G. Li, X. Zhang, Q. Cui, *J. Phys. Chem. B* **2003**, *107*, 8643 – 8653.
[308] G. Li, Q. Cui, *J. Phys. Chem. B* **2003**, *107*, 14521 – 14528.
[309] W. Yang, R. Bitetti-Putzer, M. Karplus, *J. Chem. Phys.* **2004**, *120*, 9450 – 9453.
[310] H. Hu, W. Yang, *J. Chem. Phys.* **2005**, *123*, 041102.
[311] H. Li, M. Fajer, W. Yang, *J. Chem. Phys.* **2007**, *126*, 024106.
[312] C. Jarzynski, *Phys. Rev. Lett.* **1997**, *78*, 2690 – 2693.
[313] C. Jarzynski, *Phys. Rev. E* **1997**, *56*, 5018 – 5035.
[314] G. E. Crooks, *J. Stat. Phys.* **1998**, *90*, 1481 – 1487.
[315] G. E. Crooks, *Phys. Rev. E* **1999**, *60*, 2721 – 2726.
[316] S. Park, K. Schulten, *J. Chem. Phys.* **2004**, *120*, 5946 – 5961.
[317] M. A. Cuendet, *Phys. Rev. Lett.* **2006**, *96*, 120602.
[318] W. Lechner, H. Oberhofer, C. Dellago, P. L. Geissler, *J. Chem. Phys.* **2006**, *124*, 044113.
[319] D. A. Hendrix, C. Jarzynski, *J. Chem. Phys.* **2001**, *114*, 5974 – 5981.
[320] M. Ø. Jensen, S. Park, E. Tajkhorshid, K. Schulten, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 6731 – 6736.
[321] S. Park, F. Khalili-Araghi, E. Tajkhorshid, K. Schulten, *J. Chem. Phys.* **2003**, *119*, 3559 – 3566.
[322] S. Raugei, M. Cascella, P. Carloni, *J. Am. Chem. Soc.* **2004**, *126*, 15730 – 15737.
[323] A. Crespo, M. A. Martí, D. A. Estrin, A. E. Roitberg, *J. Am. Chem. Soc.* **2005**, *127*, 6940 – 6941.
[324] D. Chandler in *Classical and Quantum Dynamics in Condensed Phase Simulations* (Eds.: B. J. Berne, G. Ciccotti, D. F. Coker), World Scientific, Singapore, **1998**, pp. 51 – 66.
[325] C. Dellago, P. G. Bolhuis, F. S. Csajka, D. Chandler, *J. Chem. Phys.* **1998**, *108*, 1964 – 1977.
[326] C. Dellago, P. G. Bolhuis, D. Chandler, *J. Chem. Phys.* **1998**, *108*, 9236 – 9245.
[327] P. G. Bolhuis, C. Dellago, D. Chandler, *Faraday Discuss.* **1998**, *110*, 421 – 436.
[328] F. S. Csajka, D. Chandler, *J. Chem. Phys.* **1998**, *109*, 1125 – 1133.
[329] C. Dellago, P. G. Bolhuis, D. Chandler, *J. Chem. Phys.* **1999**, *110*, 6617 – 6625.
[330] P. G. Bolhuis, C. Dellago, P. L. Geissler, D. Chandler, *J. Phys. Condens. Matter* **2000**, *12*, 147 – 152.
[331] P. L. Geissler, C. Dellago, D. Chandler, J. Hutter, M. Parrinello, *Science* **2001**, *291*, 2121 – 2124.
[332] P. G. Bolhuis, D. Chandler, C. Dellago, P. L. Geissler, *Annu. Rev. Phys. Chem.* **2002**, *53*, 291 – 318.
[333] C. Dellago, P. G. Bolhuis, P. L. Geissler, *Adv. Chem. Phys.* **2002**, *123*, 1 – 78.
[334] D. Zahn, *J. Chem. Phys.* **2005**, *123*, 044104.
[335] J. E. Basner, S. D. Schwartz, *J. Am. Chem. Soc.* **2005**, *127*, 13822 – 13831.
[336] A. Laio, M. Parrinello, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 12562 – 12566.
[337] M. Iannuzzi, A. Laio, M. Parrinello, *Phys. Rev. Lett.* **2003**, *90*, 238302.
[338] C. Micheletti, A. Laio, M. Parrinello, *Phys. Rev. Lett.* **2004**, *92*, 170601.
[339] Y. Wu, J. D. Schmitt, R. Car, *J. Chem. Phys.* **2004**, *121*, 1193 – 1200.
[340] A. Laio, A. Rodriguez-Fortea, F. L. Gervasio, M. Ceccarelli, M. Parrinello, *J. Phys. Chem. B* **2005**, *109*, 6714 – 6721.
[341] B. Ensing, A. Laio, M. Parrinello, M. L. Klein, *J. Phys. Chem. B* **2005**, *109*, 6676 – 6687.
[342] P. Raiteri, A. Laio, F. L. Gervasio, C. Micheletti, M. Parrinello, *J. Phys. Chem. B* **2006**, *110*, 3533 – 3539.
[343] G. Bussi, A. Laio, M. Parrinello, *Phys. Rev. Lett.* **2006**, *96*, 090601.
[344] B. Ensing, M. De Vivo, Z. W. Liu, P. Moore, M. L. Klein, *Acc. Chem. Res.* **2006**, *39*, 73 – 81.
[345] D. Min, Y. Liu, I. Carbone, W. Yang, *J. Chem. Phys.* **2007**, *126*, 194104.
[346] T. Huber, A. E. Torda, W. F. van Gunsteren, *J. Comput.-Aided Mol. Des.* **1994**, *8*, 695 – 708.
[347] H. Grubmüller, *Phys. Rev. E* **1995**, *52*, 2893 – 2906.
[348] E. M. Müller, A. de Meijere, H. Grubmüller, *J. Chem. Phys.* **2002**, *116*, 897 – 905.
[349] F. Wang, D. P. Landau, *Phys. Rev. Lett.* **2001**, *86*, 2050 – 2053.
[350] F. Wang, D. P. Landau, *Phys. Rev. E* **2001**, *64*, 056101.
[351] D. P. Landau, F. Wang, *Comput. Phys. Commun.* **2002**, *147*, 674 – 677.
[352] S. Raugei, P. Carloni, *J. Phys. Chem. B* **2006**, *110*, 3747 – 3758.
