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Ab initio and semi-empirical Molecular Dynamics simulations of chemical reactions in isolated molecules and in clusters

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Recent progress in "on-the-fly" trajectory simulations of molecular reactions, using different electronic structure methods is discussed, with analysis of the insights that such calculations can provide and of the strengths and limitations of the algorithms available. New developments in the use of both *ab initio* and semi-empirical electronic structure algorithms are described. The emphasis is on: (i) calculations of electronic properties along the reactive trajectories and the unique insights this can contribute to the processes; (ii) electronic structure methods recently introduced to this topic to improve accuracy, extend applicability or enhance computational efficiency. The methods are presented with examples, including new results, of reactions of both isolated molecules and of molecules in media, mostly clusters. Possible future directions for this fast growing field are suggested.

I. Introduction

The introduction of classical trajectory calculations in studies of molecular reaction dynamics is a major landmark in the field. This has provided understanding and remarkable insights into the way that reaction processes occur in terms of the motions in time of the atoms involved. The approach has contributed greatly to the development of experimental methods ranging from molecular beams to femtosecond pulsed-laser studies of reaction dynamics. Since the early applications to simple gas-phase reactions, *e.g.* H + H_2, the approach has been extended enormously to processes that include reactions in macromolecules and in condensed phases. The neglect of quantum effects is, of course, an important problem. Arguably, classical trajectory simulations are at present the main computational method for treating molecular reaction dynamics. However, for most reactions at ambient temperatures, classical dynamics typically

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offer a very good approximation often, though not always, of quantitative accuracy.

The main obstacle in applying the classical trajectory approach has been the need for potential energy surfaces of sufficient accuracy. Thus, developing adequate empirical force fields for processes that involve bond breaking or bond making is an exceedingly difficult task. That being said, recent developments in the field of reactive force fields show promise in accurately describing bond formation and breaking.[1] For this reason, the advent of *Ab Initio* Molecular Dynamics (AIMD) holds major promise and implications for studies of reaction processes. Since the seminal paper by Car and Parrinello[2] in 1985 that combined density function theory (DFT) with classical molecular dynamics (MD) simulations, the Car–Parrinello Molecular Dynamics (CPMD) algorithm has become an immensely popular method for performing classical trajectory calculations from first-principles potentials. Since then, a vast number of applications were pursued, and a variety of different approaches and variants have been proposed.[3] As one example, only of a very different algorithm, we mention the Born–Oppenheimer molecular dynamics (BOMD) method.[4] The first applications of AIMD did not address molecular reactions, but topics such as structure optimization, isomerization of molecules and structural changes in clusters or solutions, energy transfer, *etc.* In due course, many applications to chemical processes were made. Thus, CPMD has been applied to a large variety of chemical reactions, including classical organic chemistry reactions,[5] proton transfer reactions,[6,7] reactions on metal surfaces,[8] in aqueous solutions,[9] and organometallic catalysis,[10] to name but a few. Likewise, BOMD has been applied to many chemical processes.

The great majority of AIMD simulations carried out so far have employed for the electronic state DFT with functionals of the Generalized Gradient Approximation (GGA)[11] type, such as BLYP, BP86, PBE and HTCH. While these approximations are very successful in a range of applications, there are many chemical reactions that cannot be adequately treated by such electronic structure methods. Depending on the nature of the process, GGA functionals may be inapplicable or suffer from insufficient accuracy. However, there are certainly types of reactions in which these functionals can provide, at least, qualitative insight. To mention one example, DFT/GGA cannot treat homolytic bond breaking, a large and important class of chemical reactions.

With this motivation, one of the main themes of this Perspective article will be MD with other electronic structure methods that can address certain classes of chemical processes with significant advantages over GGA. There is, of course, no practical electronic structure method at the present time capable of describing all the types of chemical reactions. However, it should be possible to make major progress by identifying methods that work well for specific classes of reactions. We will comment briefly on a number of such methods, but will focus on a few of these in some detail. Thus, attention will be given to MD-MP2, in variants that are particularly advantageous for treating charge transfer reactions in water, and to a multi-reference algorithm

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that seems successful in treating processes in which a significant di-radical character is manifested. These methods will be presented with examples that bring out the advantages, and also the limitations, of the algorithms in each case.

An altogether different challenge to AIMD simulations in the present state of the art are the computational limitations. The CPMD and CP2K code packages[3] for Car–Parrinello simulations are powerful and efficient. However, the gap with computational speed for empirical force fields remains enormous. It is highly desirable to be able to treat larger systems, to carry out simulations for much longer timescales, and to run a larger number of trajectories for a given process. Analysis of product state distributions, for example, is of great interest for many reactions, and it requires running many trajectories for good statistics. In this Perspective article, we will examine SEMD, molecular dynamics with semi-empirical potentials, as a possible alternative to AIMD in some such cases. A number of semi-empirical electronic structure methods are expected to be valid for certain reactions. Validation of the method for such cases is essential, but this is a frontier that in our view holds great promise, and its development is still at relatively early stages.

Finally, the third major theme of this article is the calculation of electronic properties along AIMD or SEMD reactive trajectories. This provides an approach for determining observables such as ultrafast electronic spectroscopy of reactive processes, but it also has tremendous value simply through providing additional insights into the dynamics of the processes. Calculation of the partial charges of the participating atoms as a function of time is one of the possible sources of insight, and there are many others. Again, it is our impression that this direction has not been sufficiently explored so far.

The paper is structured as follows: Section II deals with calculations using MP2 on-the-fly for reaction processes. Section III addresses direct trajectory calculations for systems requiring multi-reference electronic wavefunctions. Section IV describes SEMD simulations. In Section V, calculations of electronic properties along trajectories of reactive processes are discussed. Concluding remarks, with a view to possible future directions, are brought in Section VI.

II. Direct Molecular Dynamics with MP2 potentials (MD-MP2)

Early applications of MD-MP2 date from over 10 years now. The method was used to study the formation[12] and protonation of nitric acid,[13] as well as related systems;[14] photodetachment of an anion complex, $(F^-)(H_2O)_4$,[15] S_N2 reactions;[16] unimolecular dissociation of H_2CO and related molecules;[17,18] abstraction reactions of H atoms[19] and a few others. As the merits of MP2 in MD calculations became increasingly recognized, many more applications of the method were reported, including additional studies of nitric acid formation;[20–24] ionization dynamics (and the reverse process of electron capture);[25–31] S_N2 reactions;[32–34] dynamics in the transition state region, also in the context of unimolecular reactions;[35–38] hydrogen atom abstraction and elimination reactions[39–44] and a host of other processes. In the last several years, the use of MD-MP2 has become quite extensive, especially for polyatomic systems of small to moderate sizes.

We consider as an example a most recent MD-MP2 study that demonstrates the reaction of $ONONO_2$ in an environment of 4 water molecules, leading to the simultaneous formation of nitric acid, HNO_3, and nitrous acid, HONO.[45] This reaction is of considerable atmospheric interest, as it is part of a proposed mechanism for the formation of HONO in the atmosphere.[46] This example will help illustrate the merits of MD-MP2 for yielding insights into charge transfer reactions of molecular species in water.

In a study of formation and isomerization of N_2O_4 Liu and Goddard[47] found that with density functional theory, specifically the B3LYP functional, the ion pair isomer $(NO^+)(NO_3^-)$ is a minimum of the potential surface, while at the CCSD(T) level of theory this structure is a transition state. However, MP2 reproduced this portion of the N_2O_4 potential surface in qualitative agreement with the higher level of theory. As the ion pair species has been proposed as an intermediate in the reaction of $ONONO_2$ with water,[46] this is an example of a process for which the incorrect description by a more standard method for AIMD, B3LYP, necessitates replacement with MP2.

