

# PCCP

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

*Accepted Manuscripts* are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

**Ab Initio and Semi-empirical Molecular Dynamics Simulations  
of Chemical Reactions in Isolated Molecules and in Clusters**

R.B. Gerber<sup>(a,b,c)</sup>, D. Shemesh<sup>(a)</sup>, M.E. Varner<sup>(b)</sup>, J. Kalinowski<sup>(c)</sup> and B. Hirshberg<sup>(a)</sup>

<sup>(a)</sup>Institute of Chemistry and The Fritz Haber Research Center,  
The Hebrew University of Jerusalem, Jerusalem 91904, Israel

<sup>(b)</sup>Department of Chemistry, University of California, Irvine 92697, USA

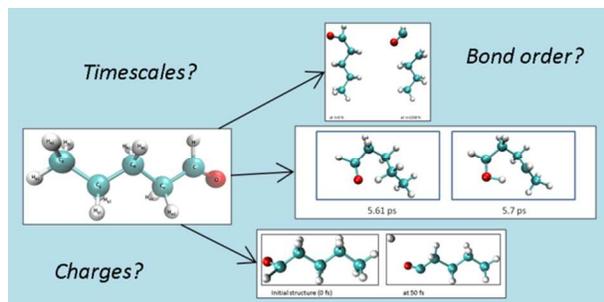
<sup>(c)</sup>Department of Chemistry, University of Helsinki, P.O. Box 55, FIN-00014, Finland

**Abstract**

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.

Table of Content graphic:



**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	– <b>M</b> olecular <b>D</b> ynamics using <b>PM3</b> Potential
MLWF	– <b>M</b> aximally <b>L</b> ocalized <b>W</b> annier <b>F</b> unctions
MNDO	– <b>M</b> odified <b>N</b> eglect of <b>D</b> iatomic <b>O</b> verlap
MOPAC	– <b>M</b> olecular <b>O</b> rbital <b>P</b> ACkage
MP2	– <b>M</b> øller- <b>P</b> lesset <b>second</b> -order perturbation theory
MR-CI	– <b>M</b> ulti- <b>R</b> eference <b>C</b> onfiguration <b>I</b> nteraction
MR-PT2	– <b>M</b> ultireference <b>second</b> -order <b>P</b> erturbation <b>T</b> heory
NBO	– <b>N</b> atural <b>B</b> ond <b>O</b> rbitals
NO	– <b>N</b> atural <b>O</b> rbitals
OM2	– <b>O</b> rthogonalization <b>M</b> ethod <b>2</b>
OM2/MRCI	– <b>O</b> rthogonalization <b>M</b> ethod <b>2</b> / <b>M</b> ulti- <b>R</b> eference <b>C</b> onfiguration <b>I</b> nteraction
PBE	– <b>P</b> erdew, <b>B</b> urke, <b>E</b> rnzerhof (functional)
PES	– <b>P</b> otential <b>E</b> nergy <b>S</b> urface
PM3	– <b>P</b> arameterized <b>M</b> odel number <b>3</b>
QM/MM	– <b>Q</b> uantum <b>M</b> echanics/ <b>M</b> olecular <b>M</b> echanics
RDA	– <b>R</b> etro <b>D</b> iels <b>A</b> lder
RI-MP2	– <b>MP2</b> with <b>R</b> esolution of <b>I</b> ntity approximation
SE	– <b>S</b> emi- <b>E</b> mpirical
SEMD	– <b>S</b> emi- <b>E</b> mpirical <b>M</b> olecular <b>D</b> ynamics
SH-TD-DFT	– <b>S</b> urface <b>H</b> opping <b>M</b> olecular <b>D</b> ynamics with <b>TD-DFT</b> potential
SI	– <b>S</b> elf <b>I</b> nteraction
S <sub>N</sub> 2	– <b>S</b> ubstitution <b>N</b> ucleophilic <b>B</b> imolecular
SOS-MP2	– <b>MP2</b> with <b>S</b> caling of <b>O</b> pposite <b>S</b> pin components
SRP	– <b>S</b> pecific <b>R</b> eaction <b>P</b> arameter
TD-DFT	– <b>T</b> ime- <b>D</b> ependent <b>D</b> ensity <b>F</b> unctional <b>T</b> heory
UQCISD	– <b>U</b> nrestricted <b>Q</b> uadratic <b>C</b> onfiguration <b>I</b> nteraction with <b>S</b> ingles and <b>D</b> oubles

## Biographies

### R. Benny Gerber



R. Benny Gerber is Saerree K. and Louis P. Fiedler Professor Emeritus at the Hebrew University of Jerusalem, Professor of Chemistry at the University of California at Irvine and Finland Distinguished Professor at the University of Helsinki. His current research interests include chemical reaction dynamics in gas and in condensed phases, vibrational spectroscopy of biological molecules, and the prediction of new molecules and solids of the noble gas elements and of other species.

### Dorit Shemesh



Dorit Shemesh has graduated from the Hebrew University under the supervision of Prof. R. Benny Gerber. After postdoctoral research as a Humboldt Fellow at the Technische Universität München in Germany with Prof. Wolfgang Domcke she returned to the research group of Prof. R. Benny Gerber. Her research focuses on photochemistry of peptides, aldehydes and other biologically and atmospherically relevant systems. In her research she mainly employs Molecular Dynamics simulations in conjunction with semiempirical methods, with emphasis on understanding the mechanisms and timescales of the simulated reactions.

**Mychel Varner**

Mychel Varner is a postdoctoral researcher at the University of California, Irvine. As part of AirUCI, she has used computational methods in collaborations with experimental groups to study atmospheric processes. These include acid-base reactions leading to particle formation and reactions at water surfaces using a cluster model. Previously, while in Austin, Texas studying with John Stanton, she worked on smaller systems with more distant, but not less excellent, experimental collaborators demonstrating the high level of agreement possible for some systems and the difficulty in properly describing the HOOO system.

**Jaroslav Kalinowski**

Jaroslav Kalinowski obtained his M.Sc. in Chemistry at the University of Wroclaw. He then started his PhD with Prof. R. Benny Gerber at University of Helsinki. His research interests include development of ab-initio electronic structure theory methods and their applications to Molecular Dynamics; algorithmic developments in ab-initio quantum chemistry. His research in chemistry focuses mostly on some aspects of noble gas chemistry and atmospheric chemistry. These include chemistry and properties of radical and biradical species.

**Barak Hirshberg**

Barak Hirshberg obtained his B.Sc. in Chemistry from the Hebrew University of Jerusalem in 2009. Since 2011 he is a graduate student with Prof. R. Benny Gerber at the Fritz Haber center for Molecular Dynamics and the institute of Chemistry at the Hebrew University. His research interests include developing and applying tools to study the electronic structure of new materials in the condensed phase as well as studying chemical reactions using ab initio molecular dynamics simulations.

## I. Introduction

The introduction of classical trajectory calculations in studies of molecular reaction dynamics was 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.  $\text{H}+\text{H}_2$ , 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 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 development in the field of reactive force fields show promise in accurately describing bond formation and breaking<sup>1</sup>. 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<sup>2</sup> 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<sup>3</sup>. As one example, only of a very different algorithm, we mention the Born-Oppenheimer molecular dynamics (BOMD) method<sup>4</sup>. 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<sup>5</sup>, proton transfer reactions<sup>6, 7</sup>, reactions on metal surfaces<sup>8</sup>, in aqueous solutions<sup>9</sup>, and organometallic catalysis<sup>10</sup>, 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)<sup>11</sup> 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 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<sup>3</sup> 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: Sec. II deals with calculations using MP2 on-the-fly for reaction processes. Sec. III addresses direct trajectory calculations for systems requiring multi-reference electronic wavefunctions. Sec. IV describes SEMD simulations. In Sec. V, calculations of electronic properties along trajectories of reactive processes are discussed. Concluding remarks, with a view to possible future directions, are brought in Sec. 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<sup>12</sup> and protonation of nitric acid<sup>13</sup>, as well as related systems<sup>14</sup>; photodetachment of an anion complex,  $(F^-)(H_2O)_4$ <sup>15</sup>,  $S_N2$  reactions<sup>16</sup>; unimolecular dissociation of  $H_2CO$  and related molecules<sup>17, 18</sup>; abstraction reactions of H atoms<sup>19</sup> 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<sup>20-24</sup>; ionization dynamics (and the reverse process of electron capture)<sup>25-31</sup>;  $S_N2$  reactions<sup>32-34</sup>; dynamics in the transition state region, also in the context of unimolecular reactions<sup>35-38</sup>; hydrogen atom abstraction and elimination reactions<sup>39-44</sup> 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,  $HONO$ <sup>45</sup>. This reaction is of considerable atmospheric interest, as it is part of a proposed mechanism for the formation of  $HONO$  in the atmosphere<sup>46</sup>.

