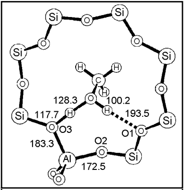
A recent development in computational chemistry: chemical reactions from first principles molecular dynamics simulations



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First-principles molecular dynamics simulations have recently been found an effective tool to study a large variety of chemical problems. Finite temperature simulations reveal unique information, including explicit dynamical effects and the evaluation of proper free energy differences. Moreover, dynamics simulations reveal information on the flexibility of molecular systems, and elucidate, often otherwise inaccessible, mechanistic details of chemical reactions. In addition this methodology allows the study of larger, periodic, systems, revealing computationally unique information which may be directly compared to experiments on realistic chemical systems. A variety of examples will be given, although most focus on the important field of catalysis.

1 Introduction

Over the last decade considerable progress has been made in the computational chemistry field, which now allows for the calculation, at the full quantum mechanical level, of realistic structures of both homogeneous and heterogeneous catalysts. As a result, we have seen a considerable growth in the number of theoretical papers in the scientific literature, with reviews available.[1–3]

One of the more recent developments is the application of the first principles (or ab-initio) Car-Parrinello (CP) Molecular Dynamics (MD) method[4] in chemistry. Excellent reviews are available.[5,6] The particular advantages of the Car-Parrinello method comprise (i) the capability to study large (100 atoms and more) systems on a regular basis, something which readily becomes unfeasible when applying traditional localised orbital methods, (ii) the study of periodic structures, of eminent relevance to, *e.g.*, zeolites and metal and supported catalysts, (iii) the possibility to perform simulations at finite, *i.e.* non-zero temperature, and (iv) the possibility to obtain free energy differences through MD simulation. The ability to study chemical reactions at finite temperature using first principles simulations is a unique feature. Moreover since all molecular motions are included in a natural way, free energy differences associated with a chemical reaction are computed more reliably. Computational times might be shortened, or very large systems can be studied, using a combination of quantum and classical (force field) methods, known as QM/MM, which has also been implemented with CP as the quantum method.[7]

The CP method is based on density functional theory (DFT), currently a very popular method for the study of many electron systems in both chemistry and solid state physics. The electrons are treated fully quantum mechanically, whereas the nuclei are treated classically. The ingeniousness of the CP method lies in the fact that dynamics of the atoms and associated wavefunctions are treated simultaneously. This makes the method ideally suited for the study of chemical reactions, during which the chemical bonding pattern changes drastically and for which the wavefunctions must be calculated on the fly. The current implementations of the CP method are based on a plane-wave basis method, since the method was originally designed for solids. This means that periodic boundary conditions are introduced and that the molecular system of interest is put in a box, which is repeated infinitely in all three dimensions, see Fig. 1. For a heterogeneous catalyst like a zeolite this is ideal, because the real system is also extended and periodic. For a

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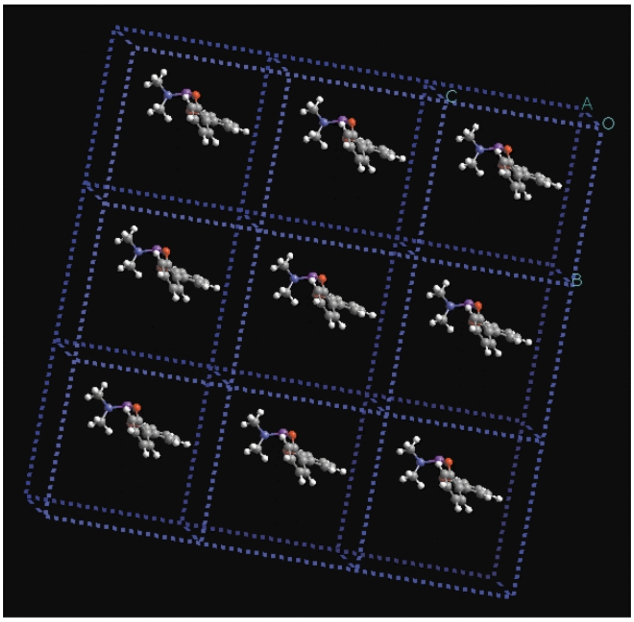


Fig. 1 Illustration of periodic boundary conditions as applied in a plane-wave based method. The molecules are put in a unit cell, as if we are dealing with a crystalline structure. For a homogeneous catalyst, as shown, some vacuum is present around the catalyst to minimize interactions between images in neighbouring cells.

homogeneous catalyst, the system in the box looks like depicted in Fig. 1, and care has to be taken that the interaction between images in neighbouring cells is minimal and does not influence structure and chemistry. Quantum calculations using a plane wave basis set and the other ingredients inherent to the CP method initially led to some scepticism among chemists on the appropriateness of such a basis set for molecular calculations and its relative accuracy. Since the first applications of the Car-Parrinello method in catalysis reported back in 1994,[8,9] this has now been largely overcome by many successful applications. It should be borne in mind, however, that wherever DFT fails, the CP method is likely to fail.