[353] C. L. Stanton, I.-F. W. Kuo, C. J. Mundy, T. Laino, K. N. Houk, *J. Phys. Chem. B* **2007**, *111*, 12573 – 12581.
[354] L. Rosso, P. Mináry, Z. Zhu, M. E. Tuckerman, *J. Chem. Phys.* **2002**, *116*, 4389 – 4402.
[355] L. Rosso, M. E. Tuckerman, *Mol. Simul.* **2002**, *28*, 91 – 112.
[356] J. VandeVondele, U. Röthlisberger, *J. Phys. Chem. B* **2002**, *106*, 203 – 208.
[357] S. Piana, D. Bucher, P. Carloni, U. Rothlisberger, *J. Phys. Chem. B* **2004**, *108*, 11139 – 11149.
[358] Z. Lu, W. Yang, *J. Chem. Phys.* **2004**, *121*, 89 – 100.
[359] W. H. Miller, N. C. Handy, J. E. Adams, *J. Chem. Phys.* **1980**, *72*, 99 – 112.
[360] H. Hu, Z. Lu, W. Yang, *J. Chem. Theory Comput.* **2007**, *3*, 390 – 406.

[361] ChemShell, a Computational Chemistry Shell, http://www.chemshell.org/.
[362] U. Ryde, L. Olsen, K. Nilsson, *J. Comput. Chem.* **2002**, *23*, 1058 – 1070.
[363] U. Ryde, K. Nilsson, *THEOCHEM* **2003**, *632*, 259 – 275.
[364] U. Ryde, K. Nilsson, *J. Am. Chem. Soc.* **2003**, *125*, 14232 – 14233.
[365] K. Nilsson, U. Ryde, *J. Inorg. Biochem.* **2004**, *98*, 1539 – 1546.
[366] K. Nilsson, H. P. Hersleth, T. H. Rod, K. K. Andersson, U. Ryde, *Biophys. J.* **2004**, *87*, 3437 – 3447.
[367] N. Källrot, K. Nilsson, T. Rasmussen, U. Ryde, *Int. J. Quantum Chem.* **2005**, *102*, 520 – 541.
[368] L. Rulíšek, U. Ryde, *J. Phys. Chem. B* **2006**, *110*, 11511 – 11518.
[369] P. Söderhjelm, U. Ryde, *THEOCHEM* **2006**, *770*, 199 – 219.
[370] H. P. Hersleth, U. Ryde, P. Rydberg, C. H. Gorbitz, K. K. Andersson, *J. Inorg. Biochem.* **2006**, *100*, 460 – 476.
[371] Y.-W. Hsiao, T. Drakenberg, U. Ryde, *J. Biomol. NMR* **2005**, *31*, 97 – 114.
[372] Y.-W. Hsiao, Y. Tao, J. E. Shokes, R. A. Scott, U. Ryde, *Phys. Rev. B* **2006**, *74*, 214101.
[373] Y.-W. Hsiao, U. Ryde, *Inorg. Chim. Acta* **2006**, *359*, 1081 – 1092.
[374] U. Ryde, Y.-W. Hsiao, L. Rulíšek, E. I. Solomon, *J. Am. Chem. Soc.* **2007**, *129*, 726 – 727.
[375] N. Yu, S. A. Hayik, B. Wang, N. Liao, C. H. Reynolds, K. M. Merz, Jr., *J. Chem. Theory Comput.* **2006**, *2*, 1057 – 1069.
[376] M. Hoffmann, M. Wanko, P. Strodel, P. H. König, T. Frauenheim, K. Schulten, W. Thiel, E. Tajkhorshid, M. Elstner, *J. Am. Chem. Soc.* **2006**, *128*, 10808 – 10818.
[377] J. A. Gascón, E. M. Sproviero, V. S. Batista, *J. Chem. Theory Comput.* **2005**, *1*, 674 – 685.
[378] J. A. Gascón, E. M. Sproviero, V. S. Batista, *Acc. Chem. Res.* **2006**, *39*, 184 – 193.
[379] M. P. Waller, M. Bühl, K. R. Geethalakshmi, D. Wang, W. Thiel, *Chem. Eur. J.* **2007**, *13*, 4723 – 4732.
[380] J. C. Schöneboom, F. Neese, W. Thiel, *J. Am. Chem. Soc.* **2005**, *127*, 5840 – 5853.
[381] S. Sinnecker, F. Neese, *J. Comput. Chem.* **2006**, *27*, 1463 – 1475.
[382] S. Sinnecker, N. Svensen, E. W. Barr, S. Ye, J. M. Bollinger, Jr., F. Neese, C. Krebs, *J. Am. Chem. Soc.* **2007**, *129*, 6168 – 6179.
[383] G. Groenhof, M. Bouxin-Cademartory, B. Hess, S. P. de Visser, H. J. C. Berendsen, M. Olivucci, A. E. Mark, M. A. Robb, *J. Am. Chem. Soc.* **2004**, *126*, 4228 – 4233.
[384] G. Groenhof, L. V. Schäfer, M. Boggio-Pasqua, M. Goette, H. Grubmüller, M. A. Robb, *J. Am. Chem. Soc.* **2007**, *129*, 6812 – 6819.
[385] A. Altun, S. Shaik, W. Thiel, *J. Comput. Chem.* **2006**, *27*, 1324 – 1337.
[386] J. Zheng, A. Altun, W. Thiel, *J. Comput. Chem.* **2007**, *28*, 2147 – 2158.
[387] B. Entsch, W. J. H. van Berkel, *FASEB J.* **1995**, *9*, 476 – 483.
[388] A. P. Jadan, M. J. H. Moonen, S. Boeren, L. A. Golovleva, I. M. C. M. Rietjens, W. J. H. van Berkel, *Adv. Synth. Catal.* **2004**, *346*, 367 – 375.
[389] W. J. H. van Berkel, N. M. Kamerbeek, M. W. Fraaije, *J. Biotechnol.* **2006**, *124*, 670 – 689.
[390] J. Vervoort, I. M. C. M. Rietjens, W. J. H. van Berkel, C. Veeger, *Eur. J. Biochem.* **1992**, *206*, 479 – 484.
[391] L. Ridder, A. J. Mulholland, J. Vervoort, I. M. C. M. Rietjens, *J. Am. Chem. Soc.* **1998**, *120*, 7641 – 7642.
[392] L. Ridder, A. J. Mulholland, I. M. Rietjens, J. Vervoort, *J. Mol. Graphics Modell.* **1999**, *17*, 163 – 175, 214.