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  $\text{N}_2\text{O}_4$  Liu and Goddard<sup>47</sup> found that with density functional theory, specifically the B3LYP functional, the ion pair isomer  $(\text{NO}^+)(\text{NO}_3^-)$  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  $\text{N}_2\text{O}_4$  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  $\text{ONONO}_2$  with water<sup>46</sup>, 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  $(\text{NO}^+) \cdot (\text{H}_2\text{O})_n$  clusters, revealed a water configuration that promoted the reaction resulting in formation of HONO for  $n=4$ <sup>48</sup>. This, and a related study on the prediction of the vibrational spectra of  $(\text{NO}^+) \cdot (\text{H}_2\text{O})_3$  isomers from AIMD simulations<sup>49</sup>, 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 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  $\text{ONONO}_2 \cdot (\text{H}_2\text{O})_4$  potential surface<sup>45</sup>. At this level each gradient step took an average of 3 to 4 minutes on four processors, or roughly 5 days per ps.

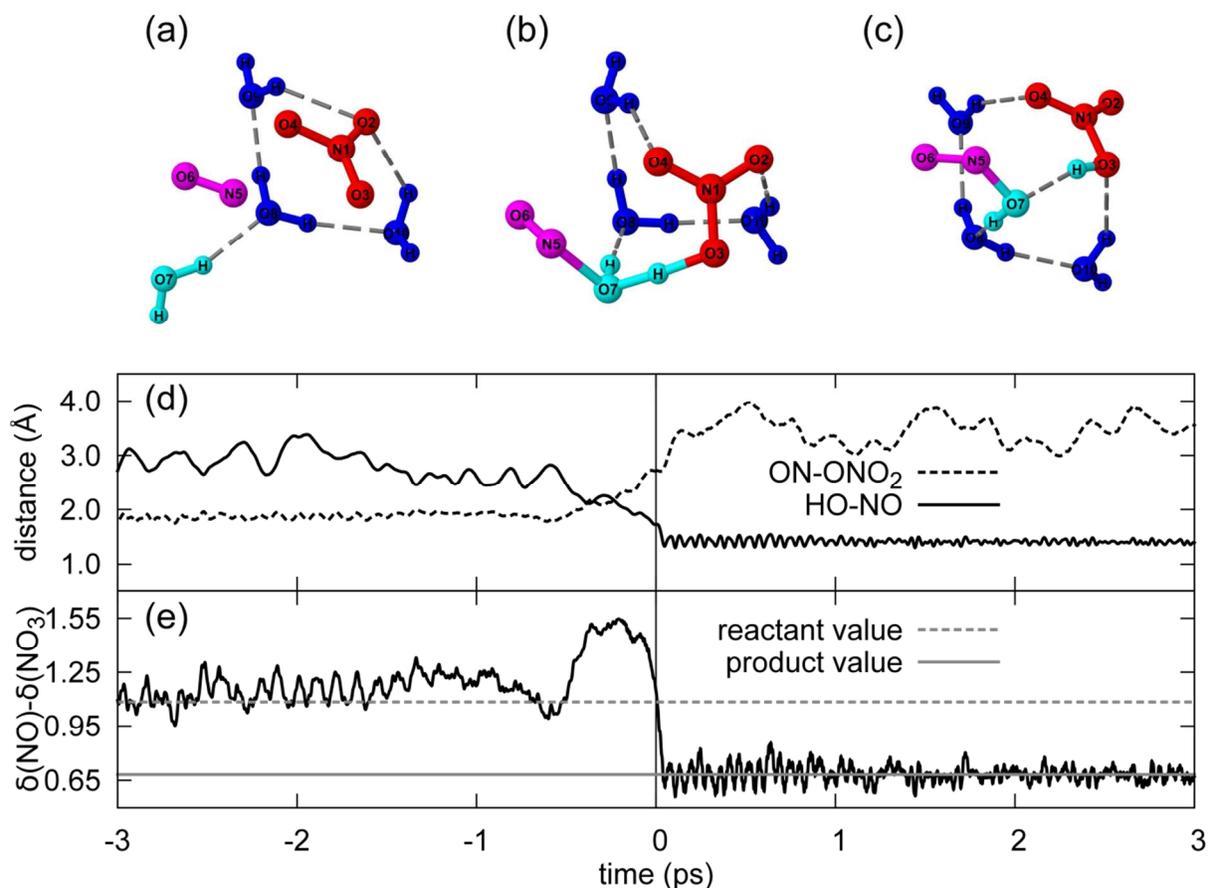


Fig. 1: MD-SOS-MP2 results for the reaction of  $(\text{NO}^+)(\text{NO}_3^-)$  with  $(\text{H}_2\text{O})_4$  to form  $\text{HONO} + \text{HNO}_3$ : structures of (a) the reactant cluster at -2 ps, (b) the transition state at 0 ps and (c) the product cluster at 2 ps are included with the NO fragment in magenta, the  $\text{NO}_3$  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  $\text{NO}_3$  groups.

Based on the water configuration that promotes HONO formation in  $(\text{NO}^+) \cdot (\text{H}_2\text{O})_4$  isomers, a reactive  $\text{ONONO}_2 \cdot (\text{H}_2\text{O})_4$  isomer was identified. From this structure, a transition state in which the reacting water inserts between the NO and  $\text{NO}_3$  fragments of  $\text{ONONO}_2$  was also identified. This allows for simultaneous formation of HONO, through combination of  $\text{NO}^+$  and  $\text{OH}^-$ , and nitric acid, through proton transfer to  $\text{NO}_3^-$ . The transition state structure is presented in Figure 1(b). Initial velocities were assigned based on a temperature of 50 K 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<sup>50</sup>. 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 Figure 1 as images (a) and (c), respectively.

Figure 1(d) includes a trace of the ON-ONO<sub>2</sub> distance,  $r(\text{N5-O3})$ , revealing association/dissociation of the ONONO<sub>2</sub> reactant. Inclusion of the HO-NO distance,  $r(\text{O7-N5})$ , 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<sup>+</sup>)(NO<sub>3</sub><sup>-</sup>) 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<sub>3</sub> fragment,  $\delta(\text{NO}) - \delta(\text{NO}_3)$ , is plotted in Figure 1(e).

In the transition state structure, at  $t=0$ , the  $r(\text{O7-N5})$  distance between the reacting water and the NO fragment which is just under 2Å, is approximately equivalent to the  $r(\text{N5-O3})$  distance between the NO fragment and the NO<sub>3</sub> fragment in the reactant cluster. The charge separation at the transition state,  $\delta(\text{NO}) - \delta(\text{NO}_3) = 1.15$ , is also quite similar to the reactant value,  $\delta(\text{NO}) - \delta(\text{NO}_3) = 1.08$ . The insertion of the reacting water supports a charge separation similar to that in minimum energy ONONO<sub>2</sub> 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<sub>3</sub> 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<sup>+</sup> and OH<sup>-</sup> association with proton transfer to the solvating water to form H<sub>3</sub>O<sup>+</sup> 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<sup>51</sup>.

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<sup>52, 53</sup>, 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<sup>54</sup> provides a very accurate treatment of the electron correlation, in other cases an alternate, optimized scaling of the spin components may be more appropriate<sup>55</sup>.