In this paper we review applications of the CP method in chemistry, but we have excluded polymeric and other materials properties as this would make up a story on its own. We will particularly focus on examples illustrating the explicit strengths of CP simulations: explicit dynamical features, free energy simulation, and the capability to study large extended systems. A significant fraction of the applications of the CP method in chemistry deal with the important field of homogeneous and heterogeneous catalysis. In view of its length, this review must be restricted to some characteristic highlights.

2 Method

Molecular dynamics simulations have become an indispensable tool in the characterization of molecular processes in complex systems. They can provide a window into the microscopic dynamical behaviour of the system and have become a well-established tool in chemistry, physics and biology. Classical trajectories of the atoms are obtained by solving the equations of motion. MD requires, however, the input of the inter-particle interactions. When this is done in a classical way, *i.e.* without solving the electronic many-body problem, one needs to introduce some kind of force field. Such methods are very well suited for large, *e.g.*, biological systems. For chemical reactions where the electronic pattern changes drastically, this is not realistic and the potential must be calculated on the 'fly' for each configuration of the atoms during the simulation. In 1985, Car and Parrinello[4] introduced an ingenious algorithm which is based on a generalized Lagrangian that combines the classical dynamics of the atoms and the electronic wavefunctions as introduced within the Density Functional Scheme. The time evolution of the wavefunctions is obtained by setting up a fictitious classical dynamics for the electronic degrees of freedom. In this way one obtains a set of coupled equations of motions for the ionic and electronic degrees of freedom and the potential is calculated in an *ab initio* way at each configuration of the nuclei, without performing a consuming DFT calculation at each time step.

Typical time scales that can be covered with *ab initio* Molecular Dynamics are limited to a few picoseconds, since the time step must be small to guarantee the adiabatic Born Oppenheimer approximation. Within the covered time frame, events with high or moderate barriers (>30 kJ mol^{-1}) occur sparsely or not at all. Most of the simulation time the system is spent in the more trivial places of phase space. A way to circumvent this problem is to introduce constraints on the reaction coordinate and thus to sample phase space in the vicinity of the Transition State. Such method has been successfully applied to generate free energy differences along the reaction path. This gives values for the entropy in better agreement with experiment. Moreover, a distinct advantage obtaining vibrational spectra from *ab initio* MD simulation is that anharmonicities, which is definitely relevant for weakly bonded systems including hydrogen-bonding, are inherently taken into account. The method of constraints works well provided the reaction coordinate can be well defined such as a single geometrical variable and provided the sampling frequency is high enough to prevent hysteresis in the free energy profile.

For very large systems, the CP method is still computationally too demanding, and several attempts have been introduced to extend the size of the system in a computationally attractive way. The combined quantum mechanics and molecular mechanics (QM/MM) method implemented into the Car-Parrinello scheme is becoming attractive for systems in which the chemical reaction occurs in a small part of the system. The smaller chemical active centre is described by a quantum mechanical method, while the larger part is taken into account by molecular mechanics methods. The QM/MM method implemented in the CP scheme has proven its success for various large systems occurring in transition metal catalysis and biological systems.[7]

3 Chemical applications of the Car-Parrinello method

3.1 Small molecule base chemistry

Reinhardt *et al.*[10] studied the influence of excess ammonia on the mechanism of the reaction of BCl_3 with ammonia with formation of boron nitride. From the CP MD simulations, other than from static simulations, excess ammonia could be taken into account in a straightforward manner. The simulations pointed to a reaction differing from a simple two-step gas-phase mechanism. The resulting reaction path is schematically shown in Fig. 2. From finite temperature MD simulations it was revealed that the reaction was very fast (picosecond range), and the free energy of reaction therefore quite small. This study nicely shows the unique features of a full MD simulation to model a chemical reaction including explicit solvent molecules on a fully quantum mechanical level.

3.2 Olefin polymerisation

Olefin polymerisation comprises an industrially and academically extremely important field of research. It might therefore not be surprising that one of the early applications of CP