[393] L. Ridder, B. A. Palfey, J. Vervoort, I. M. C. M. Rietjens, *FEBS Lett.* **2000**, *478*, 197 – 201.
[394] L. Ridder, J. N. Harvey, I. M. C. M. Rietjens, J. Vervoort, A. J. Mulholland, *J. Phys. Chem. B* **2003**, *107*, 2118 – 2126.
[395] S. R. Billeter, C. F. W. Hanser, T. Z. Mordasini, M. Scholten, W. Thiel, W. F. van Gunsteren, *Phys. Chem. Chem. Phys.* **2001**, *3*, 688 – 695.
[396] J. Kästner, W. Thiel, *J. Chem. Phys.* **2005**, *123*, 144104.
[397] P. D. Lyne, A. J. Mulholland, W. G. Richards, *J. Am. Chem. Soc.* **1995**, *117*, 11345 – 11350.
[398] S. Martí, J. Andrés, V. Moliner, E. Silla, I. Tuñón, J. Bertrán, *Theor. Chem. Acc.* **2001**, *105*, 207 – 212.
[399] Y. S. Lee, S. E. Worthington, M. Krauss, B. R. Brooks, *J. Phys. Chem. B* **2002**, *106*, 12059 – 12065.
[400] S. Martí, J. Andrés, V. Moliner, E. Silla, I. Tuñón, J. Bertrán, *J. Phys. Chem. B* **2000**, *104*, 11308 – 11315.
[401] S. Martí, J. Andrés, V. Moliner, E. Silla, I. Tuñón, J. Bertrán, M. J. Field, *J. Am. Chem. Soc.* **2001**, *123*, 1709 – 1712.
[402] H. Guo, Q. Cui, W. N. Lipscomb, M. Karplus, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 9032 – 9037.
[403] C. R. W. Guimarães, M. P. Repasky, J. Chandrasekhar, J. Tirado-Rives, W. L. Jorgensen, *J. Am. Chem. Soc.* **2003**, *125*, 6892 – 6899.
[404] S. Hur, T. C. Bruice, *J. Am. Chem. Soc.* **2003**, *125*, 1472 – 1473.
[405] S. Hur, T. C. Bruice, *J. Am. Chem. Soc.* **2003**, *125*, 5964 – 5972.
[406] S. Hur, T. C. Bruice, *J. Am. Chem. Soc.* **2003**, *125*, 10540 – 10542.
[407] S. Hur, T. C. Bruice, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 12015 – 12020.
[408] M. Štrajbl, A. Shurki, M. Kato, A. Warshel, *J. Am. Chem. Soc.* **2003**, *125*, 10228 – 10237.
[409] S. Martí, J. Andrés, V. Moliner, E. Silla, I. Tuñón, J. Bertrán, *THEOCHEM* **2003**, *632*, 197 – 206.
[410] S. Martí, J. Andrés, V. Moliner, E. Silla, I. Tuñón, J. Bertrán, *Chem. Eur. J.* **2003**, *9*, 984 – 991.
[411] S. Martí, J. Andrés, V. Moliner, E. Silla, I. Tuñón, J. Bertrán, *J. Am. Chem. Soc.* **2004**, *126*, 311 – 319.
[412] K. E. Ranaghan, A. J. Mulholland, *Chem. Commun.* **2004**, 1238 – 1239.
[413] F. Claeyssens, K. E. Ranaghan, F. R. Manby, J. N. Harvey, A. J. Mulholland, *Chem. Commun.* **2005**, 5068 – 5070.
[414] X. Zhang, X. Zhang, T. C. Bruice, *Biochemistry* **2005**, *44*, 10443 – 10448.
[415] K. E. Ranaghan, L. Ridder, B. Szefczyk, W. A. Sokalski, J. C. Hermann, A. J. Mulholland, *Mol. Phys.* **2003**, *101*, 2695 – 2714.
[416] K. E. Ranaghan, L. Ridder, B. Szefczyk, W. A. Sokalski, J. C. Hermann, A. J. Mulholland, *Org. Biomol. Chem.* **2004**, *2*, 968 – 980.
[417] B. Szefczyk, A. J. Mulholland, K. E. Ranaghan, W. A. Sokalski, *J. Am. Chem. Soc.* **2004**, *126*, 16148 – 16159.
[418] B. Szefczyk, F. Claeyssens, A. J. Mulholland, W. A. Sokalski, *Int. J. Quantum Chem.* **2007**, *107*, 2274 – 2285.
[419] J. Giraldo, D. Roche, X. Rovira, J. Serra, *FEBS Lett.* **2006**, *580*, 2170 – 2177.
[420] H. Guo, Q. Cui, W. N. Lipscomb, M. Karplus, *Angew. Chem.* **2003**, *115*, 1546 – 1549; *Angew. Chem. Int. Ed.* **2003**, *42*, 1508 – 1511.
[421] C. R. W. Guimarães, M. Udier-Blagović, I. Tubert-Brohman, W. L. Jorgensen, *J. Chem. Theory Comput.* **2005**, *1*, 617 – 625.
[422] S. Martí, V. Moliner, I. Tuñón, I. H. Williams, *Org. Biomol. Chem.* **2003**, *1*, 483 – 487.
[423] H. L. Woodcock, M. Hodošček, P. Sherwood, Y. S. Lee, H. F. Schaefer III, B. R. Brooks, *Theor. Chem. Acc.* **2003**, *109*, 140 – 148.
[424] J. J. Ruiz-Pernía, E. Silla, I. Tuñón, S. Martí, V. Moliner, *J. Phys. Chem. B* **2004**, *108*, 8427 – 8433.
[425] J. J. Ruiz-Pernía, E. Silla, I. Tuñón, S. Martí, *J. Phys. Chem. B* **2006**, *110*, 17663 – 17670.
[426] A. Crespo, D. A. Scherlis, M. A. Martí, P. Ordejón, A. E. Roitberg, D. A. Estrin, *J. Phys. Chem. B* **2003**, *107*, 13728 – 13736.

[427] H. L. Woodcock, M. Hodošček, B. R. Brooks, *J. Phys. Chem. A* **2007**, *111*, 5720 – 5728.
[428] H. L. Woodcock III, M. Hodošček, A. T. B. Gilbert, P. M. W. Gill, H. F. Schaefer III, B. R. Brooks, *J. Comput. Chem.* **2007**, *28*, 1485 – 1502.