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.,  $\text{NO}_2 + \text{H}_2\text{O}$ ,  $\text{OH} + \text{H}_2\text{O}$ ), electron transfer reactions, and others. Interesting ideas, both of empirical approaches and of more fundamental treatments, have been proposed for this difficulty<sup>56-59</sup> and these led to successes in applications of MD-DFT for a number of challenging problems<sup>57</sup>. 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 Perspective article of Müller and Paulus along with an overview of other methods for treating electron correlation in extended systems<sup>60</sup>. Currently, many approaches are limited to the calculation of correlation energy. One exception is the fragment molecular-orbital approach<sup>61</sup>, which has been extended to molecular dynamics simulations of water<sup>62</sup> with periodic boundary conditions<sup>63</sup>. Another natural direction is to pursue a hybrid approach of the QM/MM type<sup>64</sup>, with MP2 as the QM part. Dynamics QM/MM studies employing MP2 have been carried out<sup>65, 66</sup>, 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<sup>67, 68</sup> Several very interesting suggestions were put forward recently, with very promising applications for MD-MP2<sup>69, 70</sup>.

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.<sup>71</sup> The description of the electronic states in this approach is by time-dependent density functional theory (TD-DFT)<sup>72</sup>. A key issue is the evaluation of the derivative couplings that drive the non-adiabatic transitions between different electronic states<sup>73</sup>. This was accomplished analytically<sup>73</sup>, in very high precision, which is important for stable dynamics in such systems. However, it seems that second-order couplings<sup>74</sup> 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<sup>75</sup>. Ref. 72 analyzes comparisons between SH-TD-DFT simulations and experiments for several systems, including cyclohexadiene, several vitamin derivatives<sup>76</sup> 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<sup>77-79</sup>. Also these authors find that the TD-DFT potential surfaces seem to have adequate accuracy for realistic non-adiabatic systems<sup>77</sup>.

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)<sup>80-82</sup>, or, where appropriate, a simple complete active space self-consistent field (CASSCF)<sup>25, 83-87</sup> 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<sup>87</sup> 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  $N_2$ <sup>87</sup>. 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, CASSCF/MCSCF potentials are not generally accurate enough, due to the absence of dynamical correlations. At present, analytical gradients are available also e.g. for CASPT2<sup>88</sup>. 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<sup>89</sup>. Advantages and disadvantages of using CAS and multi-reference wavefunctions in dynamics simulations can be deduced from this analysis. Martinez and coworkers<sup>80-85, 90-92</sup> 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 of 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<sup>93, 94</sup>. In both cases, an algorithmic variant was introduced that made the calculations feasible. The method used in these studies is MR-PT2<sup>95</sup>, and critical acceleration of the algorithms was achieved by using a massively parallelized code for the numerically computed forces that act on the atoms<sup>93</sup>. 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.

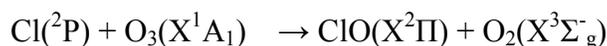
Multireference methods are generally much more expensive than their single reference counterparts. However, comparison between the cost of EOM-CC and MR-PT2 as approaches for multiconfigurational wavefunctions is more complicated. Cost of EOM-CC methods depend only on the number of correlated orbitals, 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 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<sup>93</sup> of the reaction between a chlorine atom and ozone:



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<sub>2</sub> 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<sup>96</sup>.

A second example is from a recent MD-MR-PT2 exploration of the decomposition dynamics of a Criegee Intermediate,  $\text{CH}_2\text{OO}^{94}$ . Criegee Intermediates are of great current interest, in view of evidence that these species play a major role as oxidants in atmospheric chemistry processes<sup>97</sup>, and also in certain combustion reactions. These species are highly reactive and very difficult to isolate and characterize<sup>98, 99</sup>. Several calculations were reported on the electronic structure of Criegee Intermediate species at their equilibrium configurations<sup>100, 101</sup>. 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. <sup>94</sup> are an exploration of a sequence of isomerization processes followed by decomposition into  $\text{CO-H}_2\text{O}$ . The simulations are for  $T = 300\text{K}$ , starting from the first transition state along the reaction sequence. This transition state corresponds to the barrier between  $\text{CH}_2\text{OO}$  and dioxirane  $\text{CH}_2\text{O}_2$ , which by transition state rate calculations takes about 2 hours to surmount. Snapshots from the dynamics are shown in Fig. 2.

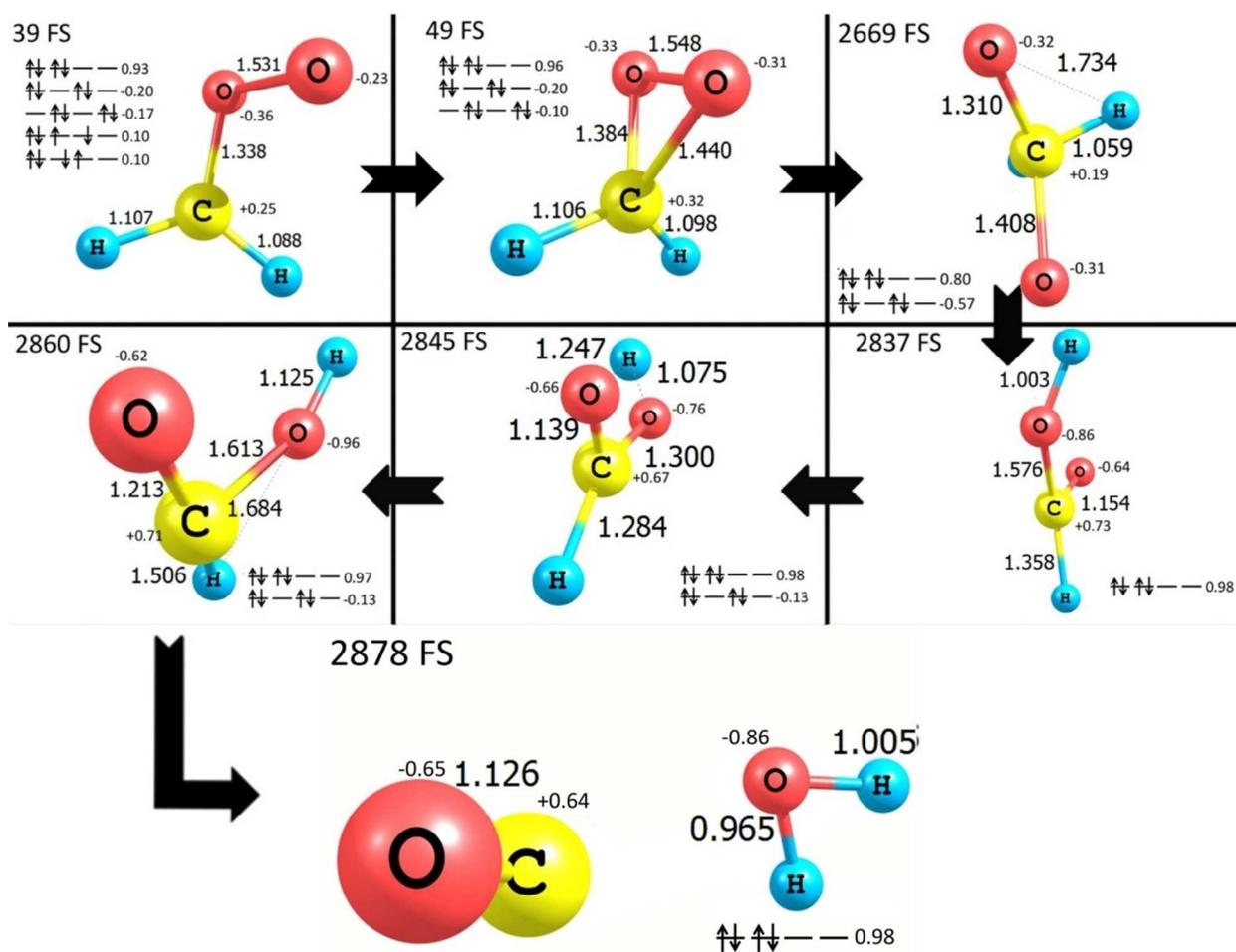


Figure 2: Snapshots from Ab-Initio Molecular Dynamics simulation of thermal decomposition of  $\text{CH}_2\text{OO}$  started from transition structure. For each structure main contributions to multi-reference wave functions are presented together with partial charges and distances in Angstroms.