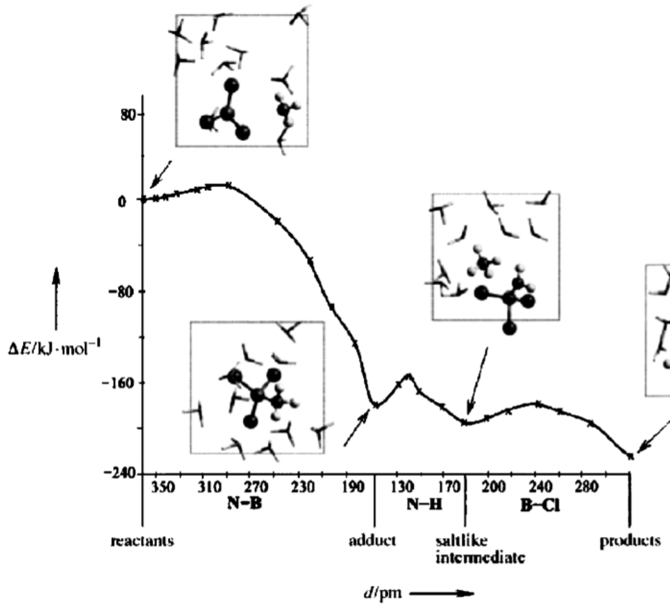


Fig. 2 Mechanism and constrained minimum energy path of the reaction of one BCl_3 molecule with eleven NH_3 molecules. The reaction proceeds in three steps: 1/formation of an adduct complex ($H_3N.BCl_3$ + $10NH_3$); 2/elimination of a proton to yield a salt-like intermediate ($[NH_4^+][BCl_3NH_2^-]$+$10NH_3$); 3/formation of the products (BCl_2NH_2 + NH_4Cl + $10NH_3$) by abstraction of a chloride anion. [Reproduced from ref. 10, with permission from Wiley-VCH.]

simulations in chemistry involved metallocene based ethylene polymerisation.[8] There are several theories to describe olefin polymerisation, with those due to Cossee and Brookhart/Green well-known. The latter involves agostic interaction in the insertion process. Fig. 3 displays on the left hand side the reaction profile in the form of the internal ethylene C=C bond length and the distance between one of the ethylene carbon atoms and the methyl carbon bonded to the metal centre in $(SiH_2)Cp_2ZrCH_3$ $(C_2H_4)^+$, revealing insertion of ethylene. The right-hand side plot of Fig. 3 displays the Zr–H distances for all three methyl hydrogens as a function of time. Note that an agostic interaction, characterised by one very short Zr–H distance, is formed *prior* to ethylene insertion. Another possibly noteworthy aspect revealed from these simulations is the