[429] T. Ishida, D. G. Fedorov, K. Kitaura, *J. Phys. Chem. B* **2006**, *110*, 1457 – 1463.
[430] *Cytochrome P450: Structure, Mechanism, and Biochemistry* (Ed.: P. R. Ortiz de Montellano), 2nd ed., Plenum, New York, **1995**.
[431] *Cytochrome P450: Structure, Mechanism, and Biochemistry* (Ed.: P. R. Ortiz de Montellano), 3rd ed., Kluwer/Plenum, New York, **2005**.
[432] I. G. Denisov, T. M. Makris, S. G. Sligar, I. Schlichting, *Chem. Rev.* **2005**, *105*, 2253 – 2277.
[433] S. Shaik, D. Kumar, S. P. de Visser, A. Altun, W. Thiel, *Chem. Rev.* **2005**, *105*, 2279 – 2328.
[434] J. C. Schöneboom, H. Lin, N. Reuter, W. Thiel, S. Cohen, F. Ogliaro, S. Shaik, *J. Am. Chem. Soc.* **2002**, *124*, 8142 – 8151.
[435] V. Guallar, M. H. Baik, S. J. Lippard, R. A. Friesner, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 6998 – 7002.
[436] J. C. Schöneboom, S. Cohen, H. Lin, S. Shaik, W. Thiel, *J. Am. Chem. Soc.* **2004**, *126*, 4017 – 4034.
[437] V. Guallar, R. A. Friesner, *J. Am. Chem. Soc.* **2004**, *126*, 8501 – 8508.
[438] J. C. Schöneboom, W. Thiel, *J. Phys. Chem. B* **2004**, *108*, 7468 – 7478.
[439] H. Lin, J. C. Schöneboom, S. Cohen, S. Shaik, W. Thiel, *J. Phys. Chem. B* **2004**, *108*, 10083 – 10088.
[440] A. Altun, W. Thiel, *J. Phys. Chem. B* **2005**, *109*, 1268 – 1280.
[441] M. Swart, A. R. Groenhof, A. W. Ehlers, K. Lammertsma, *Chem. Phys. Lett.* **2005**, *403*, 35 – 41.
[442] A. Altun, V. Guallar, R. A. Friesner, S. Shaik, W. Thiel, *J. Am. Chem. Soc.* **2006**, *128*, 3924 – 3925.
[443] J. Zheng, D. Wang, W. Thiel, S. Shaik, *J. Am. Chem. Soc.* **2006**, *128*, 13204 – 13215.
[444] J. Zurek, N. Foloppe, J. N. Harvey, A. J. Mulholland, *Org. Biomol. Chem.* **2006**, *4*, 3931 – 3937.
[445] A. Altun, S. Shaik, W. Thiel, *J. Am. Chem. Soc.* **2007**, *129*, 8978 – 8987.
[446] M. Freindorf, Y. Shao, J. Kong, T. R. Furlani, *J. Inorg. Biochem.* **2008**, *102*, 427 – 432.
[447] D. Wang, J. Zheng, S. Shaik, W. Thiel, *J. Phys. Chem. B* **2008**, *112*, 5126 – 5138.
[448] A. Altun, D. Kumar, F. Neese, W. Thiel, *J. Phys. Chem. A* **2008**, *112*, 12904 – 12910.
[449] D. Wang, W. Thiel, *THEOCHEM* **2009**, DOI: 10.1016/j.theochem.2008.06.011.
[450] S. H. Kim, R. Perera, L. P. Hager, J. H. Dawson, B. M. Hoffman, *J. Am. Chem. Soc.* **2006**, *128*, 5598 – 5599.
[451] D. Kumar, H. Hirao, S. P. de Visser, J. Zheng, D. Wang, W. Thiel, S. Shaik, *J. Phys. Chem. B* **2005**, *109*, 19946 – 19951.
[452] H. Hirao, D. Kumar, W. Thiel, S. Shaik, *J. Am. Chem. Soc.* **2005**, *127*, 13007 – 13018.
[453] C. M. Bathelt, J. Zurek, A. J. Mulholland, J. N. Harvey, *J. Am. Chem. Soc.* **2005**, *127*, 12900 – 12908.
[454] D. Fishelovitch, C. Hazan, H. Hirao, H. J. Wolfson, R. Nussinov, S. Shaik, *J. Phys. Chem. B* **2007**, *111*, 13822 – 13832.
[455] E. Derat, S. Cohen, S. Shaik, A. Altun, W. Thiel, *J. Am. Chem. Soc.* **2005**, *127*, 13611 – 13621.
[456] C. M. Bathelt, A. J. Mulholland, J. N. Harvey, *Dalton Trans.* **2005**, 3470 – 3476.
[457] J. N. Harvey, C. M. Bathelt, A. J. Mulholland, *J. Comput. Chem.* **2006**, *27*, 1352 – 1362.
[458] C. Rovira, M. Alfonso-Prieto, X. Biarnés, X. Carpena, I. Fita, P. C. Loewen, *Chem. Phys.* **2006**, *323*, 129 – 137.
[459] K.-B. Cho, E. Derat, S. Shaik, *J. Am. Chem. Soc.* **2007**, *129*, 3182 – 3188.
[460] S. Cohen, D. Kumar, S. Shaik, *J. Am. Chem. Soc.* **2006**, *128*, 2649 – 2653.
[461] E. Derat, S. Shaik, *J. Phys. Chem. B* **2006**, *110*, 10526 – 10533.
[462] E. Derat, S. Shaik, *J. Am. Chem. Soc.* **2006**, *128*, 8185 – 8198.
[463] T. Kamachi, K. Yoshizawa, *J. Am. Chem. Soc.* **2005**, *127*, 10686 – 10692.
[464] P. R. Callis, T. Liu, *Chem. Phys.* **2006**, *326*, 230 – 239.
[465] S. Bhattacharyya, M. T. Stankovich, D. G. Truhlar, J. Gao, *J. Phys. Chem. A* **2007**, *111*, 5729 – 5742.
[466] R. C. Walker, I. P. Mercer, I. R. Gould, D. R. Klug, *J. Comput. Chem.* **2007**, *28*, 478 – 490.
[467] T. Wymore, D. W. Deerfield II, J. Hempel, *Biochemistry* **2007**, *46*, 9495 – 9506.