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 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)<sup>102</sup>. An excellent review of these methods is by A.I. Krylov<sup>102</sup>. Several very interesting dynamics simulations with EOM-CC potentials were reported by Krylov and coworkers<sup>103-105</sup>.

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<sup>106</sup> 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<sup>107</sup> 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<sup>108</sup>, 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<sup>109-113</sup>. 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<sup>109-113</sup>. 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<sub>2</sub> and ClF in Ar, later confirmed experimentally<sup>113</sup>. 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 methods 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<sub>3</sub>, H<sub>2</sub>SO<sub>4</sub> 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<sup>114-122</sup>. 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<sup>123, 124</sup>. 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 multireference 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<sup>125-135</sup>. 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<sup>136-138</sup>. 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<sup>139, 140</sup> 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<sup>141</sup>. 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<sub>3</sub>COOH at the frozen water surface<sup>142</sup> 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<sup>143</sup>. The main reaction channels in aldehyde photochemistry include the Norrish type I (the first step is the C-C<sub>γ</sub> cleavage), Norrish type II ( $\gamma$ -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<sub>γ</sub> bond resulting in a CHO and a C<sub>4</sub>H<sub>9</sub> radical) whereas 66 % of the trajectories tend to transfer a hydrogen from the C<sub>γ</sub> 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: Figure 3 show a histogram of the timescale distribution of Norrish I vs. Norrish II reactions.

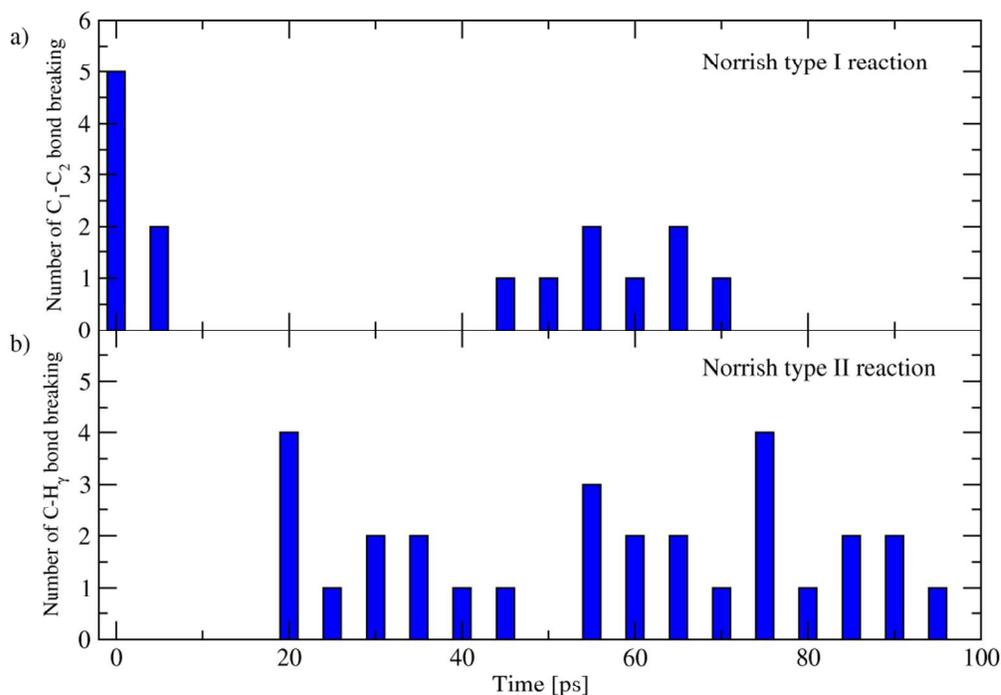


Fig. 3: Histogram of (a) Norrish type I reactions and (b) Norrish type II reactions in the time of 100 ps. Reprinted with permission from “D. Shemesh, Z. Lan and R. B. Gerber, *Journal of Physical Chemistry A*, 2013, **117**, 11711.” Copyright 2013 American Chemical Society.

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. Figure 4 shows snapshots of one trajectory showing the first step of the Norrish type II reaction.

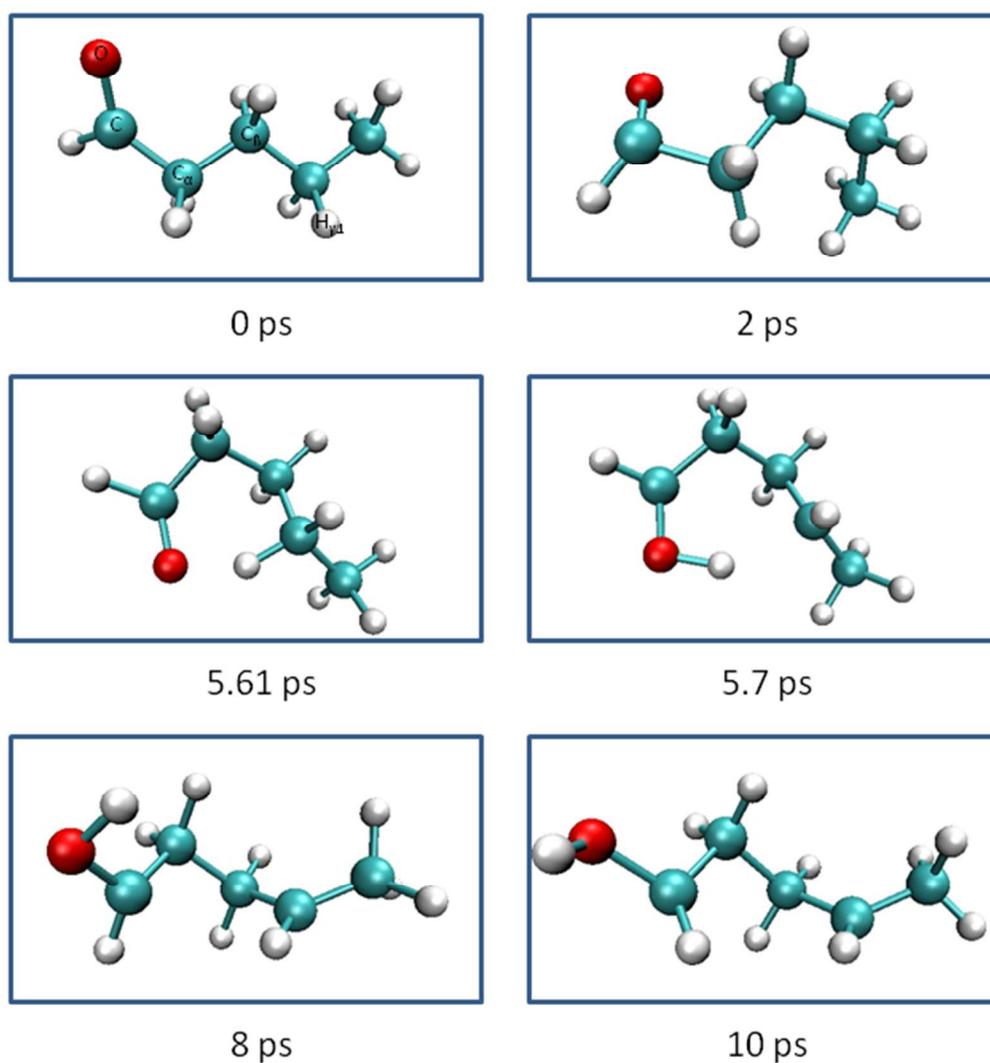


Fig.4: Snapshots of the  $\gamma$ -H transfer. Reprinted with permission from “D. Shemesh, Z. Lan and R. B. Gerber, *Journal of Physical Chemistry A*, 2013, **117**, 11711.” Copyright 2013 American Chemical Society.

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 $\gamma$  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<sup>144</sup> and ADC(2)<sup>145</sup> implemented in TURBOMOLE and found to be in very good agreement. As an example for the validation process we show here with Figure 5 the HOMO orbital along the dynamics of the C-C $\gamma$  cleavage, the first step in the Norrish I reaction.