A combined experimental and theoretical study of $(NO^+)\cdot(H_2O)_n$ clusters revealed a water configuration that promoted the reaction resulting in the formation of HONO for $n = 4$.[48] This, and a related study on the prediction of the vibrational spectra of $(NO^+)\cdot(H_2O)_3$ isomers from AIMD simulations,[49] demonstrated the ability of MP2 in conjunction with a double-zeta basis set including diffuse functions to describe the shared nature of the protons in these clusters as indicated by a large redshift in the OH stretch. One isomer, in which the nitrogen atom of the NO fragment interacts with the oxygen atoms of two neighboring water molecules, was found to present a challenge. Additional correlation at the CCSD level was required for a correct description of the NO stretch.

Test calculations showed that there is no significant loss in accuracy by using the RI-MP2 instead of MP2. However, additional calculations were carried out to guide selection of an appropriate method for simulations described below, it was found that a double-zeta basis set with diffuse functions, as well as MP2 with scaling of the opposite-spin component (SOS-MP2), were required for a qualitatively correct and more accurate description of the relevant portion of the $ONONO_2\cdot(H_2O)_4$ potential surface.[45] At this level each gradient step took an average of 3 to 4 minutes on four processors, or roughly 5 days per ps.

Based on the water configuration that promotes HONO formation in $(NO^+)\cdot(H_2O)_4$ isomers, a reactive $ONONO_2\cdot(H_2O)_4$ isomer was identified. From this structure, a transition state in which the reacting water inserts between the NO and NO_3 fragments of $ONONO_2$ was also identified. This allows for simultaneous formation of HONO, through combination of NO^+ and OH^-, and nitric acid, through proton transfer to NO_3^-. The transition state structure is presented in Fig. 1(b). Initial velocities were assigned based on a temperature of 50 K

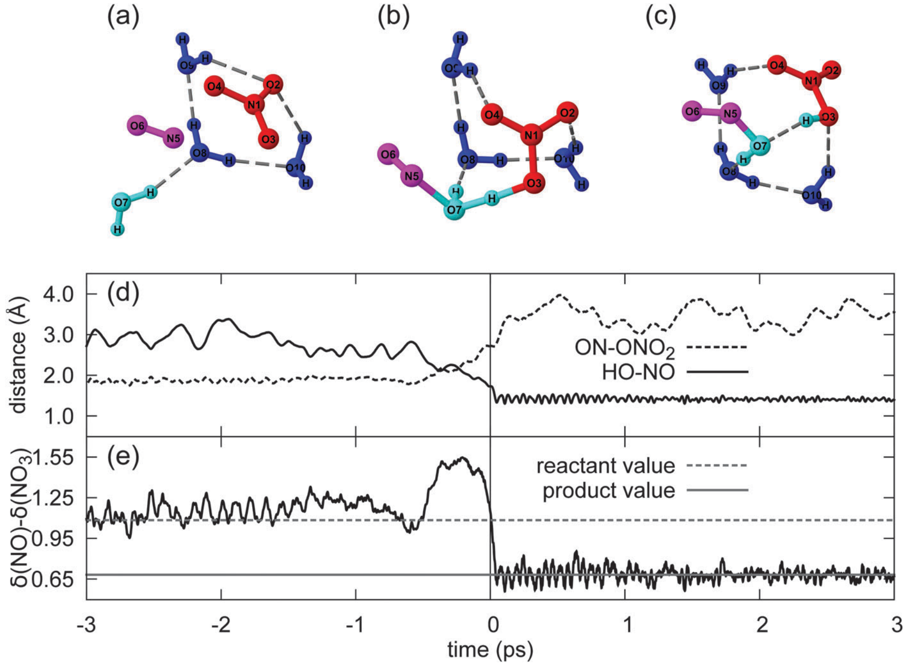

Fig. 1 MD-SOS-MP2 results for the reaction of $(NO^+)(NO_3^-)$ with $(H_2O)_4$ to form HONO + HNO_3: structures of (a) the reactant cluster at −2 ps, (b) the transition state at 0 ps and (c) the product cluster at 2 ps are included with the NO fragment in magenta, the NO_3 fragment in red, the solvating waters in dark blue and the reacting water in a lighter blue; (d) shows distances in time and (e) shows difference in time between partial charges on NO and NO_3 groups.

to examine the system in a state with sufficient energy to overcome the reaction barrier, but without large excess kinetic energy. The velocities were propagated with a 20 au timestep using the Leapfrog Verlet algorithm as implemented in the Turbomole program package.[50] The velocities were also reversed and propagated so that reformation of the reactant cluster, in addition to formation of products, could be monitored. Structures extracted at −2 ps and 2 ps are presented in Fig. 1 as images (a) and (c), respectively.

Fig. 1(d) includes a trace of the ON–ONO_2 distance, *r*(N5–O3), revealing association/dissociation of the $ONONO_2$ reactant. Inclusion of the HO–NO distance, *r*(O7–N5), shows the proximity of the reacting water and the NO fragment on the reactant side, −3 to 0 ps, and the formation of HONO on the product side, 0 to 3 ps. The proposed role of an $(NO^+)(NO_3^-)$ ion pair in the reaction prompted the use of partial charges in monitoring the progress of the reaction in addition to bond distances. The difference in the partial charge on the NO fragment and the partial charge on the NO_3 fragment, $\delta(NO) - \delta(NO_3)$, is plotted in Fig. 1(e).

In the transition state structure, at $t = 0$, the *r*(O7–N5) distance between the reacting water and the NO fragment which is just under 2 Å, is approximately equivalent to the *r*(N5–O3) distance between the NO fragment and the NO_3 fragment in the reactant cluster. The charge separation at the transition state, $\delta(NO) - \delta(NO_3) = 1.15$, is also quite similar to the reactant value, $\delta(NO) - \delta(NO_3) = 1.08$. The insertion of the reacting water supports a charge separation similar to that in minimum energy $ONONO_2$ structure. As the reacting water drifts out of this position between 0 and −0.2 ps, the charge separation increases to a maximum of nearly 1.55. This transient species with the NO fragment nearly equidistant from the neighboring water and the NO_3 fragment is not a true ion pair, which would have a charge separation of 2, but does demonstrate the role of a charge-separated species in this process.

On the product side, the HO–NO bond distance and the charge separation drop quickly to the values of the product cluster. From this transition state nitrous and nitric acids form simultaneously. An alternate transition state for the NO^+ and OH^- association with proton transfer to the solvating water to form H_3O^+ was also identified. However, this may be followed by proton transfer along a ''water wire'' yielding nitric acid shortly thereafter.

Several arguments suggest merits of MD-MP2 for a class of related systems, beyond the specific example presented above. MP2 seems to be very successful for water clusters, and for polar molecules in water clusters. Over-binding can be a significant problem for MP2 for systems dominated by dispersion interaction. To our knowledge, this has not been observed in the case of strongly polar species, for which van der Waals forces play a necessary but a secondary role. Results in good agreement with experiment were found also for water-polar molecule clusters in which charge transfer can take place.[51]

Given the importance of GGA methods in AIMD simulations, it is useful to comment on MD-MP2 and MD-GGA (and DFT in general) in the context of dispersion. The introduction of Grimme dispersion corrections to DFT,[52,53] by now almost universally used in MD-DFT simulations, has greatly improved the performance of these methods in relevant applications. Arguably, however, MP2 has some conceptual advantage here, because dispersion arises inherently from the theory, rather than an essentially empirical correction. For some systems such as the example presented above, the SOS correction for MP2[54] provides a very accurate treatment of the electron correlation; in other cases an alternate, optimized scaling of the spin components may be more appropriate.[55]

Another problem that arises when performing MD-DFT is the self-interaction (SI) error. It may lead to incorrect treatment of systems that include dissociation into radicals, interaction of radicals with closed-shell molecules (*e.g.*, NO_2 + H_2O, OH + H_2O), electron transfer reactions, and others. Interesting ideas, both of empirical approaches and of more fundamental treatments, have been proposed for this difficulty[56–59] and these led to successes in applications of MD-DFT for a number of challenging problems.[57] However, the fact that the SI problem does not arise at all for MD-MP2 must count as an advantage of the latter.