[468] J. E. Gready, I. Rostov, P. L. Cummins in *Modelling Molecular Structure and Reactivity in Biological Systems* (Eds.: K. J. Naidoo, J. Brady, M. J. Field, J. Gao, M. Hann), Royal Society of Chemistry, Cambridge, **2006**, pp. 101 – 118.
[469] J. Pang, J. Pu, J. Gao, D. G. Truhlar, R. K. Allemann, *J. Am. Chem. Soc.* **2006**, *128*, 8015 – 8023.
[470] P. L. Cummins, I. V. Rostov, J. E. Gready, *J. Chem. Theory Comput.* **2007**, *3*, 1203 – 1211.
[471] K. E. Ranaghan, L. Masgrau, N. S. Scrutton, M. J. Sutcliffe, A. J. Mulholland, *ChemPhysChem* **2007**, *8*, 1816 – 1835.
[472] L. Masgrau, A. Roujeinikova, L. O. Johannissen, P. Hothi, J. Basran, K. E. Ranaghan, A. J. Mulholland, M. J. Sutcliffe, N. S. Scrutton, D. Leys, *Science* **2006**, *312*, 237 – 241.
[473] L. Masgrau, *Science* **2006**, *312*, 1600.
[474] L. Masgrau, K. E. Ranaghan, N. S. Scrutton, A. J. Mulholland, M. J. Sutcliffe, *J. Phys. Chem. B* **2007**, *111*, 3032 – 3047.
[475] A. V. Nemukhin, B. L. Grigorenko, I. A. Topol, S. K. Burt, *Int. J. Quantum Chem.* **2006**, *106*, 2184 – 2190.
[476] M. Lundberg, K. Morokuma, *J. Phys. Chem. B* **2007**, *111*, 9380 – 9389.
[477] I. Tejero, À. González-Lafont, J. M. Lluch, *J. Comput. Chem.* **2007**, *28*, 997 – 1005.
[478] S. Cohen, S. Kozuch, C. Hazan, S. Shaik, *J. Am. Chem. Soc.* **2006**, *128*, 11028 – 11029.
[479] E. Derat, S. Shaik, C. Rovira, P. Vidossich, M. Alfonso-Prieto, *J. Am. Chem. Soc.* **2007**, *129*, 6346 – 6347.
[480] M. Alfonso-Prieto, A. Borovik, X. Carpena, G. Murshudov, W. Melik-Adamyan, I. Fita, C. Rovira, P. C. Loewen, *J. Am. Chem. Soc.* **2007**, *129*, 4193 – 4205.
[481] P. Vidossich, M. Alfonso-Prieto, X. Carpena, P. C. Loewen, I. Fita, C. Rovira, *J. Am. Chem. Soc.* **2007**, *129*, 13436 – 13446.
[482] M. A. Martí, L. Capece, D. E. Bikiel, B. Falcone, D. A. Estrin, *Proteins Struct. Funct. Bioinf.* **2007**, *68*, 480 – 487.
[483] M. A. Marti, A. Crespo, L. Capece, L. Boechi, D. E. Bikiel, D. A. Scherlis, D. A. Estrin, *J. Inorg. Biochem.* **2006**, *100*, 761 – 770.
[484] M. Freindorf, Y. Shao, S. T. Brown, J. Kong, T. R. Furlani, *Chem. Phys. Lett.* **2006**, *419*, 563 – 566.
[485] M. Meuwly, *ChemPhysChem* **2006**, *7*, 2061 – 2063.
[486] V. Guallar, A. A. Jarzecki, R. A. Friesner, T. G. Spiro, *J. Am. Chem. Soc.* **2006**, *128*, 5427 – 5435.
[487] N. Strickland, A. J. Mulholland, J. N. Harvey, *Biophys. J.* **2005**, *90*, L27 – L29.
[488] L. Capece, M. A. Marti, A. Crespo, F. Doctorovich, D. A. Estrin, *J. Am. Chem. Soc.* **2006**, *128*, 12455 – 12461.
[489] M. Unno, H. Chen, S. Kusama, S. Shaik, M. Ikeda-Saito, *J. Am. Chem. Soc.* **2007**, *129*, 13394 – 13395.
[490] C. Greco, M. Bruschi, J. Heimdal, P. Fantucci, L. De Gioia, U. Ryde, *Inorg. Chem.* **2007**, *46*, 7256 – 7258.
[491] C. Greco, M. Bruschi, L. De Gioia, U. Ryde, *Inorg. Chem.* **2007**, *46*, 5911 – 5921.

[492] D. Rinaldo, D. M. Philipp, S. J. Lippard, R. A. Friesner, *J. Am. Chem. Soc.* **2007**, *129*, 3135 – 3147.
[493] K. Yoshizawa, N. Kihara, T. Kamachi, Y. Shiota, *Inorg. Chem.* **2006**, *45*, 3034 – 3041.
[494] A. Crespo, M. A. Martí, A. E. Roitberg, L. M. Amzel, D. A. Estrin, *J. Am. Chem. Soc.* **2006**, *128*, 12817 – 12828.
[495] K. Yoshizawa, Y. Shiota, *J. Am. Chem. Soc.* **2006**, *128*, 9873 – 9881.
[496] M. Sundararajan, I. H. Hillier, N. A. Burton, *J. Phys. Chem. B* **2007**, *111*, 5511 – 5517.
[497] M. Sundararajan, I. H. Hillier, N. A. Burton, *J. Phys. Chem. A* **2006**, *110*, 785 – 790.
[498] K. Paraskevopoulos, M. Sundararajan, R. Surendran, M. A. Hough, R. R. Eady, I. H. Hillier, S. S. Hasnain, *Dalton Trans.* **2006**, 3067 – 3076.
[499] M. Cascella, M. A. Cuendet, I. Tavernelli, U. Rothlisberger, *J. Phys. Chem. B* **2007**, *111*, 10248 – 10252.
[500] R. Prabhakar, T. Vreven, M. J. Frisch, K. Morokuma, D. G. Musaev, *J. Phys. Chem. B* **2006**, *110*, 13608 – 13613.
[501] A. T. P. Carvalho, P. A. Fernandes, M. J. Ramos, *J. Comput. Chem.* **2006**, *27*, 966 – 975.
[502] X. Zhang, S. Y. Reddy, T. C. Bruice, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 745 – 749.
[503] N. Nakatani, J.-Y. Hasegawa, H. Nakatsuji, *J. Am. Chem. Soc.* **2007**, *129*, 8756 – 8765.