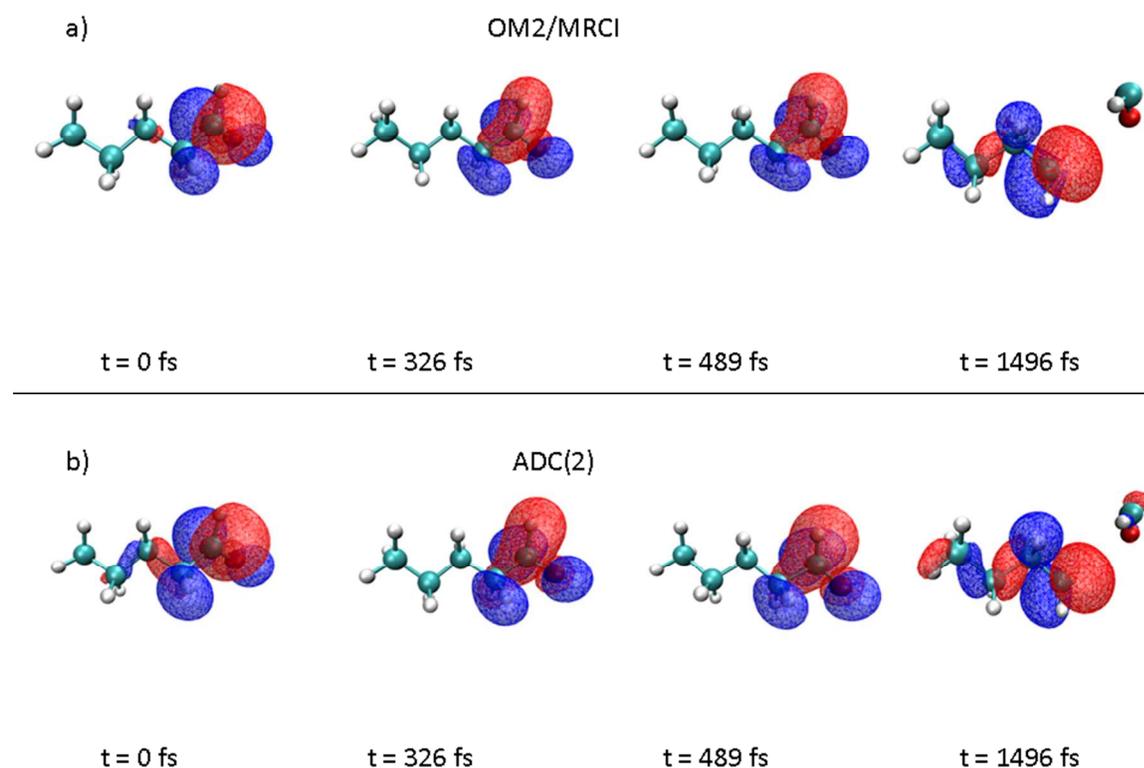


Fig. 5: HOMO orbital structure for snapshots in the dynamics of C-C $\gamma$  cleavage (a) as calculated by OM2/MRCI and (b) as calculated by ADC(2). Reprinted with permission from “D. Shemesh, Z. Lan and R. B. Gerber, *Journal of Physical Chemistry A*, 2013, **117**, 11711.” Copyright 2013 American Chemical Society.

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  $\pi^*$  orbital. After the cleavage, 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 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<sup>146</sup>. 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 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 it 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<sup>147</sup>. 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 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. An excellent review is by Weinhold<sup>148</sup>. 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<sup>149</sup>. 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<sup>148, 150</sup>. The theory of Natural Bond Orbitals (NBO) has been applied to a large variety of topics using static electronic structure calculations. However, there has been few uses of NBO as an analysis tool in AIMD simulations<sup>151, 152</sup>. To the best of our knowledge, the first application of the NBO method to analyze AIMD simulations was by Hirshberg and Gerber<sup>151</sup>. 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. 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 steps 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<sup>153</sup>. Analysis of the NBO bond orders and partial charges obtained using Natural Resonance Theory allowed the identification of a retro Diels Alder (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. Figure 6 shows the decomposition mechanisms for 3 isomers of  $N_6$  and the changes in partial charges and bond orders along these trajectories.

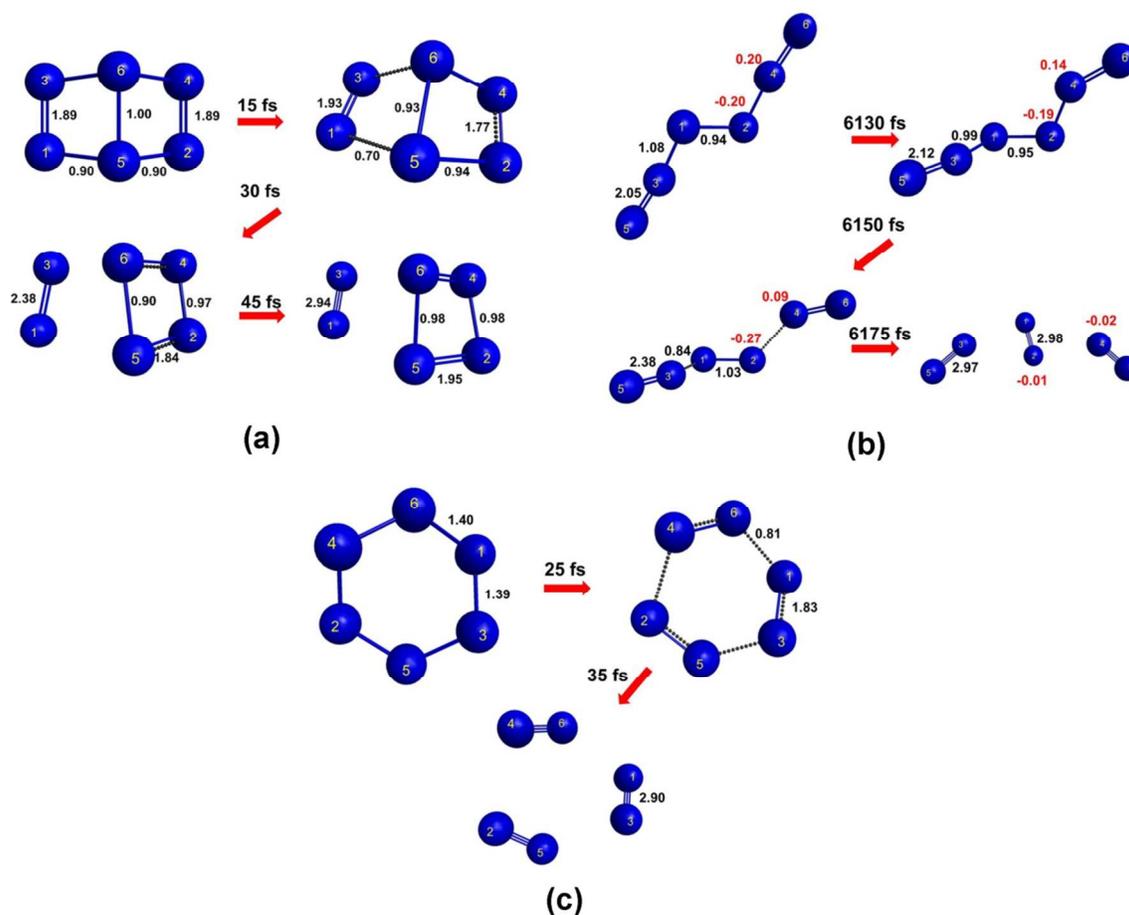


Fig.6: NBO bond orders and partial charges along the decomposition dynamics of 3 isomers of  $N_6$ . Bond orders are in black and partial charges are in red. Panel (a) shows the Dewar benzene isomer. Following the bond orders on-the-fly revealed a two step decomposition mechanism. The first step is shown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

Another recent application of NBO theory to the study of changes in electronic properties during AIMD simulations was done by Kroger et al<sup>152</sup>. The authors studied the hydrolysis of polyphosphazenes using the B3LYP level of theory and the atom-centered density matrix propagation (ADMP) scheme<sup>154</sup>. 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  $\sigma$  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<sup>143</sup>. 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 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<sup>155</sup>. 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.<sup>156-166</sup>

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

Hammerich et al. used<sup>167</sup> MLWF to analyze the mechanism of the reaction of NO<sub>x</sub> 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.<sup>167</sup> used CPMD simulations done at the BLYP-D level of theory to study the reaction of the NO<sub>2</sub> asymmetric dimer (ONONO<sub>2</sub>) 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<sub>2</sub> 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 attempted 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 semi-empirical 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 insight 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 for 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<sup>168</sup>. We believe that this may be one of the most exciting goals for studying dynamics of chemical reactions using directly electronic structure methods.