One difficulty with MD-MP2 is that it is computationally much less efficient than MD-GGA. For the system presented as an example above, the model for solvation effects on the reaction was limited to a small water cluster whereas in many DFT studies a water slab may be used to model reactions at a water surface. For finite systems, MD-B3LYP is faster than MD-MP2, and MD-GGA methods are much faster. A brief discussion of the development, application and current limitations of local MP2 methods for periodic systems is included in the Perspective article of Müller and Paulus along with an overview of other methods for treating electron correlation in extended systems.[60] Currently, many approaches are limited to the calculation of correlation energy. One exception is the fragment molecular-orbital approach,[61] which has been extended to molecular dynamics simulations of water[62] with periodic boundary conditions.[63] Another natural direction is to pursue a hybrid approach of the QM/MM type,[64] with MP2 as the QM part. Dynamics QM/MM studies employing MP2 have been carried out,[65,66] though finding an optimal way for coupling the QM and MM subsystems remains an open question. A very different direction for ''accelerating'' MD-MP2, and indeed MD with other high level *ab initio* methods, is by more efficient algorithms for the dynamics[67,68] Several very interesting suggestions were put forward recently, with very promising applications for MD-MP2.[69,70]

In summary, MD-MP2 has advantages of accuracy and of conceptual rigor for certain classes of important chemical reactions. However, computationally it is still limited to small or moderate size systems.

III. Molecular dynamics with multi-configurational and multi-reference electronic structure methods

High-level *ab initio* methods are generally required to describe processes such as reactions in excited electronic states; reactions involving radicals and other open-shell systems; and non-adiabatic reactions where the system goes through conical intersections. Needless to say, such processes are very challenging to treat, but reactions of these types are not at all unusual, and there are vast numbers of examples across chemistry. Progress on this topic is relatively recent. Several of the processes mentioned above have, however, been treated more extensively by DFT approaches. An excellent recent overview of ''on-the-fly'' DFT dynamics studies of nonadiabatic processes is by Tapavicza *et al.*[71] The description of the electronic states in this approach is by time-dependent density functional theory (TD-DFT).[72] A key issue is the evaluation of the derivative couplings that drive the non-adiabatic transitions between different electronic states.[73] This was accomplished analytically,[73] in very high precision, which is important for stable dynamics in such systems. However, it seems that second-order couplings[74] were not hitherto included in the calculations. These second-order couplings are often neglected in calculations of non-adiabatic transitions. While some qualitative arguments for justifying this were made, it is not clear what is the effect of this approximation on the results. The treatment of the non-adiabatic transitions on the dynamics of the trajectories employed, in the studies of ref. 72, the familiar surface-hopping approach introduced by Tully.[75] Ref. 72 analyzes comparisons between SH-TD-DFT simulations and experiments for several systems, including cyclohexediene, several vitamin derivatives[76] and a bicyclic cyclobutene. The authors find that with few exceptions, the calculated quantum yields and the excited state lifetimes agree qualitatively with experiment. This is encouraging, though it is not clear where the barrier for more quantitative agreement lies.

Several contributions to SH-TDDFT studies of non-adiabatic reactions were made by U. Röthlisberger and coworkers.[77–79] Also these authors find that the TD-DFT potential surfaces seem to have adequate accuracy for realistic non-adiabatic systems.[77]

We turn attention now to on-the-fly trajectory simulations that use *ab initio* multi-reference electronic structure methods to describe the potential surfaces for the processes considered here. In principle, one hopes that such methods may yield, when suitably developed, a higher level of accuracy than given by TD-DFT, if only because wavefunction-based electronic structure theory provides hierarchies of algorithms, with options of systematic improvements. Unfortunately, the computational limitations do not allow for very high level treatments. The computational difficulties, as is well known, are much greater for multi-reference calculations than for single-reference computations. An important issue is that systems with non-adiabatic events and systems with strong multi-configurational character involve rapid changes of the electronic wavefunction in the course of the dynamics. The methods employed in on-the-fly simulations must meet this requirement. Experience indicates that methods such as multi-reference configuration interaction (MR-CI),[80–82] or, where appropriate, a simple complete active space self-consistent field (CASSCF)[25,83–87] have advantages that help in their application in direct dynamics simulations. The CASSCF algorithm was the first to be used in direct dynamics simulations since analytic derivatives were available at the time. In a seminal paper on direct dynamics with CASSCF/MCSCF, M. S. Gordon and coworkers[87] were able to demonstrate advantages of AIMD in gaining insights into complex chemical processes, though in small systems. These authors studied the issue of competing reaction pathways in the dissociation of N_2O_2, and the mechanism and timescale in the decomposition of FN_3 into NF and N_2.[87] On-the-fly simulations with MCSCF are computationally not very demanding and the interpretations of the roles of the electronic configurations involved are simple and appealing. However, CASSF/MCSCF potentials are not generally accurate enough, due to the absence of dynamical correlations. At present, analytical gradients are also available, *e.g.* for CASPT2.[88] However, due to the high computational requirements for this algorithm in comparison with MCSCF, it seems that the latter is still in greater use. For quantitative purposes, the present authors believe that a suitable CASPT2, or equivalent methods, is called for.

Development of analytic gradients and therefore lowering the cost of calculating the forces has solved only one difficulty with using these multi-reference wavefunctions in direct dynamics simulations. Another challenge is to keep the active space constant along the entire dynamics. A very helpful analysis on the construction of a suitable case, also for the purpose of dynamics, and on its interpretation, is by Schmidt and Gordon.[89] Advantages and disadvantages of using CAS and multi-reference wavefunctions in dynamics simulations can be deduced from this analysis. Martinez and coworkers[80–85,90–92] made several important contributions to AIMD studies of non-adiabatic processes. First, these authors introduced approximate configuration interaction and MR-CI variants to the study of processes such as excited state isomerization of ethylene, and of several biological chromophores. These have provided a wealth of insights. Second, Martinez and coworkers have developed the multiple-spawning approach for quantum treatment of non-adiabatic transitions. This approach is a realistic alternative to the semiclassical surface-hopping treatment. While quantum effects in dynamics are not within the scope this Perspective article, this is clearly an issue that will have to be addressed in the field. At the very least, it is an obvious next frontier for AIMD. There are issues that must be examined with the multiple spawning approach to treat the quantum mechanics of the transition by a set of frozen Gaussians. However, this is a bold attempt that should be applauded. Importantly, Martinez and coworkers were able to combine the AIMD aspect, and the quantum treatment of the nuclei in several of their studies.

As examples of MD with multi-reference potential, we will present two recent studies from our group.[93,94] In both cases, an algorithmic variant was introduced that made the calculations feasible. The method used in these studies is MR-PT2,[95] and critical acceleration of the algorithms was achieved by using a massively parallelized code for the numerically computed forces that act on the atoms.[93] Massive parallelization did not change the actual cost of the calculations, but it made possible to utilize many CPUs in an efficient way. Simulations that normally would take about a year to finish with 32 CPUs were done in the timescale of 3 weeks utilizing the power of 512 CPUs on average. The new algorithmic developments enabled the possibility of MD-MR-PT2 simulations, but high costs still limit the size of investigated systems to around 8 atoms.

Multireference methods are generally much more expensive than their single reference counterparts. However, comparison between the cost of EOM-CC and MR-PT2 as approaches for multiconfigurational wavefunctions is more complicated. Cost of EOM-CC methods depend only on the number of correlated orbitals, while the cost of multireference methods depend also on the size and the structure of the active space. Generally for small active spaces multireference methods are up to an order of magnitude cheaper than EOM-CC methods, but with the growth of the active space MR-PT2 has about the same cost as EOM-CCSD(T).