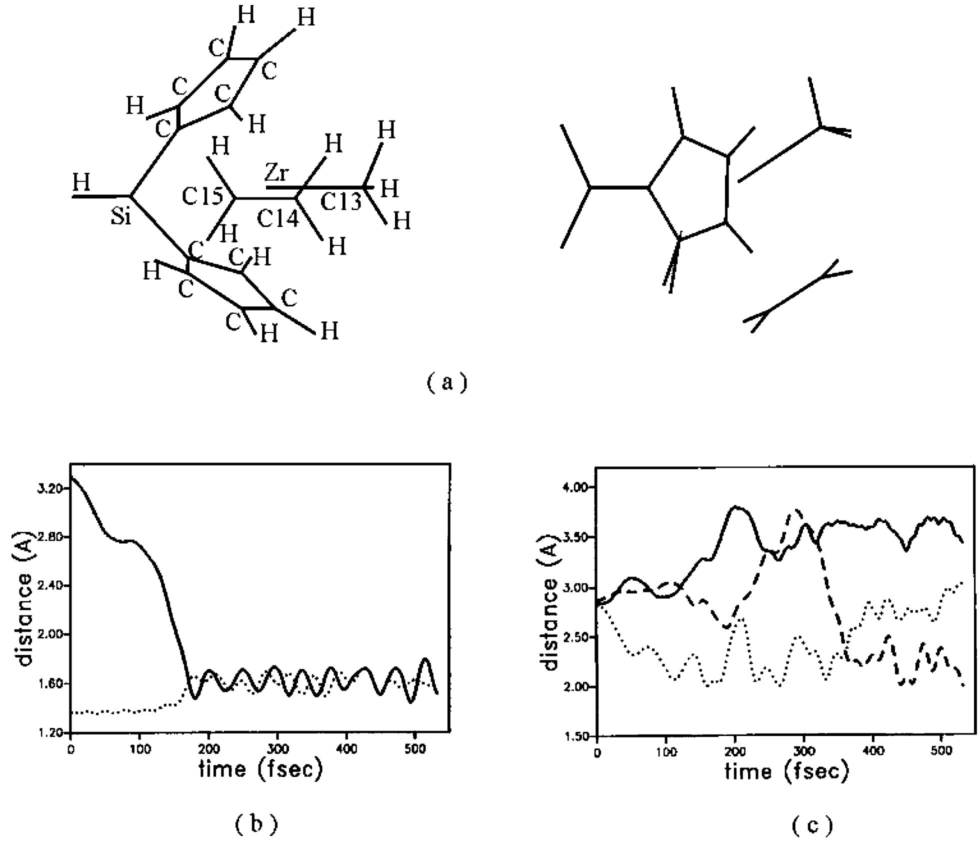


Fig. 3 (a) Structure of $(SiH_2)Cp_2ZrCH_3$ $(C_2H_4)^+$ complex. (b) Time-evolution of methyl/ethyl C–C distances during CP MD simulation. Solid curve represents distance between methyl carbon and nearest ethylene carbon (C13–C14). Broken line represents ethylene internal C–C bond length (C14–C15). (c) Time-evolution of the distance between the Zr atom and each of the methyl hydrogen atoms (original methyl bonded to Zr). The time-evolution of one of the hydrogen atoms (dotted curve) shows development of α-H agostic interaction. Later on (after about 450 femtoseconds) one of the other protons (broken curve) exhibits (γ-H agostic interaction).[8]

flexibility of the bis-Cp system; significant fluctuations in the Si–C–Cp angle have been observed from the simulations. These early results illustrate the potential of first principles dynamics simulations to show explicit dynamics effects and their relation to flexibility and stiffness of molecular species.

Ziegler *et al.* have, apart from extensive traditional DFT studies, applied CP simulations to obtain free energies for ethylene insertion and chain termination by β-hydrogen transfer in the metallocene $Cp_2Zr\ (C_2H_5)^+$.[11] From the dynamics it was revealed that the ethylene moiety is quite mobile throughout the reaction, and quite capable of dissociating from the metal center at 300 K. It was considered likely therefore that in solution complexed ethylene will partake in rapid exchange with solvent. Agostic interactions were found important, as they stabilize the transition states. The activation free energy for the hydrogen transfer termination reaction was computed markedly higher (35 kJ mol^{-1}) than for ethylene insertion (20 kJ mol^{-1}), which are numerically realistic values and in accordance with experiment that this catalyst is very active in polymerization.

The power of MD simulation was also noted explicitly when a simulation revealed a reaction pathway which is normally overlooked by static methods. A CP study of a Ti(IV) homogeneous catalyst revealed a path leading to the formation of a stable dihydrogen ligand at the Ti(IV) center,[12] see Fig. 4. Experimentally indeed some metallocenes do give rise to H_2 production under certain polymerisation conditions.

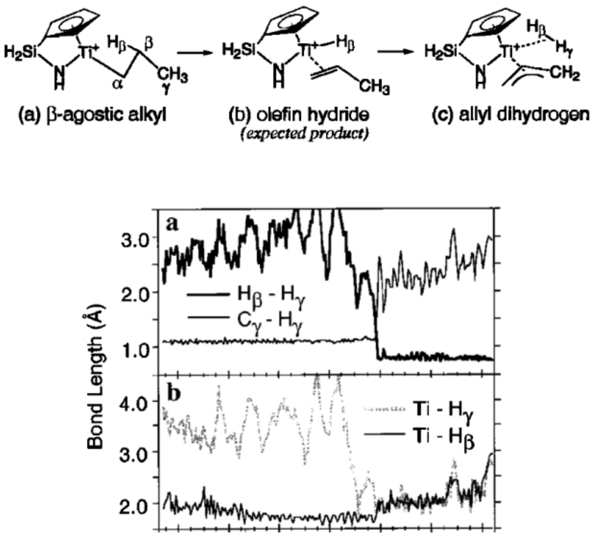


Fig. 4 Characteristic bond lengths as a function of the Reaction Coordinate (RC). Onset of dihydrogen formation at RC ≈ 1.6 Å. The reaction coordinate is defined as the distance between the β-carbon and the centroid of the two β-hydrogen atoms [Reproduced from ref. 12, with permission from the American Chemical Society.]

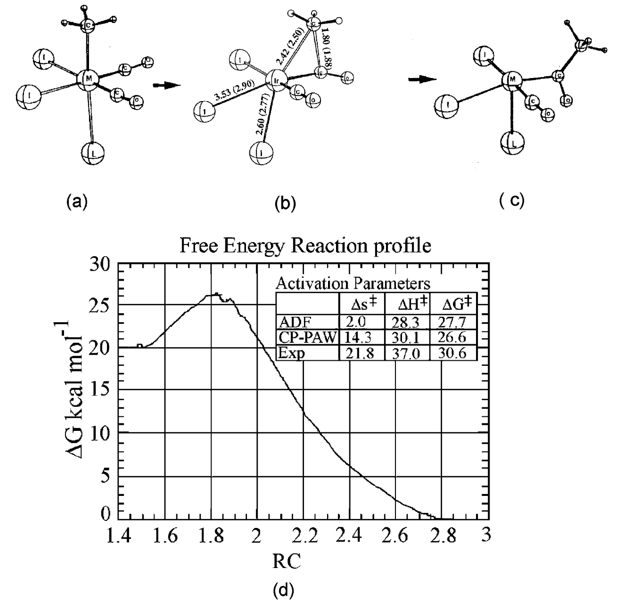
Recently prepared homogeneous aluminium based catalysts, tested for olefin polymerisation, were studied with the CP method. Quite interestingly, it was corroborated that explicit account of finite temperature effects, leading to a deformation of a dinuclear structure and a corresponding lowering of the insertion barrier, was necessary to explain the experimentally observed polymerisation behaviour.[13]