#### Acknowledgement

We thank Professor A.D.Hammerich and Drs. S.Riikonen and G.Murdachaew for helpful discussions.

Research described in this paper was supported by the Israel Science Foundation (ISF grant 172/12), the National Science Foundation, USA (AirUCI grant CHE 0909227 and GreenPlanet Computing Facility CHE 0840513), Resources in the framework of the Fi.Di.Pro.Program (RGB) at the University of Helsinki, and the CSC-IT Center for Science Computing (Finland).

#### References:

1. A. C. T. van Duin, S. Dasgupta, F. Lorant and W. A. Goddard, *Journal of Physical Chemistry A*, 2001, **105**, 9396.
2. R. Car and M. Parrinello, *Physical Review Letters*, 1985, **55**, 2471.
3. D. Marx and J. Hutter, *An Initio Molecular Dynamics: Basic Theory and Advanced Methods*, Cambridge University Press, New York, 2009.
4. R. N. Barnett and U. Landman, *Physical Review B*, 1993, **48**, 2081.
5. M. Pagliai, S. Raugei, G. Cardini and V. Schettino, *Physical Chemistry Chemical Physics*, 2001, **3**, 4870.
6. K. Leung and S. B. Rempe, *Journal of Chemical Physics*, 2005, **122**, 184506.

7. M. Tuckerman, K. Laasonen, M. Sprik and M. Parrinello, *Journal of Chemical Physics*, 1995, **103**, 150.
8. Y. X. Wang and P. B. Balbuena, *Journal of Physical Chemistry B*, 2005, **109**, 14896.
9. X. H. Qian, M. R. Nimlos, M. Davis, D. K. Johnson and M. E. Himmel, *Carbohydrate Research*, 2005, **340**, 2319.
10. S. Schenk, B. Kirchner and M. Reiher, *Chemistry-a European Journal*, 2009, **15**, 5073.
11. J. P. Perdew and Y. Wang, *Physical Review B*, 1992, **45**, 13244.
12. Y. Ishikawa, R. C. Binning and N. S. Shramek, *Chemical Physics Letters*, 1999, **313**, 341.
13. Y. Ishikawa and R. C. Binning, *Chemical Physics Letters*, 2001, **338**, 353.
14. Y. Ishikawa and R. C. Binning, *Chemical Physics Letters*, 2002, **358**, 509.
15. Y. Ishikawa, T. Nakajima, T. Yanai and K. Hirao, *Chemical Physics Letters*, 2002, **363**, 458.
16. L. Sun, W. L. Hase and K. Song, *Journal of the American Chemical Society*, 2001, **123**, 5753.
17. X. S. Li, J. M. Millam and H. B. Schlegel, *Journal of Chemical Physics*, 2000, **113**, 10062.
18. S. Anand and H. B. Schlegel, *Journal of Physical Chemistry A*, 2002, **106**, 11623.
19. S. Rudic, C. Murray, J. N. Harvey and A. J. Orr-Ewing, *Journal of Chemical Physics*, 2004, **120**, 186.
20. Y. Miller and R. B. Gerber, *Physical Chemistry Chemical Physics*, 2008, **10**, 1091.
21. Y. Miller, B. J. Finlayson-Pitts and R. B. Gerber, *Journal of the American Chemical Society*, 2009, **131**, 12180.
22. S. T. Ishikawa and T. Nakajima, *International Journal of Quantum Chemistry*, 2009, **109**, 2143.
23. J. D. Raff, B. Njagic, W. L. Chang, M. S. Gordon, D. Dabdub, R. B. Gerber and B. J. Finlayson-Pitts, *Proceedings of the National Academy of Sciences of the United States of America*, 2009, **106**, 13647.
24. B. Njagic, J. D. Raff, B. J. Finlayson-Pitts, M. S. Gordon and R. B. Gerber, *Journal of Physical Chemistry A*, 2010, **114**, 4609.
25. A. Kumar, M. Kolaski, H. M. Lee and K. S. Kim, *Journal of Physical Chemistry A*, 2008, **112**, 5502.
26. H. Tachikawa and A. J. Orr-Ewing, *Journal of Physical Chemistry A*, 2008, **112**, 11575.
27. H. Tachikawa, *Journal of Physical Chemistry A*, 2010, **114**, 10309.
28. H. Tachikawa, *Physical Chemistry Chemical Physics*, 2011, **13**, 11206.
29. M. Sugimoto, M. Shiga and M. Tachikawa, *Computational and Theoretical Chemistry*, 2011, **975**, 31.
30. H. M. Lee and K. S. Kim, *Journal of Computational Chemistry*, 2013, **34**, 1589.
31. H. Tachikawa and T. Takada, *Chemical Physics*, 2013, **415**, 76.
32. S. Cheon, K. Song and W. L. Hase, *Journal of Molecular Structure-Theochem*, 2006, **771**, 27.

33. J. Mikosch, S. Trippel, C. Eichhorn, R. Otto, U. Lourderaj, J. X. Zhang, W. L. Hase, M. Weidemuller and R. Wester, *Science*, 2008, **319**, 183.
34. J. X. Zhang, U. Lourderaj, R. Sun, J. Mikosch, R. Wester and W. L. Hase, *Journal of Chemical Physics*, 2013, **138**, 114309.
35. L. P. Sun and W. L. Hase, *Journal of Chemical Physics*, 2004, **121**, 8831.
36. S. Anand and H. B. Schlegel, *Physical Chemistry Chemical Physics*, 2004, **6**, 5166.
37. J. Zhou and H. B. Schlegel, *Journal of Physical Chemistry A*, 2009, **113**, 1453.
38. L. P. Sun and W. L. Hase, *Journal of Chemical Physics*, 2010, **133**.
39. J. P. Camden and G. C. Schatz, *Journal of Physical Chemistry A*, 2006, **110**, 13681.
40. A. L. Brunsvold, J. M. Zhang, H. P. Upadhyaya, T. K. Minton, J. P. Camden, J. T. Paci and G. C. Schatz, *Journal of Physical Chemistry A*, 2007, **111**, 10907.
41. X. F. Tian, T. Gao, N. He and Z. H. Zhang, *Molecular Physics*, 2008, **106**, 2717.
42. X. F. Tian, T. Gao, N. He and Z. H. Zhang, *Chemical Physics*, 2008, **354**, 142.
43. H. G. Yu, *Astrophysical Journal Letters*, 2009, **706**, L52.
44. P. Lu, X. Y. Kuang, H. F. Li and H. Q. Wang, *International Journal of Quantum Chemistry*, 2011, **111**, 4433.
45. M. E. Varner, B. J. Finlayson-Pitts and R. B. Gerber, *Physical Chemistry Chemical Physics*, 2014, DOI: 10.1039/c3cp55024a.
46. B. J. Finlayson-Pitts, L. M. Wingen, A. L. Sumner, D. Syomin and K. A. Ramazan, *Physical Chemistry Chemical Physics*, 2003, **5**, 223.
47. W. G. Liu and W. A. Goddard, *Journal of the American Chemical Society*, 2012, **134**, 12970.
48. R. A. Relph, T. L. Guasco, B. M. Elliott, M. Z. Kamrath, A. B. McCoy, R. P. Steele, D. P. Schofield, K. D. Jordan, A. A. Viggiano, E. E. Ferguson and M. A. Johnson, *Science*, 2010, **327**, 308.
49. R. P. Steele, M. Head-Gordon and J. C. Tully, *Journal of Physical Chemistry A*, 2010, **114**, 11853.
50. R. Ahlrichs, M. Bar, M. Haser, H. Horn and C. Kolmel, *Chemical Physics Letters*, 1989, **162**, 165.
51. I. Wolf, A. Shapira, R. Giniger, Y. Miller, R. B. Gerber and O. Cheshnovsky, *Angewandte Chemie-International Edition*, 2008, **47**, 6272.
52. S. Grimme, *Journal of Computational Chemistry*, 2004, **25**, 1463.
53. S. Grimme, *Journal of Computational Chemistry*, 2006, **27**, 1787.
54. Y. S. Jung, R. C. Lochan, A. D. Dutoi and M. Head-Gordon, *Journal of Chemical Physics*, 2004, **121**, 9793.
55. R. A. Distasio and M. Head-Gordon, *Molecular Physics*, 2007, **105**, 1073.
56. J. VandeVondele and M. Sprik, *Physical Chemistry Chemical Physics*, 2005, **7**, 1363.
57. O. Marsalek, F. Uhlig, J. VandeVondele and P. Jungwirth, *Accounts of Chemical Research*, 2012, **45**, 23.
58. I. Tavernelli, *Journal of Physical Chemistry A*, 2007, **111**, 13528.
59. R. Baer and D. Neuhauser, *Physical Review Letters*, 2005, **94**, 043002.
60. C. Muller and B. Paulus, *Physical Chemistry Chemical Physics*, 2012, **14**, 7605.