In the case of MD-MR-PT2 the size of the active space has a major impact on both the accuracy and the cost of the simulation, whereas the choice of the basis set for simulations has only a minor effect on them. The choice of the basis set in these simulations should include accurate internal, valence and polarization functions whereas the usage of augmented functions seems to be insignificant.

The importance of the examples presented lies in illustrating the power of molecular dynamics simulations with multi-reference potentials in unraveling mechanisms and features of challenging chemical reactions.

The first example of a simulation with MD-MR-PT2 is from a recent study[93] of the reaction between a chlorine atom and ozone:

$$\mathrm{Cl}(^2\mathrm{P}) + \mathrm{O}_3(\mathrm{X}^1\mathrm{A}_1) \rightarrow \mathrm{ClO}(\mathrm{X}^2\Pi) + \mathrm{O}_2(\mathrm{X}^3\Sigma_g^-)$$

This reaction is of considerable interest in view of its role in depleting the stratospheric ozone layer. This system poses a challenge to electronic structure theory not only because of the open-shell involved, but also because of the complicated electronic structure of ozone. The reagents are in a doublet state, but the products can be described by two doublet configurations or by a quartet configuration and all these electronic configurations of the product system are in principle degenerate at sufficiently large distances. It was shown in ref. 93 that although both the reagent system and the product system can be described as doublets, in the dynamics of the process the system jumps from a doublet surface into a quartet potential energy surface along the reaction trajectory, before reaching the situation where the ClO and O_2 are far apart, and the quartet and doublets are actually degenerate. The ultrafast spin-flip transition between the degenerate doublet states and a quartet state emerges only in dynamics simulations, and it does not seem obvious how such insight may be obtained from a static approach, such as an IRC reaction path calculation. Also, a high level of electronic structure theory was necessary to identify the spin-flip transition in this case. It was shown in previous work that single-reference approaches, including UQCISD, or even CASSCF, do not reveal any electronic transition.[96]

A second example is from a recent MD-MR-PT2 exploration of the decomposition dynamics of a Criegee Intermediate, CH_2OO.[94] Criegee Intermediates are of great current interest, in view of evidence that these species play a major role as oxidants in atmospheric chemistry processes,[97] and also in certain combustion reactions. These species are highly reactive and very difficult to isolate and characterize.[98,99] Several calculations were reported on the electronic structure of Criegee Intermediate species at their equilibrium configurations.[100,101] It seems that both zwitterionic and diradical character make some contributions to the state. However, there seems to have been no dynamics study of chemical processes of Criegee Intermediates, such as decomposition, formation and reactions with other species. The MD-MR-PT2 simulations of ref. 94 are an exploration of a sequence of isomerization processes followed by decomposition into CO–H_2O. The simulations are for $T = 300$ K, starting from the first transition state along the reaction sequence. This transition state corresponds to the barrier between CH_2OO and dioxirane CH_2O_2, which by transition state rate calculations takes about 2 hours to surmount. Snapshots from the dynamics are shown in Fig. 2.

Shown in the figure for each snapshot, in addition to the geometry and partial charges on the atoms, are also the coefficients of electronic configurations that contribute significantly to the multiconfigurational wavefunctions. There are a number of very interesting findings. First, the whole process, from the initial transition state to decomposition, is completed in about 3 picoseconds. Such a fast process is unlikely to be slowed down by environmental effects such as collisions, and probably not even by a surrounding medium, if present. Multiple transfers of H occur in the process; some of these correspond roughly to "H atom transfer", while other events correspond roughly to "proton transfer". Diradical contributions for several snapshots that correspond roughly to transition states are very significant, much larger than for geometries corresponding to the Criegee Intermediate or dioxirane. This insight, supported by the analysis of the multi-configurational wavefunction "on-the-fly", is crucial for obtaining these insights, and demonstrates the unique power of MD simulations with multi-reference (or multi-configurational) *ab initio* techniques. Multi-reference methods are not the only multi-configurational approach that can be successfully employed for studying such complex chemical dynamics. A strong alternative are Coupled Cluster algorithms, in particular Equation of Motion-Coupled Clusters (EOM-CC).[102] An excellent review of these methods is by A. I. Krylov.[102] Several very interesting dynamics simulations with EOM-CC potentials were reported by Krylov and coworkers.[103–105]

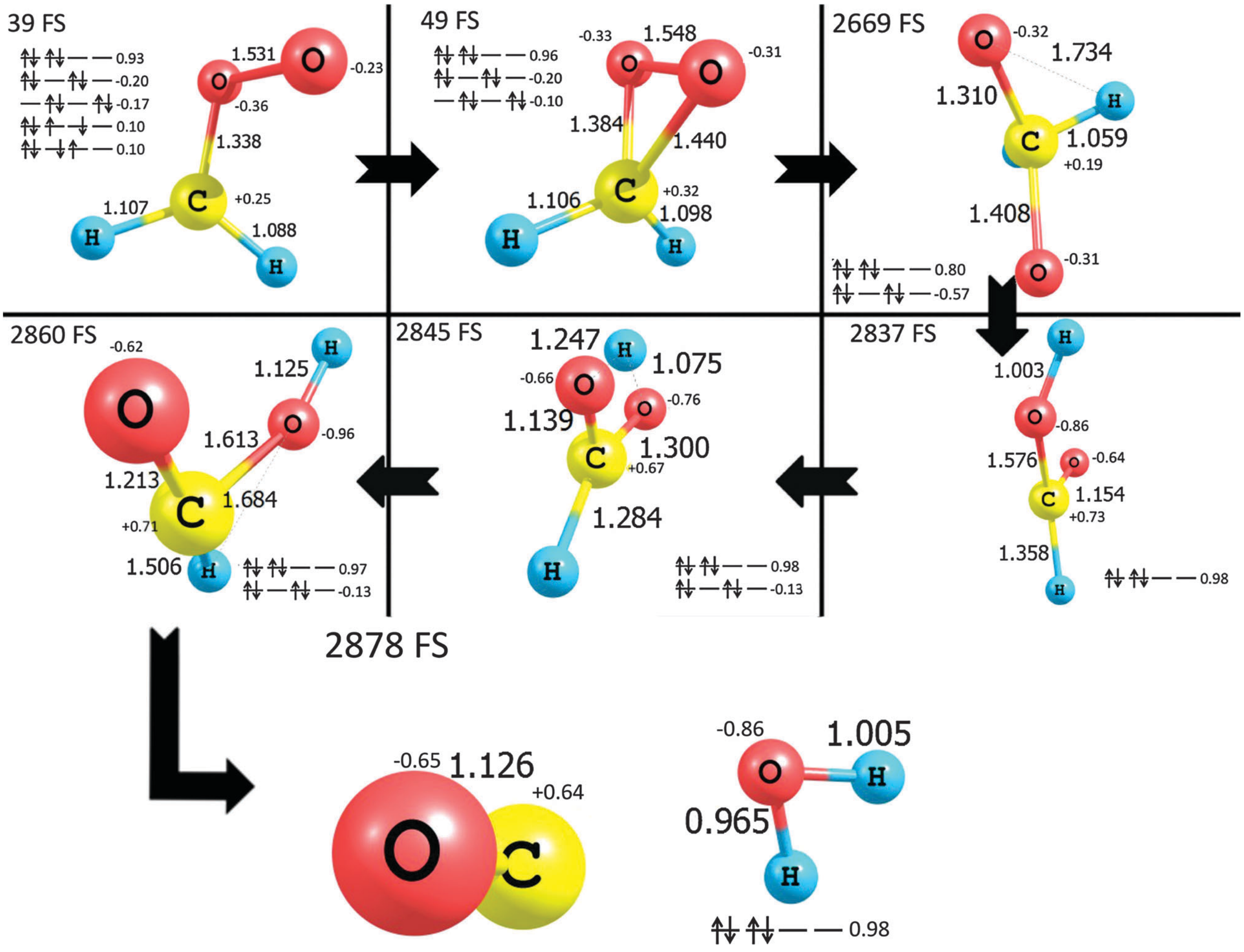

Fig. 2 Snapshots from *Ab-Initio* Molecular Dynamics simulation of thermal decomposition of CH_2OO started from transition structure. For each structure main contributions to multi-reference wave functions are presented together with partial charges and distances in Angstroms.