Heterogeneous Ziegler–Natta type catalysts have been studied in the form of $Ti/MgCl_2$ supported systems.[14–16] A 5-fold coordinated Ti-site was found capable of polymerizing both ethylene and propylene. As for the homogeneous catalysts, agostic interactions were found crucial. However, further ethylene additions made the growing polymer chain drop along the substrate, leaving one side of the active center unshielded, and ruling out the flip-flop mechanism usually assumed for homogeneous catalysis. Thus, the CP method, in practical computations being able to treat larger, periodic, systems, helped to reveal such interesting mechanistic differences. In addition, the (100), (110) and (104) $MgCl_2$ surfaces were compared. $TiCl_4$ failed to stick to a (100) surface. Stable $TiCl_4$ geometries only occurred on the (110) surface. Ti_2Cl_6 species have been suggested as active species, but the CP simulations revealed that whereas these dinuclear complexes formed a vary stable geometry on the surface, do not remain stable during polymerization.

3.3 Homogeneous catalysis

Enantio-selectivity is of extreme importance in the production of many fine chemicals, and therefore asymmetric hydrogenation, amination, *etc.*, are therefore crucial chemical reaction steps. Blöchl and Togni reported[17] on asymmetric allylic amination with Pd complexes. The system studied was, certainly for the mid-ninety-nineties, of very considerable size. Asymmetric catalysis offers a great challenge to computations as systems often comprise more than 100 atoms, and energy differences are in the kJ mol^{-1} range. This study revealed that, for the system of interest, enantioselectivity results from an interplay of electronic and steric effects. In this case CP MD calculations enable the study of large systems on a fully quantum mechanical basis, which is required to appropriately study enantioselectivity.

The migratory insertion step in the carbonylation of methanol catalysed by $[IrCO)_2I_2]^-$ has been studied by both static and CP MD simulations.[18] The reaction is shown in Fig. 5, along with the free energy reaction profile obtained from MD simulation. Interestingly, whereas the enthalpy differences for static and dynamic simulations are pretty close, the entropy differences are quite different. Importantly, the MD derived value is in much better agreement with experiment (see inset in Fig. 5). The reason for this was found in significant differences in bond lengths at the transition state as obtained from static and the T = 300 K dynamics simulations, respectively (see Fig.5). Time-averaged, one of the Ir–I bonds is considerably longer (3.53 Å) at T = 300 K compared to the static calculations (2.90 Å). Although the final free energy differences are not that different (inset in Fig. 5), the MD results reveal that the reaction is entirely driven by entropy changes.



	Δs‡	ΔH‡	ΔG‡
ADF	2.0	28.3	27.7
CP-PAW	14.3	30.1	26.6
Exp	21.8	37.0	30.6

Fig. 5 (a), (b), (c): Key structures in the migratory insertion process. (b) Optimized structures for the migratory insertion transition state TS[2–3] involving $[Ir(CO)_2I_3(CH_3)]^-$. Number in parentheses are from static DFT calculations. Numbers outside of parentheses are average values around the maximum on the free energy profile (d). All distances are in Å. [Reproduced from ref. 18 with permission from the American Chemical Society.]

A highly interesting class of ruthenium-carbene olefin metathesis catalysts is due to the Grubbs group. A detailed experimental study on the catalyst $Cl_2(PCy_3)_2Ru{=}CHPh$ to investigate the mechanism of olefin metathesis clearly indicated that the most active species is a mono-phosphine complex, the bis-phosphine complex being less active, and Scheme 1 the most probably pathway.

A CP-based simulation study[19] on $Cl_2(PH_3)_2Ru{=}CH_2$ and its mono-phosphine counterpart $Cl_2PH_3Ru{=}CH_2$ started from the recognition that molecules undergo a chemical reaction when they have sufficient energy to overcome the activation energy for that reactive process. In an ensemble of molecules, a non-negligible fraction has molecular speeds 2–2.5 times the average speed, and therefore 4–6 times the average kinetic energy. Thus, higher temperature MD simulations could help to unravel the chemistry of reactive molecules. By applying this approach the intimate details of the above reaction mechanism were observed including, in order of appearance, relative easiness of Cl–Ru–Cl *cis–trans* configurational exchange, carbene rotation and loss of one phosphine, formation of a metallacyclobutane intermediate, and finally completion of the metathesis reaction. The presence of a fraction of the mono-phosphine complex was confirmed by simulations, *i.e.* a phosphine group was lost at higher temperatures, and the higher activity of the mono-phosphine system compared to bis-phosphines complexes could be rationalised.