61. D. G. Fedorov, T. Nagata and K. Kitaura, *Physical Chemistry Chemical Physics*, 2012, **14**, 7562.
62. Y. Mochizuki, T. Nakano, Y. Komeiji, K. Yamashita, Y. Okiyama, H. Yoshikawa and H. Yamataka, *Chemical Physics Letters*, 2011, **504**, 95.
63. T. Fujita, T. Nakano and S. Tanaka, *Chemical Physics Letters*, 2011, **506**, 112.
64. A. Warshel and M. Levitt, *Journal of Molecular Biology*, 1976, **103**, 227.
65. L. P. Sun, E. Y. Chang, K. Y. Song and W. L. Hase, *Canadian Journal of Chemistry-Revue Canadienne De Chimie*, 2004, **82**, 891.
66. C. N. Rowley and B. Roux, *Journal of Chemical Theory and Computation*, 2012, **8**, 3526.
67. U. Lourderaj, K. Song, T. L. Windus, Y. Zhuang and W. L. Hase, *Journal of Chemical Physics*, 2007, **126**, 044105.
68. E. J. Bylaska, J. Q. Weare and J. H. Weare, *Journal of Chemical Physics*, 2013, **139**.
69. R. P. Steele and J. C. Tully, *Chemical Physics Letters*, 2010, **500**, 167.
70. R. P. Steele, *Journal of Chemical Physics*, 2013, **139**, 011102.
71. E. Tapavicza, G. D. Bellchambers, J. C. Vincent and F. Furche, *Physical Chemistry Chemical Physics*, 2013, **15**, 18336.
72. E. Runge and E. K. U. Gross, *Physical Review Letters*, 1984, **52**, 997.
73. R. Send and F. Furche, *Journal of Chemical Physics*, 2010, **132**, 044107.
74. M. Born and K. Huang, *Dynamical Theory of Crystal Lattices*, Clarendon Press, Oxford, 1954.
75. J. C. Tully, *Journal of Chemical Physics*, 1990, **93**, 1061.
76. E. Tapavicza, A. M. Meyer and F. Furche, *Physical Chemistry Chemical Physics*, 2011, **13**, 20986.
77. B. F. E. Curchod, U. Rothlisberger and I. Tavernelli, *Chemphyschem*, 2013, **14**, 1314.
78. I. Tavernelli, B. F. E. Curchod and U. Rothlisberger, *Chemical Physics*, 2011, **391**, 101.
79. I. Tavernelli, E. Tapavicza and U. Rothlisberger, *Journal of Molecular Structure-Theochem*, 2009, **914**, 22.
80. M. Ben-Nun and T. J. Martinez, *Chemical Physics Letters*, 1998, **298**, 57.
81. K. K. Baeck and T. J. Martinez, *Chemical Physics Letters*, 2003, **375**, 299.
82. H. C. Choi, K. K. Baeck and T. J. Martinez, *Chemical Physics Letters*, 2004, **398**, 407.
83. B. G. Levine and T. J. Martinez, *Annual Review of Physical Chemistry*, 2007, **58**, 613.
84. A. M. Virshup, C. Punwong, T. V. Pogorelov, B. A. Lindquist, C. Ko and T. J. Martinez, *Journal of Physical Chemistry B*, 2009, **113**, 3280.
85. T. J. Martinez, *Accounts of Chemical Research*, 2006, **39**, 119.
86. M. Kayanuma, T. Taketsugu and K. Ishii, *Theoretical Chemistry Accounts*, 2008, **120**, 191.
87. M. S. Gordon, G. Chaban and T. Taketsugu, *Journal of Physical Chemistry*, 1996, **100**, 11512.
88. P. Celani and H. J. Werner, *Journal of Chemical Physics*, 2003, **119**, 5044.

89. M. W. Schmidt and M. S. Gordon, *Annual Review of Physical Chemistry*, 1998, **49**, 233.
90. M. Ben-Nun, J. Quenneville and T. J. Martinez, *Journal of Physical Chemistry A*, 2000, **104**, 5161.
91. M. Ben-Nun and T. J. Martinez, *Advances in Chemical Physics*, Volume 121, 2002, **121**, 439.
92. M. Ben-Nun, F. Molnar, K. Schulten and T. J. Martinez, *Proceedings of the National Academy of Sciences of the United States of America*, 2002, **99**, 1769.
93. J. Kalinowski, M. Rasanen and R. B. Gerber, *Chemical Physics Letters*, 2012, **535**, 44.
94. J. Kalinowski, M. Rasanen, P. Heinonen, I. Kilpelainen and R. B. Gerber, *Angewandte Chemie - International Edition*, 2013, DOI:10.1002/anie.201307286.
95. K. Hirao, *Chemical Physics Letters*, 1993, **201**, 59.
96. D. Y. Hwang and A. M. Mebel, *Journal of Chemical Physics*, 1998, **109**, 10847.
97. J. H. Kroll and J. H. Seinfeld, *Atmospheric Environment*, 2008, **42**, 3593.
98. O. Welz, J. D. Savee, D. L. Osborn, S. S. Vasu, C. J. Percival, D. E. Shallcross and C. A. Taatjes, *Science*, 2012, **335**, 204.
99. Y. T. Su, Y. H. Huang, H. A. Witek and Y. P. Lee, *Science*, 2013, **340**, 174.
100. D. Cremer, J. Gauss, E. Kraka, J. F. Stanton and R. J. Bartlett, *Chemical Physics Letters*, 1993, **209**, 547.
101. E. Milliodos, K. Ruedenberg and S. S. Xantheas, *Angewandte Chemie-International Edition*, 2013, **52**, 5736.
102. A. I. Krylov, *Annual Review of Physical Chemistry*, 2008, **59**, 433.
103. B. C. Shepler, E. Epifanovsky, P. Zhang, J. M. Bowman, A. I. Krylov and K. Morokuma, *Journal of Physical Chemistry A*, 2008, **112**, 13267.
104. S. V. Levchenko, H. Reisler, A. I. Krylov, O. Gessner, A. Stolow, H. C. Shi and A. L. L. East, *Journal of Chemical Physics*, 2006, **125**, 084301.
105. E. Kamarchik, O. Kostko, J. M. Bowman, M. Ahmed and A. I. Krylov, *Journal of Chemical Physics*, 2010, **132**, 194311.
106. I. S. Y. Wang and M. Karplus, *Journal of the American Chemical Society*, 1973, **95**, 8160.
107. J. J. P. Stewart, L. P. Davis and L. W. Burggraf, *Journal of Computational Chemistry*, 1987, **8**, 1117.
108. A. Gonzalezlafont, T. N. Truong and D. G. Truhlar, *Journal of Physical Chemistry*, 1991, **95**, 4618.
109. V. S. Batista and D. F. Coker, *Journal of Chemical Physics*, 1996, **105**, 4033.
110. A. I. Krylov and R. B. Gerber, *Journal of Chemical Physics*, 1997, **106**, 6574.
111. A. Borowski and O. Kuhn, *Theoretical Chemistry Accounts*, 2007, **117**, 521.
112. M. Bargheer, A. Cohen, R. B. Gerber, M. Guhr, M. V. Korolkov, J. Manz, M. Y. Niv, M. Schroder and N. Schwentner, *Journal of Physical Chemistry A*, 2007, **111**, 9573.
113. M. Bargheer, M. Y. Niv, R. B. Gerber and N. Schwentner, *Physical Review Letters*, 2002, **89**, 108301.
114. Y. Miller, G. M. Chaban, B. J. Finlayson-Pitts and R. B. Gerber, *Journal of Physical Chemistry A*, 2006, **110**, 5342.