Dynamics with multi-reference or multi-configurational electronic structure methods seem one of the exciting frontiers of AIMD. This direction is quite novel, and major methodological progress, as well as a range of very interesting applications can be expected.

IV. Reaction dynamics studied by Semi-empirical Electronic Structure Methods (SEMD)

Studies of molecular reactions by Semi-empirical MD (SEMD) date from at least 40 years ago. Wang and Karplus[106] presented in 1973 a code that combines trajectory simulations with potentials from the low cost semi-empirical method CNDO, which is in principle capable of describing at least certain organic reactions. Later, Stewart and coworkers[107] incorporated a molecular dynamics algorithm in the semi-empirical package MOPAC.

Issues of validation of the method are clearly quite critical for semi-empirical potential surfaces, since their level of accuracy generally does not compare with DFT or *ab initio* methods, and in particular their success or failure can be very system-sensitive. An interesting approach was put forward by Truhlar and coworkers,[108] who introduced the specific reaction parameter (SRP) semi-empirical Hamiltonian. In this approach, the semi-empirical parameters are optimized for a specific reaction, which is expected to much increase the accuracy of the predictions made. Semi-empirical method tailored for specific classes of systems can be very successful. An example of a successful semi-empirical method for a narrow class of systems is DIM (Diatomics in Molecules) in its version for HX and HY (X,Y – halogens) interacting with noble gas atoms Ng.[109–113] The photochemistry of several dihalogens and halogen hydrides in matrices and in cluster of noble gas atoms was explored extensively by classical dynamics with DIM potentials used on-the-fly, and with surface hopping between different potential energy surfaces of the system.[109–113] It should be noted that in these simulations, not only the potential energy surfaces were obtained by DIM, but also the non-adiabatic derivative couplings. Good semiquantitative, and in cases even quantitative agreement with experiment were achieved. In particular, MD-DIM simulations predicted the interesting ultrafast spin-flip effect in the photodissociation of F_2 and ClF in Ar, later confirmed experimentally.[113] Also MD-DIM simulations were able to reproduce aspects of the cage effect found in experiments for several of these systems. However, we are not aware of useful extensions of DIM for photochemical dynamics of other systems, so the method remains restricted to a narrow class of compounds.

An important development is that in recent years more successful applications of fairly general semi-empirical methods have appeared. This is certainly in part due to the development of more reliable and accurate semi-empirical methods. We attribute, however, the increased successes of semi-empirical methods actually to the increased power of *ab initio* methods: It is possible now to use *ab initio* calculations much more extensively to testing and validation of the semi-empirical methods, and thus to employ the latter only where these methods work. For example, our group has applied in particular the MD-PM3 methods to problems that include vibrational overtone induced dissociation of HONO, HNO_3, H_2SO_4 and their hydrates; proton transfer and dissociation of proton-bound amino-acid dimers follow OH and NH stretching mode excitations, dynamics of amino acids following ionization, and ultrafast processes following photodissociation of methyl peroxide on ice particles.[114–122] In all these cases, comparison with *ab initio* calculations were made to validate the semi-empirical methods (though these were static properties, not dynamics), and in the cases where experimental results were available, semiquantitative to quantitative agreement with MD-PM3 was found. We conclude that extensive testing and validation are the clue for success in SEMD simulations. Only in cases where the testing against *ab initio* is encouraging, should the dynamics be pursued.

Semiempirical methods have been carefully parameterized for organic systems, and are therefore expected to be successful there. Some of the ambitious applications of MD with semi-empirical potentials are for simulations of biomolecular systems. Such simulations were reported for the catalysis of hydride transfer reactions by enzymes.[123,124] In these studies, the reaction center is treated by a semi-empirical method, while the rest of the protein is described by empirical force fields. The MD simulations are thus carried out for a QM/MM potential, where the QM part is a semi-empirical model.

A major step forward for the application of semi-empirical methods to dynamical processes is the development of multi-reference semi-empirical electronic structure methods. The group of W. Thiel and coworkers has developed a powerful semi-empirical method, OM2/MRCI, combined with algorithms that include both (adiabatic) Molecular Dynamics and surface-hopping.[125–135] The many applications provided by that group include studies of isomerization and a light-driven molecular rotor, of the chromophore of the Green Fluorescent Protein and of proton transfer processes. The group of T. J. Martinez has introduced a semi-empirical MR-CI code.[136–138] An important contribution by this group is an efficient code for re-parameterization of the semi-empirical parameters. One of the applications is to dynamics at conical intersection for isomerization in solution. Toniolo, Persico and coworkers[139,140] used semiempirical methods to explore the dynamics of photochemical reactions in water.

Our group has carried out a study of the photodissociation of methyl peroxide on an ice surface, using the OM2/MR-CI code with surface hopping.[141] The key result is that the ice surface rapidly deactivates the electronically excited peroxide, converting it to a vibrationally "hot" species in the electronic ground state. Calculations of the absorption lineshape of CH_3COOH at the frozen water surface[142] are in good accord with experiment, and thus support the semi-empirical potential used.

As an example of SEMD simulations of chemical reactions we present a study by our group on the photochemistry of the aldehyde pentanal. Aldehyde photochemistry has been a field of extensive research in the last years, mainly experimentally. However, there are still open questions regarding the mechanisms and timescales of photoinduced reactions. The recent study addresses these questions using a semiempirical approach.[143] The main reaction channels in aldehyde photochemistry include the Norrish type I (the first step is the C–C_γ cleavage), Norrish type II (γ-H transfer to the carbonyl group is the first step) and H detachment reactions. Those reactions are taking place on the triplet surface following intersystem crossing from the singlet excited state. The simulation employs the OM2 hamiltonian for the molecular dynamics on the triplet state. Excitation energies are calculated by the equivalent method OM2/MRCI, a semiempirical multireference configuration interaction approach. In principle, it is also possible to treat excited state dynamics including transition between different states with the same OM2/MRCI methodology. This makes the OM2 and OM2/MRCI molecular dynamics implementation in MNDO a very effective, computationally fast and versatile method for exploring reactions on the ground state, as well as on the excited state, of large systems. The simulation timescale reached with this methodology is 100 ps. This timing for such a long trajectory with the semiempirical potential energy surface is approximately 2.5 days, about two orders of magnitude faster than *ab initio* methods. A total set of 100 trajectories has been run. The molecular dynamics simulations shed light on the ratio between both Norrish type reactions: 34% of trajectories prefer to dissociate according the Norrish type I channel (cleavage of the C–C_γ bond resulting in a CHO and a C_4H_9 radical) whereas 66% of the trajectories tend to transfer a hydrogen from the C_γ atom to the carbonyl group. This is very close to the experimental observed ratio. Furthermore, a minor pathway, namely H detachment, has been also observed in this system. The timescales of these reactions are located in different regimes: Fig. 3 show a histogram of the timescale distribution of Norrish I *vs.* Norrish II reactions.

Norrish type I reactions occur on two timescales: one is ultrafast and below 10 ps, and the second one is slower, starting at 45 ps. Norrish type II reactions occur after 20 ps. Analysis of the Mulliken charges and bond order along the trajectory reveal more mechanistic insights. Fig. 4 shows snapshots of one trajectory showing the first step of the Norrish type II reaction.