3.4 Heterogeneous catalysis

This field includes supported catalysts, zeolites, and metal catalysts. We have already given an example from the first class in olefin polymerisation, and will now discuss examples of the other types.

Zeolites are microporous alumino-silicate structures with many applications in the chemical industry as heterogeneous acid catalysts. They contain Brønsted OH groups, $SiO(H)Al(OSi)_3$, which represent the active sites and are capable of activating chemical bonds. Owing to the variety of the (alumino)silicate framework and the associated shape and size of micropores, as well as the number of reactions occurring in the cavities, the mechanisms of most processes are far from being understood. For such disordered systems with a periodic structure, the CPMD technique is more suitable than previously adopted cluster approaches that can only take into account part of the zeolite. It has been shown that the cluster size can affect the acidity of the zeolite[20] since these models ignore the long range electrostatic potential. The main objectives of CPMD simulations on zeolites can be grouped as follows (i) static (geometry and electronic structure) and vibrational properties (ii) chemical reactivity and catalysis (iii) host–guest interactions. In the following we will give some typical examples.

CPMD *ab initio* Molecular dynamic simulations are ideally suited to reveal energetic and structural information on the catalyst at finite temperatures. For systems where experimental data is available, such as (NaCl-SOD), in general excellent agreement is found between the simulated geometrical parameters and the experimental values.[21] A particularly interesting case is offretite, a zeolite exhibiting a very small unit cell. A correlation was established between the (Al/H)//Si substitution energy and site proton affinity, with the most stable sites being those having the highest proton affinity or lowest acidity.

For reactivity a particular interesting case is Methanol to Olefin conversion , a fundamental process for the production of fine chemicals. From experiment it was not clear how the specific interaction of small molecules like methanol with the zeolite framework influences the reaction route. This topic was studied by *ab initio* molecular dynamics techniques on the absorption of methanol molecules in low-aluminium sodalite cages.[22] The MD simulations revealed unique information about the crucial catalytic step, *i.e.* the nature of the hydrogen-bond connecting the Brønsted acid site of the framework and the methanol molecule and the corresponding proton transfer. It was found that at low coverage the methanol molecule does not protonate noticeably, but forms strong hydrogen bonds with the acid site of the zeolite framework (see Fig. 6). At higher coverage and finite temperatures of about 500 K, typical experimental operating conditions, the acid-site proton is transferred to the nearest methanol and is effectively shared among various methanol molecules. At such conditions the acid-catalyzed reactions in zeolites are expected to follow reaction mechanisms similar to those in a highly acidic solution, and the main role of acid sites is that of a strong Brønsted acid. In the same study the vibrational spectrum was distracted from the velocity autocorrelation function. The advantage of evaluating molecular vibrational spectra from *ab initio* MD simulation was discussed in the Methods section. It was found that the proton transfer between two OH groups, a process that typically occurs in the femto-second time scale, is influenced by the dynamics of the zeolite framework. For hydroxo-sodalite doped with ^{28}Si and ^{30}Si, it was observed that the relaxation of the proton exchange in the zeolite cavity is influenced by the differences of relaxation and oscillations of the framework atoms, associated with isotopic exchange. Such typical explicit dynamical solvent effects can be studied using a first principles MD method since it can provide dynamics at the microscopic scale and accounts for the periodic structure of the framework in an accurate way.[21]

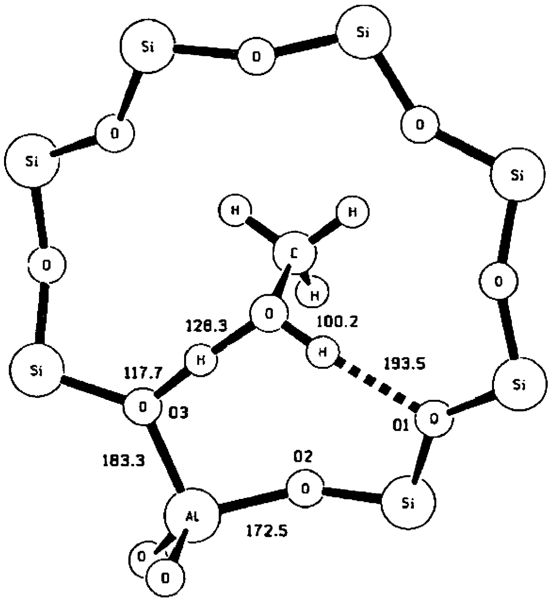
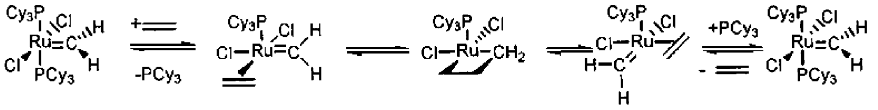


Fig. 6 Equilibrium geometry of the physisorbed complex of methanol in chabazite with acid-site proton at the O3 oxygen position. Selected bond distances are given in pm. [Reproduced from ref. 23 with permission of Elsevier Science.]