115. Y. Miller and R. B. Gerber, *Journal of the American Chemical Society*, 2006, **128**, 9594.
116. M. Shmilovits-Ofir and R. B. Gerber, *Journal of the American Chemical Society*, 2011, **133**, 16510.
117. M. Shmilovits-Ofir, Y. Miller and R. B. Gerber, *Physical Chemistry Chemical Physics*, 2011, **13**, 8715.
118. D. Shemesh and R. B. Gerber, *Journal of Physical Chemistry A*, 2006, **110**, 8401.
119. D. Shemesh and R. B. Gerber, *Journal of Chemical Physics*, 2005, **122**.
120. D. Shemesh, R. Baer, T. Seideman and R. B. Gerber, *Journal of Chemical Physics*, 2005, **122**.
121. D. Shemesh, G. M. Chaban and R. B. Gerber, *Journal of Physical Chemistry A*, 2004, **108**, 11477.
122. M. A. Kamboures, S. A. Nizkorodov and R. B. Gerber, *Proceedings of the National Academy of Sciences of the United States of America*, 2010, **107**, 6600.
123. D. Doron, D. T. Major, A. Kohen, W. Thiel and X. Wu, *Journal of Chemical Theory and Computation*, 2011, **7**, 3420.
124. A. Vardi-Kilshtain, D. T. Major, A. Kohen, H. Engel and D. Doron, *Journal of Chemical Theory and Computation*, 2012, **8**, 4786.
125. A. Koslowski, M. E. Beck and W. Thiel, *Journal of Computational Chemistry*, 2003, **24**, 714.
126. E. Fabiano, T. W. Keal and W. Thiel, *Chemical Physics*, 2008, **349**, 334.
127. T. Tuttle and W. Thiel, *Physical Chemistry Chemical Physics*, 2008, **10**, 2159.
128. A. Kazaryan, Z. G. Lan, L. V. Schafer, W. Thiel and M. Filatov, *Journal of Chemical Theory and Computation*, 2011, **7**, 2189.
129. T. W. Keal, M. Wanko and W. Thiel, *Theoretical Chemistry Accounts*, 2009, **123**, 145.
130. T. Benighaus and W. Thiel, *Journal of Chemical Theory and Computation*, 2008, **4**, 1600.
131. G. L. Cui, Z. G. Lan and W. Thiel, *Journal of the American Chemical Society*, 2012, **134**, 1662.
132. X. Wu, A. Koslowski and W. Thiel, *Journal of Chemical Theory and Computation*, 2012, **8**, 2272.
133. G. L. Cui and W. Thiel, *Physical Chemistry Chemical Physics*, 2012, **14**, 12378.
134. J. B. Schonborn, A. Koslowski, W. Thiel and B. Hartke, *Physical Chemistry Chemical Physics*, 2012, **14**, 12193.
135. L. Sporkel, G. L. Cui and W. Thiel, *Journal of Physical Chemistry A*, 2013, **117**, 4574.
136. K. Sastry, D. D. Johnson, A. L. Thompson, D. E. Goldberg, T. J. Martinez, J. Leiding and J. Owens, *Materials and Manufacturing Processes*, 2007, **22**, 553.
137. A. Toniolo, S. Olsen, L. Manohar and T. J. Martinez, *Faraday Discussions*, 2004, **127**, 149.
138. A. Toniolo, G. Granucci and T. J. Martinez, *Journal of Physical Chemistry A*, 2003, **107**, 3822.
139. A. Toniolo, G. Granucci, S. Inglesse and M. Persico, *Physical Chemistry Chemical Physics*, 2001, **3**, 4266.

140. M. Persico, G. Granucci, S. Inglesse, T. Laino and A. Toniolo, *Journal of Molecular Structure-Theochem*, 2003, **621**, 119.
141. D. Shemesh and R. B. Gerber, *Molecular Physics*, 2012, **110**, 605.
142. S. A. Epstein, D. Shemesh, V. T. Tran, S. A. Nizkorodov and R. B. Gerber, *Journal of Physical Chemistry A*, 2012, **116**, 6068.
143. D. Shemesh, Z. Lan and R. B. Gerber, *Journal of Physical Chemistry A*, 2013, **117**, 11711.
144. F. Weigend and M. Haser, *Theoretical Chemistry Accounts*, 1997, **97**, 331.
145. J. Schirmer, *Physical Review A*, 1982, **26**, 2395.
146. H. Lignell, S. A. Epstein, M. R. Marvin, D. Shemesh, R. B. Gerber and S. A. Nizkorodov, *Journal of Physical Chemistry*, 2013, **117**, 12930.
147. M. P. Allen and D. J. Tildesley, *Computer Simulations of Liquids*, Oxford University Press, New York, 1987.
148. F. Weinhold, *Journal of Computational Chemistry*, 2012, **33**, 2363.
149. P. O. Löwdin, *Reviews of Modern Physics*, 1960, **32**, 328.
150. E. D. Glendening, C. R. Landis and F. Weinhold, *Wiley Interdisciplinary Reviews-Computational Molecular Science*, 2012, **2**, 1.
151. B. Hirshberg and R. B. Gerber, *Chemical Physics Letters*, 2012, **531**, 46.
152. J. L. Kroger, J. R. Fried and A. A. Skelton, *International Journal of Quantum Chemistry*, 2013, **113**, 63.
153. M. T. Nguyen, *Coordination Chemistry Reviews*, 2003, **244**, 93.
154. H. B. Schlegel, J. M. Millam, S. S. Iyengar, G. A. Voth, A. D. Daniels, G. E. Scuseria and M. J. Frisch, *Journal of Chemical Physics*, 2001, **114**, 9758.
155. N. Marzari, I. Souza and D. Vanderbilt, *Psi-K Newsletter*, 2003, **57**, 129.
156. M. Citroni, R. Bini, M. Pagliai, G. Cardini and V. Schettino, *Journal of Physical Chemistry B*, 2010, **114**, 9420.
157. F. Costanzo, P. L. Silvestrelli, M. Gleria and A. B. Boscoletto, *Journal of Inorganic and Organometallic Polymers and Materials*, 2013, **23**, 1397.
158. P. H. L. Sit, F. Zipoli, J. Chen, R. Car, M. H. Cohen and A. Selloni, *Chemistry-a European Journal*, 2011, **17**, 12136.
159. N. J. Mosey, *Journal of Chemical Physics*, 2010, **132**.
160. M. Mugnai, M. Pagliai, G. Cardini and V. Schettino, *Journal of Chemical Theory and Computation*, 2008, **4**, 646.
161. J. W. Handgraaf and E. J. Meijer, *Journal of the American Chemical Society*, 2007, **129**, 3099.
162. F. Zipoli, M. Bernasconi and A. Laio, *Chemphyschem*, 2005, **6**, 1772.
163. J. M. Stubbs and D. Marx, *Chemistry-a European Journal*, 2005, **11**, 2651.
164. M. Mugnai, G. Cardini and V. Schettino, *Physical Review B*, 2004, **70**.
165. M. Mugnai, G. Cardini and S. V, *Journal of Chemical Physics*, 2004, **120**, 5327.
166. D. Aktah, D. Passerone and M. Parrinello, *Journal of Physical Chemistry A*, 2004, **108**, 848.
167. A. D. Hammerich, B. J. Finlayson-Pitts and R. B. Gerber, *Journal of Physical Chemistry Letters*, 2012, **3**, 3405.
168. T. K. Roy and R. B. Gerber, *Physical Chemistry Chemical Physics*, 2013, **15**, 9468.