It can be seen from the snapshots that the system has to explore a large part of the phase space, until it reaches the correct configuration for the H-transfer. This explains why the C–C_γ cleavage is much faster than the H-transfer reaction. Important geometries along the trajectory were validated using higher level *ab initio* methods such as RI-MP2 in conjunction with the resolution-of-the-identity[144] and ADC(2)[145] implemented in TURBOMOLE and found to be in very good agreement. As an example for the validation process we show here with Fig. 5 the HOMO orbital along the dynamics of the C–C_γ cleavage, the first step in the Norrish I reaction.

The HOMO orbital is very important since it is involved in different excitations. The HOMO orbital is calculated on-the-fly along the trajectory by the OM2/MRCI method and by ADC(2), a high level *ab initio* method. In the first 500 fs there are only minor changes in the orbital. This is in very good agreement with the ADC(2) method. The HOMO orbital constitutes a π^* orbital. After the cleavage, a large part of the orbital is located on the large fragment. ADC(2) predicts a very similar three-dimensional structure of the orbital. As can be seen, important properties of the system calculated by OM2/MRCI are nicely recovered with ADC(2). This supports our approach of employing semiempirical potential energy surface in the simulation of

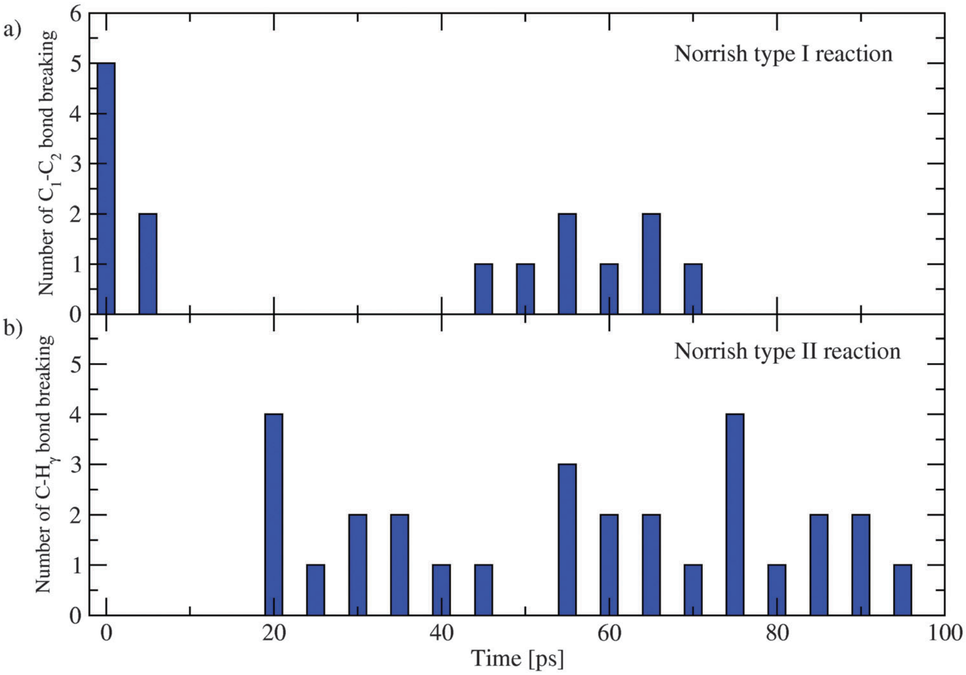

Fig. 3 Histogram of (a) Norrish type I reactions and (b) Norrish type II reactions in the time of 100 ps. Reprinted with permission from "D. Shemesh, Z. Lan and R. B. Gerber, *J. Phys. Chem. A*, 2013, **117**, 11711." Copyright 2013 American Chemical Society.

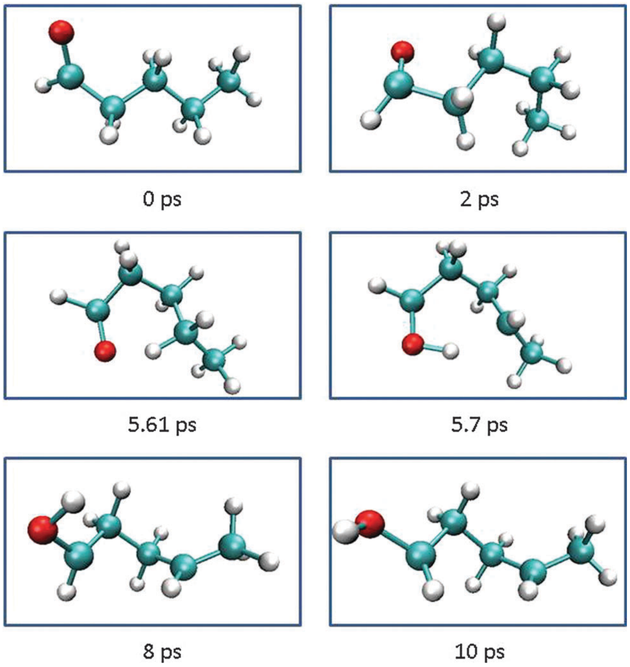

Fig. 4 Snapshots of the γ-H transfer. Reprinted with permission from "D. Shemesh, Z. Lan and R. B. Gerber, *J. Phys. Chem. A*, 2013, **117**, 11711." Copyright 2013 American Chemical Society.

reactions. The reduced computational cost makes this methodology applicable to a wide range of reactive processes of large organic systems.

In summary, this SEMD study elucidates the crossover from a Norrish I and a Norrish II mechanism in a medium-size aldehyde, and explains why this transition as a function of time occurs. This seems to answer a long-standing question in the literature on the nature of the competition between Norrish I and Norrish II in the triplet-state photochemistry of aldehydes.

A related study was carried out by us for pinonic acid.[146] The results are in accord with the experimental work on pinonic acid, and the agreement strongly supports the method.

In summary, there has been major recent progress in the study of chemical reactions by SEMD, and the field now is active, and in our view in one of promising frontier in classical dynamics simulations in electronic structure methods for the potentials. This development stems, in our view, from the fact that is has become possible to test SE methods much more extensively against *ab initio*, so the applications when presented are more reliable. Also, more powerful SE methods have been developed, especially the multireference ones. This greatly increases the arsenal of SEMD.

V. On-the-fly calculations of electronic properties along reaction trajectories

One of the most powerful tools for obtaining insight from MD simulations is just by analyzing the positions of the atomic nuclei, snapshot by snapshot along the trajectories.[147] For AIMD and SEMD there is an additional tool that can provide insights and interpretation into the processes studied, namely calculations of electronic properties along the trajectories. Such information cannot be obtained from MD using empirical potentials. A simple example of such electronic properties that can be studied on-the-fly for AIMD and SEMD are partial charges on the atoms involved in the process. While in principle the study of electronic properties can be carried out also for non-chemical processes, the benefits of such analysis for reactions are expected to be especially large. In chemical reactions, there are often large changes in properties such as partial charges on some of the atoms, the bond orders between neighboring atoms, *etc.* Furthermore, such changes, being electronic in nature occur sometimes on very fast timescales, and are not generally accompanied by significant nuclear displacements on the same timescales. In brief, electronic properties may serve as signatures of major events in a chemical process that cannot be easily deduced from snapshots of atomic positions. In our view, the