[504] J. Bergès, G. Rickards, A. Rauk, C. Houée-Levin, *Chem. Phys. Lett.* **2006**, *421*, 63 – 67.
[505] A. L. Bowman, L. Ridder, I. M. C. M. Rietjens, J. Vervoort, A. J. Mulholland, *Biochemistry* **2007**, *46*, 6353 – 6363.
[506] M. Roca, V. Moliner, J. J. Ruiz-Pernía, E. Silla, I. Tuñón, *J. Phys. Chem. A* **2006**, *110*, 503 – 509.
[507] T. H. Rod, P. Rydberg, U. Ryde, *J. Chem. Phys.* **2006**, *124*, 174503.
[508] P. Hu, Y. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 1272 – 1278.
[509] H.-B. Guo, H. Guo, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 8797 – 8802.
[510] S. Wang, P. Hu, Y. Zhang, *J. Phys. Chem. B* **2007**, *111*, 3758 – 3764.
[511] X. Zhang, T. C. Bruice, *Biochemistry* **2007**, *46*, 14838 – 14844.
[512] X. Zhang, T. C. Bruice, *Biochemistry* **2007**, *46*, 9743 – 9751.
[513] A. Soriano, R. Castillo, C. Christov, J. Andrés, V. Moliner, I. Tuñón, *Biochemistry* **2006**, *45*, 14917 – 14925.
[514] X. Zhang, T. C. Bruice, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 6148 – 6153.
[515] X. Zhang, T. C. Bruice, *Biochemistry* **2007**, *46*, 5505 – 5514.
[516] X.-F. Gao, X.-R. Huang, C.-C. Sun, *J. Struct. Biol.* **2006**, *154*, 20 – 26.
[517] Y. Cheng, Y. Zhang, J. A. McCammon, *Protein Sci.* **2006**, *15*, 672 – 683.
[518] M. Valiev, J. Yang, J. A. Adams, S. S. Taylor, J. H. Weare, *J. Phys. Chem. B* **2007**, *111*, 13455 – 13464.
[519] J. H. Alzate-Morales, R. Contreras, A. Soriano, I. Tuñon, E. Silla, *Biophys. J.* **2006**, *92*, 430 – 439.
[520] M. De Vivo, A. Cavalli, P. Carloni, M. Recanatini, *Chem. Eur. J.* **2007**, *13*, 8437 – 8444.
[521] T. Rungrotmongkol, A. J. Mulholland, S. Hannongbua, *J. Mol. Graphics Modell.* **2007**, *26*, 1 – 13.
[522] C. N. Alves, S. Martí, R. Castillo, J. Andrés, V. Moliner, I. Tuñón, E. Silla, *Chem. Eur. J.* **2007**, *13*, 7715 – 7724.
[523] C. N. Alves, S. Martí, R. Castillo, J. Andrés, V. Moliner, I. Tuñón, E. Silla, *Bioorg. Med. Chem.* **2007**, *15*, 3818 – 3824.
[524] N. Nunthaboot, S. Pianwanit, V. Parasuk, J. O. Ebalunode, J. M. Briggs, S. Kokpol, *Biophys. J.* **2007**, *93*, 3613 – 3626.
[525] I. L. Alberts, Y. Wang, T. Schlick, *J. Am. Chem. Soc.* **2007**, *129*, 11100 – 11110.
[526] L. Wang, X. Yu, P. Hu, S. Broyde, Y. Zhang, *J. Am. Chem. Soc.* **2007**, *129*, 4731 – 4737.
[527] A. Thomas, M. J. Field, *J. Am. Chem. Soc.* **2006**, *128*, 10096 – 10102.
[528] S. F. Sousa, P. A. Fernandes, M. J. Ramos, *J. Comput. Chem.* **2007**, *28*, 1160 – 1168.
[529] S. Kozmon, I. Tvaroška, *J. Am. Chem. Soc.* **2006**, *128*, 16921 – 16927.
[530] P. Lin, W. Yang, L. C. Pedersen, M. Negishi, L. G. Pedersen, *Int. J. Quantum Chem.* **2006**, *106*, 2981 – 2998.
[531] N. Kanaan, S. Martí, V. Moliner, A. Kohen, *Biochemistry* **2007**, *46*, 3704 – 3713.
[532] S. Pieraccini, M. Sironi, G. Colombo, *Chem. Phys. Lett.* **2006**, *418*, 373 – 376.
[533] J. Blumberger, G. Lamoureux, M. L. Klein, *J. Chem. Theory Comput.* **2007**, *3*, 1837 – 1850.
[534] T. Ishida, *Biochemistry* **2006**, *45*, 5413 – 5420.
[535] Q. Xu, H. Guo, A. Wlodawer, H. Guo, *J. Am. Chem. Soc.* **2006**, *128*, 5994 – 5995.
[536] H. Guo, A. Wlodawer, T. Nakayama, Q. Xu, H. Guo, *Biochemistry* **2006**, *45*, 9129 – 9137.
[537] K. Bravaya, A. Bochenkova, B. Grigorenko, I. Topol, S. Burt, A. Nemukhin, *J. Chem. Theory Comput.* **2006**, *2*, 1168 – 1175.
[538] Q. Xu, H.-B. Guo, A. Wlodawer, T. Nakayama, H. Guo, *Biochemistry* **2007**, *46*, 3784 – 3792.
[539] C. Oliva, A. Rodríguez, M. González, W. Yang, *Proteins Struct. Funct. Bioinf.* **2007**, *66*, 444 – 455.
[540] P. Vidossich, P. Carloni, *J. Phys. Chem. B* **2006**, *110*, 1437 – 1442.
[541] S. Saen-oon, O. Aruksakunwong, K. Wittayanarakul, P. Sompornpisut, S. Hannongbua, *J. Mol. Graphics Modell.* **2007**, *26*, 720 – 727.
[542] C. Corminboeuf, P. Hu, M. E. Tuckerman, Y. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 4530 – 4531.
[543] S. Ma, L. S. Devi-Kesavan, J. Gao, *J. Am. Chem. Soc.* **2007**, *129*, 13633 – 13645.
[544] M. Mladenovic, T. Schirmeister, S. Thiel, W. Thiel, B. Engels, *ChemMedChem* **2007**, *2*, 120 – 128.
[545] J. C. Hermann, L. Ridder, H.-D. Höltje, A. J. Mulholland, *Org. Biomol. Chem.* **2006**, *4*, 206 – 210.
[546] D. Xu, D. Xie, H. Guo, *J. Biol. Chem.* **2006**, *281*, 8740 – 8747.