The adsorption of small molecules such as CO and NO on metal study has been the subject of quite a few studies,[24] either



Scheme 1

using the cluster approach or using periodic codes to simulate a real surface. In particular the adsorption of CO on Pt has been and still is the subject of debate. It is well-known, from in-depth experimental studies, that small molecules including H_2 exhibit sticking probability depending on kinetic energy and rotational excitation. More recently computational studies have been reported in which the adsorption dynamics was simulated based on a first principles derived potential energy surface.[25,26] Differences between a pure H_2/Pd(111) surface and the H_2/Pd+subsurface V could be rationalised.

An absolutely fascinating development is the application of CP calculations in the prediction of optimum catalytic activity for several classes of heterogeneous catalysis, most commonly comprising two elements. The studies by Nørskov *et al.*[27] and Toulhoat *et al.*[28,29] suggest a computational way to predict the so-called volcano plot, which in turn is related to the Sabatier principle, by first principles calculations. According to the Sabatier principle, a too weak heat of adsorption of a species to the surface of the catalyst will not be sufficient to cleave the necessary bond(s) in the reactant, whereas a too high heat of adsorption will poison the catalyst, as release of a species from the surface is made energetically difficult. So optimum catalytic activity corresponds to an intermediate, or moderately strong, reactant–catalyst interaction. When catalytic activity is plotted *versus* the relevant bond strength, a vulcano shaped plot results as illustrated in Fig. 7. Using first principles calculations this bond strength can be evaluated in a more or less straightforward manner. New highly active catalysts can now be predicted by calculating this bond strength for a series of new systems, and selecting those which have the optimum bond strength. Although successful examples are very limited still, this approach seems to have a high potential regarding predictive power, as it is based on the old well-recognised Sabatier principle.

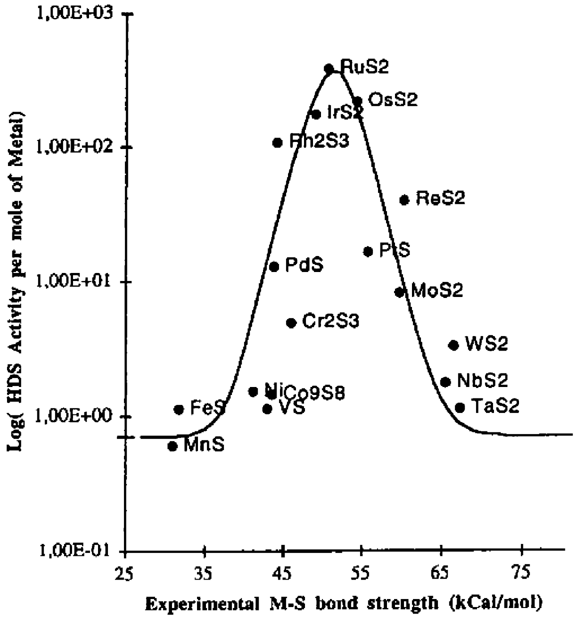


Fig. 7 Experimental specific activities in dibenzothiophene (DBT) hydrodesulfurization (HDS) *versus* M–S bond strengths of transition metal sulfides (black dots). The solid line is a fit of a kinetic model assuming a heterolytic mechanism for HDS. Experimental end calculated cohesive energies are in very good agreement, with a linear regression Ec GGA = 1.03 Ec exp +0.04 (R = 0.99). [Reproduced from ref. 30, with permission of Elsevier Science.]

3.5 Polymorphism

Polymorphs are very important in the pharmaceutical industry. Their relative stabilities are of eminent important in the production process of certain fine chemicals. As this is often trial and error, computational leads would be really helpful. Rovira and Novoa studied the low-energy polymorphs of acetic acid using first principle CP simulations.[31] Only the zone center of the Brillouin zone, the so-called (Γ-point, was considered. The results were compared to relative stabilities obtained through the UPACK polymorph predictor program in conjunction with the GROMOS force field. Experimental energies are only reproduced well when a correction to the DFT energy is added (R^{-6} dispersion), but this term was not necessary to recover the order of stability of the lowest energy polymorphs. Importantly, compared to experimental information, the CP simulations revealed the right polymorph as the most stable one. This structure ranked 15 in the UPACK/GROMOS simulations, however. First principles optimization of this too densely packed UPACK/GROMOS structure was found to expand and transform to the low energy first principles structure. This work thus clearly revealed an advantage of first principles simulation compared to traditional, much practised, force field approaches.