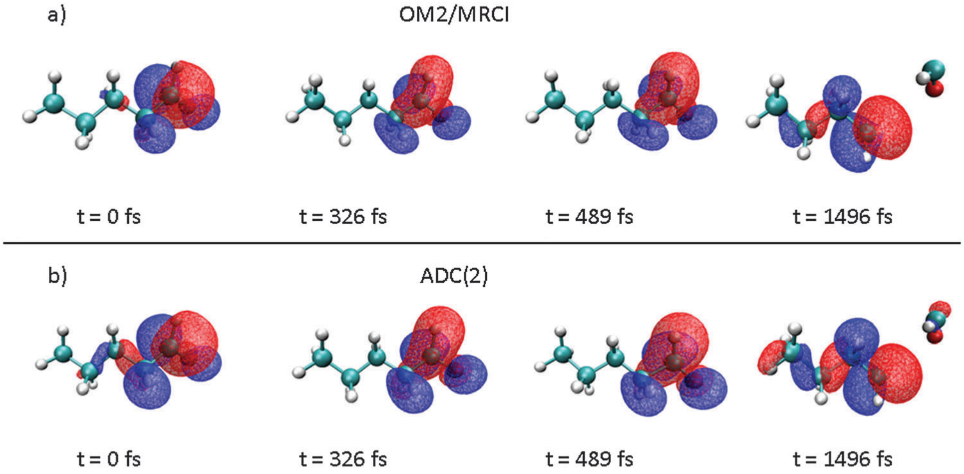

Fig. 5 HOMO orbital structure for snapshots in the dynamics of C–C_γ cleavage (a) as calculated by OM2/MRCI and (b) as calculated by ADC(2). Reprinted with permission from "D. Shemesh, Z. Lan and R. B. Gerber, *J. Phys. Chem. A*, 2013, **117**, 11711." Copyright 2013 American Chemical Society.

on-the-fly studies are a largely new, powerful way for obtaining detailed insights into mechanisms of complex chemical processes. There is a rich variety of methods for analyzing electronic properties for a given configuration of the atoms. There is an excellent review by Weinhold.[148] It is appealing to use these methods also in dynamics.

1. Analysis of natural bond orbitals along reactive trajectories

The concept of Natural Orbitals (NO) dates back to the work of Löwdin.[149] However, it has since been much developed as a tool for analyzing the bonding patterns and partial charges in molecules by the contributions of Weinhold and coworkers.[148,150] The theory of Natural Bond Orbitals (NBO) has been applied to a large variety of topics using static electronic structure calculations. However, there have been few uses of NBO as an analysis tool in AIMD simulations.[151,152] From our experience NBO bond orders (and partial charges) are very insensitive to the size of the basis set ranging from cc-pVDZ to aug-cc-PVTZ. This makes the NBO analysis applicable in AIMD simulations which usually utilize relatively modest basis sets due to the significant computational demands. To the best of our knowledge, the first application of the NBO method to analyze AIMD simulations was by Hirshberg and Gerber.[151] That work focused on the exotic molecule N_6 which may find possible applications as an energetic material. The decomposition dynamics of 3 different isomers of N_6 were studied in the gas phase using both MP2 and B3LYP levels of theory. The analysis of different points on the trajectory using NBO revealed three decomposition mechanisms for each of the isomers. While two isomers were found to decompose in a concerted mechanism, the third isomer – a Dewar benzene isomer – was found to decompose in a two-step mechanism in which the first step is decomposition of N_6 into N_4 isomer with a D_{2h} symmetry and N_2. The second step was not viewed directly in the AIMD simulations but was studied previously by high level electronic structure theory.[153] Analysis of the NBO bond orders and partial charges obtained using Natural Resonance Theory allowed the identification of a retro Diels Alder

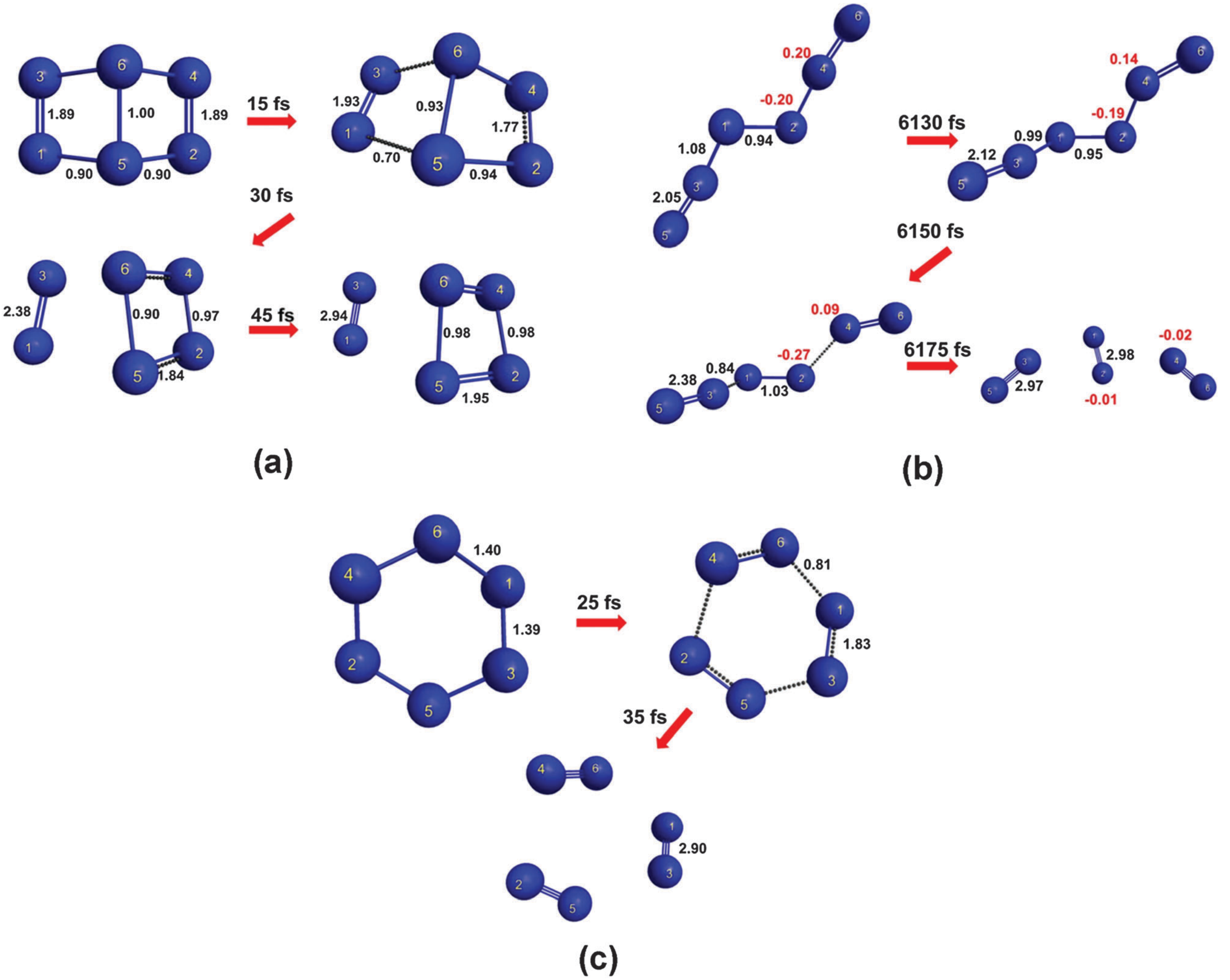

Fig. 6 NBO bond orders and partial charges along the decomposition dynamics of 3 isomers of N_6. Bond orders are in black and partial charges are in red. Panel (a) shows the Dewar benzene isomer. Following the bond orders on-the-fly revealed a two step decomposition mechanism. The first step is shown and found to occur *via* a retro Diels Alder (RDA) mechanism. Panels (b) and (c) show the concerted decomposition mechanisms found for 2 additional isomers.

(RDA) mechanism for the first step of the reaction. The authors also showed that the changes in electronic properties occur on a 10 fs time scale. Analysis based solely on the nuclei positions would not have been able to identify the RDA mechanism due to the time scale limitations. Fig. 6 shows the decomposition mechanisms for 3 isomers of N_6 and the changes in partial charges and bond orders along these trajectories.