[547] C. Wang, H. Guo, *J. Phys. Chem. B* **2007**, *111*, 9986 – 9992.
[548] D. Xu, H. Guo, Q. Cui, *J. Am. Chem. Soc.* **2007**, *129*, 10814 – 10822.
[549] D. Xu, H. Guo, Q. Cui, *J. Phys. Chem. A* **2007**, *111*, 5630 – 5636.
[550] N. Díaz, D. Suárez, T. L. Sordo, *J. Phys. Chem. B* **2006**, *110*, 24222 – 24230.
[551] C. Xiao, Y. Zhang, *J. Phys. Chem. B* **2007**, *111*, 6229 – 6235.
[552] S. Senapati, Y. Cheng, J. A. McCammon, *J. Med. Chem.* **2006**, *49*, 6222 – 6230.
[553] Y. Cheng, X. Cheng, Z. Radić, J. A. McCammon, *J. Am. Chem. Soc.* **2007**, *129*, 6562 – 6570.
[554] D. Gao, C.-G. Zhan, *Proteins Struct. Funct. Bioinf.* **2006**, *62*, 99 – 110.
[555] X. Biarnés, J. Nieto, A. Planas, C. Rovira, *J. Biol. Chem.* **2006**, *281*, 1432 – 1441.
[556] M. Dittrich, K. Schulten, *Structure* **2006**, *14*, 1345 – 1353.
[557] K.-Y. Wong, J. Gao, *Biochemistry* **2007**, *46*, 13352 – 13369.
[558] Y. Xiong, H.-T. Lu, Y. Li, G.-F. Yang, C.-G. Zhan, *Biophys. J.* **2006**, *91*, 1858 – 1867.
[559] J. Wu, D. Xu, X. Lu, C. Wang, H. Guo, D. Dunaway-Mariano, *Biochemistry* **2006**, *45*, 102 – 112.
[560] L. Yao, H. Yan, R. I. Cukier, *J. Phys. Chem. B* **2006**, *110*, 26320 – 26326.
[561] Q. Xu, H. Guo, A. Gorin, H. Guo, *J. Phys. Chem. B* **2007**, *111*, 6501 – 6506.
[562] L. Yao, R. I. Cukier, H. Yan, *J. Phys. Chem. B* **2007**, *111*, 4200 – 4210.

[563] M. De Vivo, B. Ensing, M. Dal Peraro, G. A. Gomez, D. W. Christianson, M. L. Klein, *J. Am. Chem. Soc.* **2007**, *129*, 387 – 394.
[564] D. Riccardi, P. König, X. Prat-Resina, H. Yu, M. Elstner, T. Frauenheim, Q. Cui, *J. Am. Chem. Soc.* **2006**, *128*, 16302 – 16311.
[565] T. Kamachi, T. Toraya, K. Yoshizawa, *Chem. Eur. J.* **2007**, *13*, 7864 – 7873.
[566] M. W. van der Kamp, F. Perruccio, A. J. Mulholland, *Proteins Struct. Funct. Bioinf.* **2007**, *69*, 521 – 535.
[567] M. W. van der Kamp, F. Perruccio, A. J. Mulholland, *J. Mol. Graphics Modell.* **2007**, *26*, 676 – 690.
[568] G. A. Cisneros, M. Wang, P. Silinski, M. C. Fitzgerald, W. Yang, *J. Phys. Chem. A* **2006**, *110*, 700 – 708.
[569] T. Tuttle, E. Keinan, W. Thiel, *J. Phys. Chem. B* **2006**, *110*, 19685 – 19695.
[570] T. Tuttle, W. Thiel, *J. Phys. Chem. B* **2007**, *111*, 7665 – 7674.
[571] E. Puig, M. Garcia-Viloca, À. González-Lafont, J. M. Lluch, *J. Phys. Chem. A* **2006**, *110*, 717 – 725.
[572] D. T. Major, K. Nam, J. Gao, *J. Am. Chem. Soc.* **2006**, *128*, 8114 – 8115.
[573] D. T. Major, J. Gao, *J. Am. Chem. Soc.* **2006**, *128*, 16345 – 16357.
[574] S. Donnini, G. Groenhof, R. K. Wierenga, A. H. Juffer, *Proteins Struct. Funct. Bioinf.* **2006**, *64*, 700 – 710.
[575] A. Dybala-Defratyka, P. Paneth, R. Banerjee, D. G. Truhlar, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 10774 – 10779.
[576] J. J. Ruiz-Pernía, E. Silla, I. Tuñón, *J. Phys. Chem. B* **2006**, *110*, 20686 – 20692.
[577] J. J. Ruiz-Pernía, E. Silla, I. Tuñón, *J. Am. Chem. Soc.* **2007**, *129*, 9117 – 9124.
[578] S. Sinnecker, M. Flores, W. Lubitz, *Phys. Chem. Chem. Phys.* **2006**, *8*, 5659 – 5670.
[579] M. Sugihara, J. Hufen, V. Buss, *Biochemistry* **2006**, *45*, 801 – 810.
[580] K. Bravaya, A. Bochenkova, A. Granovsky, A. Nemukhin, *J. Am. Chem. Soc.* **2007**, *129*, 13035 – 13042.
[581] K. Fujimoto, S. Hayashi, J.-y. Hasegawa, H. Nakatsuji, *J. Chem. Theory Comput.* **2007**, *3*, 605 – 618.
[582] A.-N. Bondar, J. C. Smith, S. Fischer, *Photochem. Photobiol. Sci.* **2006**, *5*, 547 – 552.
[583] Y. Sato, M. Hata, S. Neya, T. Hoshino, *J. Phys. Chem. B* **2006**, *110*, 22804 – 22812.
[584] K. Fujimoto, J.-y. Hasegawa, S. Hayashi, H. Nakatsuji, *Chem. Phys. Lett.* **2006**, *432*, 252 – 256.
[585] R. J. Trabanino, N. Vaidehi, W. A. Goddard III, *J. Phys. Chem. B* **2006**, *110*, 17230 – 17239.
[586] S. S. Patnaik, S. Trohalaki, R. R. Naik, M. O. Stone, R. Pachter, *Biopolymers* **2007**, *85*, 253 – 263.
[587] M. Kamiya, S. Saito, I. Ohmine, *J. Phys. Chem. B* **2007**, *111*, 2948 – 2956.