3.6 Biochemical related applications

The status and perspective of CPMD calculations in biological systems has been reviewed.[32] Already in 1996 Parrinello and co-workers showed the feasibility of studying *large* systems with the first principles CP MD method. A hydrated RNA duplex structure consisting of 368 atoms containing the basic ingredients regarding the stability of the nucleic acid helix was studied.[33]

Recently, HIV-1 protease was studied by Piana *et al.*[34] It is one of the main targets for a therapy for AIDS. The peculiar conformation of the active side, more specifically the catalytic Asp dyad, was studied. It was argued that classical MM/MD studies on this system often involved *ad hoc* assumptions or a *posteriori* models. Current first principles studies were expected to be capable of providing direct detailed and unbiased insight. The study revealed that the peculiar Asp dyad structure is due to interaction of the aspartyl negative charge with a Thr-Gly dipole moment, along with a low-energy barrier hydrogen bond. Polarization forces and temperature effects were also found important factors. Finally, the interpretation of NMR studies was criticised as being non-consistent with a number of other observations.

Most antiherpes therapies use the substrate acceptance of herpes simplex virus thymidine kinase. Sulpizi *et al.* performed calculations on a series of ligands representing sugar-mimicking moiety.[35] In the same work experimental results were reported. The fundamental questions addressed were related to the nature of the interactions between the ribose-like moiety and the enzyme. This study revealed a correlation, *viz.* Fig. 8, between the dipole moment of the sugar-mimicking ligand and the rate constant associated with the phosphorylation reaction. Moreover, in particular the interaction between this named dipole moment and the negative charge of the Glu^{225} residue was found a critical factor for this reaction. These studies show the high potential of these first principles studies towards eminent questions in biochemistry.

4 Conclusions and outlook

The first principle molecular dynamics method, as was proposed by Car and Parrinello, originates from the solid state community but has proven to be a potentially successful method within chemistry. This is illustrated in this paper by some typical chemical examples from olefin polymerisation, homogeneous and heterogeneous catalysis, polymorphism and some biochemical applications. The chosen examples particularly show the strengths of the method such as accounting for explicit

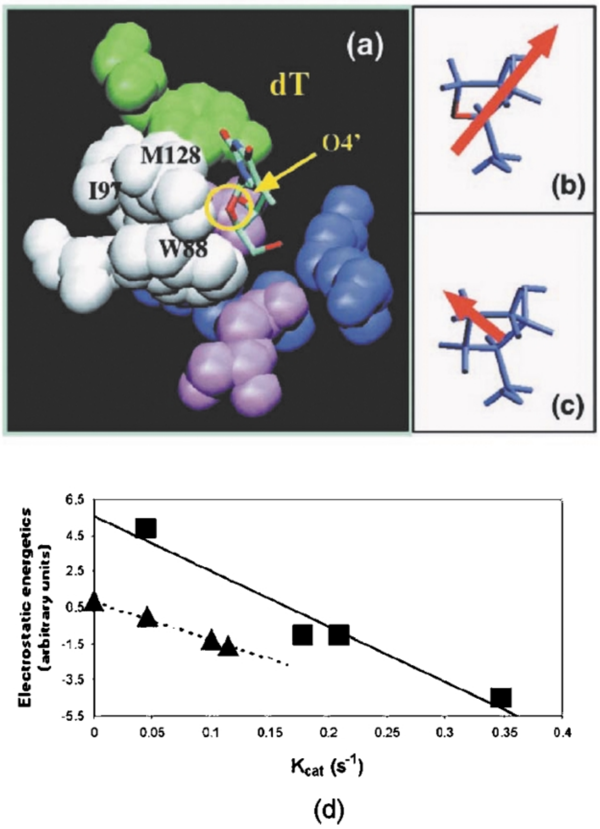


Fig. 8 (a) Dt-TK$_{HSV1}$ complex. Orientation of O-4′ in its hydrophobic pocket. (b) and (c), sugar (b) and methylene derivative (c) electric dipoles. (d) Correlation between k_{cat} and the sugar-moiety-dipole-Glu^{225} electrostatic energy (electrostatic energetics). Thymine and guanine derivatives are displayed as squares and triangles, respectively. Linear fits are also plotted (R^2 values of thymine and guanine are 0.954 and 0.994, respectively). [Reproduced from ref. 35 with permission from the American Society for Biochemistry and Molecular Biology.]

dynamical properties, free energy simulations and the potential to study large systems. Despite its success it must be born in mind that the method has its limitations in covering large timescales and studying highly activated processes. On the other hand the method succeeds in simulating extended systems which can not be handled by traditional localized orbital methods.

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