Another recent application of NBO theory to the study of changes in electronic properties during AIMD simulations was done by Kroger *et al.*[152] The authors studied the hydrolysis of polyphosphazenes using the B3LYP level of theory and the atom-centered density matrix propagation (ADMP) scheme.[154] The model system used was a dichlorophosphazene trimer surrounded by 2 water molecules. The simulations were started from an intermediate structure on the PES after the addition of a hydroxyl anion on the central P atom and a neighboring hydronium cation. The use of NBO theory to analyze the trajectory showed the dissociation of the backbone P–N σ bond occurs *via* a proton transfer from the hydronium ion to the central N atom. Following the atomic positions alone suggested that the P–N bond dissociates after 25 fs when the bond length exceeds 1.7 Å. However, NBO analysis showed that the bond does not dissociate until a bond length of 2.04 Å. In addition, NBO analysis of partial charges allowed confirmation that the decomposition does occur in the suggested mechanism.

As mentioned in chapter IV, Shemesh *et al.* analyzed Mulliken partial charges and bond orders to study the photochemistry of pentanal.[143] The photochemistry of aldehydes in general is a very important topic in atmospheric chemistry. Much of the reaction mechanisms involved in the photochemistry of aldehydes in the atmosphere are still unknown. Using the semiempirical method OM2, Shemesh *et al.* studied three possible reactions of pentanal: the Norrish I, Norrish II and H abstraction reaction. Analysis of the partial charges and bond orders allowed mechanistic insights for the different reactions. The Mulliken analysis seems a useful method for studying changes in electronic structure during chemical reactions. It is less rigorous and reliable than NBO, but it should suffice at best for qualitative insights into many cases.

Although the methodology of following NBO orders and partial charges has found only few applications so far, in our view the method has the potential of becoming a major tool in providing a detailed understanding of chemical reaction mechanisms.

2. Maximally Localized Wannier Centers

Maximally Localized Wannier Functions (MLWF) can be easily thought of as the condensed phase analog to the localized molecular orbitals concept. This concept has been developed and used in the context of DFT simulations of extended systems. Specifically, the charge centers of the MLWF are often regarded as the classical localization of an electron in the molecule.[155] Therefore, the analysis of the shape, symmetry and charge centers of MLWF along AIMD simulations can be a powerful tool for understanding chemical reactions in the solid state and also in liquids and at surfaces. Indeed, MLWF analysis has been applied in previous studies to different reactions.[156–166]

MLWF have found many more applications so far than the NBO method for following AIMD trajectories. We discuss here work done in the authors' group in the recent years.

Hammerich *et al.* used[167] MLWF to analyze the mechanism of the reaction of NO_x species with HCl on water surfaces. These reactions are very important in atmospheric chemistry due to the fact that the reaction product, ClNO is a source for reactive chlorine atoms which catalyze ozone depletion. Specifically, Hammerich *et al.*[167] used CPMD simulations done at the BLYP-D level of theory to study the reaction of the NO_2 asymmetric dimer ($ONONO_2$) with HCl impinging on a water surface. Using the MLWF centers, the authors were able to identify the breaking of the nitroso bond in the $ONONO_2$ molecule and the formation of the new Cl–NO bond in the reaction product. Using this analysis during simulations of a thin water film helped suggesting a new possible mechanism for ClNO production, which was not previously seen in simulations on water clusters.

VI. Concluding remarks

Molecular dynamics simulations using potentials or forces computed directly from quantum-chemical methods are already a major tool in the study of chemical reactions. Such simulations were already applied to a large range of processes and systems, including isolated molecules, microcondensed systems (*i.e.* clusters), and models of reactions at surfaces or in bulk. AIMD and SEMD are providing insights into the detailed mechanisms of the reactions, and also timescales, and produces quantitative rates. Yet, the field is still at a relatively early stage of development. There is a great potential for further developments that will greatly enlarge the scope of reactions that can be addressed, and will improve the accuracy of the approach in applications.

In this article, we attempt to highlight several recent directions that seem to promise significant progress in the near future. These include the use of quantum chemical methods that have hitherto not been extensively used in the context of AIMD or SEMD: MD-MP2, MD with potentials from multireference *ab initio* methods or multiconfigurational semiempirical algorithms. While no single electronic structure method available at present can handle the many challenges posed by the vast variety of chemical reactions, the above methods and certainly other DFT and *ab initio* algorithms can rapidly cover new topics of applications. Likewise, the topic of computing electronic properties along reaction trajectories seems to offer important directions for future progress. On-the-fly calculations of partial charges, Wannier centers, bond orders and other electronic properties not considered here, seem capable of providing useful insights for identifying important "events" in the course of complex reactions. Such insights might not be easy to obtain using other approaches. On the limited scope of the paper no consideration was given here to calculation of electronic properties that are experimentally observable, but this is obviously a topic of major potential usefulness.

One extremely important challenge that was not addressed here entirely is the incorporation of quantum effects into the nuclear dynamics. One expects this to become a very major topic in its own right, with the aim of developing semi-classical methods, or other quantum-mechanical approximations for the dynamics of the nuclei. We note that this has been accomplished to some extent in the field of vibrational spectroscopy, where the methodological challenge is admittedly less severe: methods are now at hand that compute directly and quantum-mechanically the vibrational states from quantum chemical methods for the potential.[168] We believe that this may be one of the most exciting goals for studying dynamics of chemical reactions using directly electronic structure methods.

Glossary

ADC(2)	Algebraic diagrammatic construction method
ADMP	Atom-centered density matrix propagation
AIMD	*Ab initio* molecular dynamics
B3LYP	Becke's 3 parameters hybrid functional with Lee, Young, Parr correlation (functional)
BLYP	Becke, Lee, Yang, Parr (functional)
BOMD	Born–Oppenheimer molecular dynamics
BP86	Becke, Perdew 86 (functional)
CAS	Complete active space
CASPT2	Complete active space second-order perturbation theory
CASSCF	Complete active space self-consistent field
CCSD(T)	Coupled cluster singles and doubles level with a perturbative treatment of triple excitations
CNDO	Complete neglect of differential overlap
CP2K	Car Parrinello 2000 (for the new millennium)
CPMD	Car–Parrinello molecular dynamics
DFT	Density functional theory
DIM	Diatomic in molecules
EOM-CC	Equation of motion coupled cluster
GGA	Generalized gradient approximation
HOMO	Highest occupied molecular orbital
HTCH	Hamprecht, Cohen, Tozer, Handy (functional)
MCSCF	Multi-configurational self-consistent field
MD	Molecular dynamics
MD-B3LYP	Molecular dynamics with B3LYP potential
MD-DFT	Molecular dynamics with DFT potential
MD-DIM	Molecular dynamics using DIM potential
MD-GGA	Molecular dynamics with GGA potential
MD-MP2	Molecular dynamics with MP2 potentials
MD-MR-PT2	Molecular dynamics with MR-PT2 potential
MD-PM3	Molecular dynamics using PM3 potential
MLWF	Maximally Localized Wannier Functions
MNDO	Modified neglect of diatomic overlap
MOPAC	Molecular orbital PACkage
MP2	Møller-Plesset second-order perturbation theory
MR-CI	Multi-reference configuration interaction
MR-PT2	Multireference second-order perturbation theory
NBO	Natural bond orbitals
NO	Natural orbitals
OM2	Orthogonalization method 2
OM2/MRCI	Orthogonalization method 2/multi-reference configuration interaction
PBE	Perdew, Burke, Ernzerhof (functional)
PES	Potential energy surface
PM3	Parameterized model number 3
QM/MM	Quantum mechanics/molecular mechanics
RDA	Retro Diels Alder
RI-MP2	MP2 with resolution of identity approximation
SE	Semi-empirical
SEMD	Semi-empirical molecular dynamics
SH-TD-DFT	Surface hopping molecular dynamics with TD-DFT potential
SI	Self interaction
S_N2	Substitution nucleophilic bimolecular
SOS-MP2	MP2 with scaling of opposite spin components
SRP	Specific reaction parameter
TD-DFT	Time-dependent density functional theory
UQCISD	Unrestricted quadratic configuration interaction with singles and doubles

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