[588] B. Grigorenko, A. Savitsky, I. Topol, S. Burt, A. Nemukhin, *J. Phys. Chem. B* **2006**, *110*, 18635 – 18640.
[589] B. Grigorenko, A. Savitsky, I. Topol, S. Burt, A. Nemukhin, *Chem. Phys. Lett.* **2006**, *424*, 184 – 188.
[590] E. M. Sproviero, J. A. Gascón, J. P. McEvoy, G. W. Brudvig, V. S. Batista, *J. Chem. Theory Comput.* **2006**, *2*, 1119 – 1134.
[591] E. M. Sproviero, J. A. Gascón, J. P. McEvoy, G. W. Brudvig, V. S. Batista, *Curr. Opin. Struct. Biol.* **2007**, *17*, 173 – 180.
[592] M. A. Mroginski, F. Mark, W. Thiel, P. Hildebrandt, *Biophys. J.* **2007**, *93*, 1885 – 1894.
[593] M. Boero, T. Ikeda, E. Ito, K. Terakura, *J. Am. Chem. Soc.* **2006**, *128*, 16798 – 16807.
[594] S. D. Dalosto, *J. Phys. Chem. B* **2007**, *111*, 2932 – 2940.
[595] A. Fürstner, D. Kirk, M. B. Fenster, C. Aïssa, D. De Souza, C. Nevado, T. Tuttle, W. Thiel, O. Müller, *Chem. Eur. J.* **2007**, *13*, 135 – 149.
[596] S. M. Schwarzl, J. C. Smith, S. Fischer, *Biochemistry* **2006**, *45*, 5830 – 5847.
[597] B. L. Grigorenko, A. V. Rogov, I. A. Topol, S. K. Burt, H. M. Martinez, A. V. Nemukhin, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 7057 – 7061.
[598] B. L. Grigorenko, A. V. Nemukhin, M. S. Shadrina, I. A. Topol, S. K. Burt, *Proteins Struct. Funct. Bioinf.* **2007**, *66*, 456 – 466.
[599] H. te Heesen, K. Gerwert, J. Schlitter, *FEBS Lett.* **2007**, *581*, 5677 – 5684.
[600] D. Bucher, S. Raugei, L. Guidoni, M. Dal Peraro, U. Rothlisberger, P. Carloni, M. L. Klein, *Biophys. Chem.* **2006**, *124*, 292 – 301.
[601] D. Bucher, L. Guidoni, U. Rothlisberger, *Biophys. J.* **2007**, *93*, 2315 – 2324.
[602] Y. Liu, X. Hu, *J. Phys. Chem. A* **2006**, *110*, 1375 – 1381.
[603] Z. Cao, Y. Mo, W. Thiel, *Angew. Chem.* **2007**, *119*, 6935 – 6939; *Angew. Chem. Int. Ed.* **2007**, *46*, 6811 – 6815.
[604] Z. Moosavi-Movahedi, H. Bahrami, M. Zahedi, K. Mahnam, J. Chamani, S. Safarian, A. A. Saboury, A. A. Moosavi-Movahedi, *Biophys. Chem.* **2007**, *125*, 375 – 387.
[605] J. Chen, S. L. Flaugh, P. R. Callis, J. King, *Biochemistry* **2006**, *45*, 11552 – 11563.
[606] P. R. Callis, A. Petrenko, P. L. Muiño, J. R. Tusell, *J. Phys. Chem. B* **2007**, *111*, 10335 – 10339.
[607] A. Robertazzi, J. A. Platts, *J. Phys. Chem. A* **2006**, *110*, 3992 – 4000.
[608] N. Sundaresan, C. K. S. Pillai, C. H. Suresh, *J. Phys. Chem. A* **2006**, *110*, 8826 – 8831.
[609] M. V. Rogacheva, A. V. Bochenkova, S. A. Kuznetsova, M. K. Saparbaev, A. V. Nemukhin, *J. Phys. Chem. B* **2007**, *111*, 432 – 438.
[610] Y. A. Mantz, F. L. Gervasio, T. Laino, M. Parrinello, *Phys. Rev. Lett.* **2007**, *99*, 058104.
[611] M. Valiev, K. Kowalski, *J. Chem. Phys.* **2006**, *125*, 211101.
[612] K. Kowalski, M. Valiev, *Res. Lett. Phys. Chem.* **2007**, 85978.
[613] A. Robertazzi, J. A. Platts, *Chem. Eur. J.* **2006**, *12*, 5747 – 5756.
[614] A. Magistrato, P. Ruggerone, K. Spiegel, P. Carloni, J. Reedijk, *J. Phys. Chem. B* **2006**, *110*, 3604 – 3613.
[615] K. Spiegel, U. Rothlisberger, P. Carloni, *J. Phys. Chem. B* **2006**, *110*, 3647 – 3660.
[616] A. V. Vargiu, P. Ruggerone, A. Magistrato, P. Carloni, *J. Phys. Chem. B* **2006**, *110*, 24687 – 24695.
[617] T. Tuttle, E. Kraka, W. Thiel, D. Cremer, *J. Phys. Chem. B* **2007**, *111*, 8321 – 8328.
[618] J. Villà, A. Warshel, *J. Phys. Chem. B* **2001**, *105*, 7887 – 7907.
[619] P. A. Kollman, B. Kuhn, M. Peräkylä, *J. Phys. Chem. B* **2002**, *106*, 1537 – 1542.
[620] S. Martí, M. Roca, J. Andrés, V. Moliner, E. Silla, I. Tuñón, J. Bertrán, *Chem. Soc. Rev.* **2004**, *33*, 98 – 107.
[621] A. Warshel, P. K. Sharma, M. Kato, Y. Xiang, H. Liu, M. H. M. Olsson, *Chem. Rev.* **2006**, *106*, 3210 – 3235.
[622] T. C. Bruice, *Chem. Rev.* **2006**, *106*, 3119 – 3139.
[623] M. H. M. Olsson, J. Mavri, A. Warshel, *Philos. Trans. R. Soc. London Ser. B* **2006**, *361*, 1417 – 1432.
[624] M. H. M. Olsson, W. W. Parson, A. Warshel, *Chem. Rev.* **2006**, *106*, 1737 – 1756.
[625] D. Antoniou, J. Basner, S. Núñez, S. D. Schwartz, *Chem. Rev.* **2006**, *106*, 3170 – 3187.
[626] L. Pauling, *Chem. Eng. News* **1946**, *24*, 1375 – 1377.