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Femtochemistry

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Abstract: A brief review of the developments leading to the advent of femtochemistry is presented, along with the major achievements that have marked the past fifteen years since the birth of the field.

Keywords: Biological systems · Condensed phases · Femtochemistry · Isolated molecules

The Nobel Prize for Chemistry for 1999 was awarded to Ahmed Zewail, Professor of Chemistry and Physics at the California Institute of Technology, for 'his pioneering investigation of fundamental chemical reactions, using ultra-short laser flashes, on the timescale on which the reactions actually occur. Professor Zewail's contributions have brought about a revolution in chemistry and adjacent sciences, since this type of investigation allows us to understand and predict important reactions' [1]. His works and discoveries gave birth to a new branch of chemistry, *femtochemistry*, a term he coined while celebrating his first results at a champagne party in 1987.

Femtochemistry is concerned with the visualization of elementary processes in molecules. These involve the breaking and making of chemical bonds, which occur on the very short timescale of femtoseconds (1 fs = 10^{-15} s) to picoseconds (1 ps = 10^{-12} s). This can be better understood if one thinks of an elongation or a contraction of a chemical bond, *i.e.* a motion that corresponds to half a molecular oscillation. Thus in H_2 (the lightest molecule), the vibrational period is 7.6 fs. In the I_2 molecule, the vibrational period is 160 fs. On these short timescales the distances traveled are small, typically tenths of Ångströms, but these are crucial in chemical processes. To bring things to a more 'human' scale, one femtosecond is to one second what one second is to thirty-two million years!

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1. Historical Background

The pioneering studies of A.H. Zewail and co-workers were the culmination of a century of efforts aimed at observing chemical reactions in real-time. The story starts at the end of the XIXth century, more precisely in 1889, when Svante Arrhenius presented a description of how chemical reactions vary as a function of temperature. His well-known formula describes the temperature dependence of the reaction rate k(T):

$$k(T) = A\, e^{-E_a/kT}$$

where k is the Boltzmann constant, T is the temperature (in Kelvin) and E_a is the so-called activation energy, *i.e.* the height of the barrier up to a hypothetical state called by Arrhenius, the 'activated complex' (see Fig. 1). The Arrhenius equation has been used with success by chemists and physicists to describe kinetic processes in a large class of media.

In 1931, H. Eyring and M. Polanyi [2] developed the first potential energy surface for the $H_2 + H \rightarrow H + H_2$ reaction and J. Hirschfelder, Eyring and B. Topley [3] performed the first trajectory calculation with femtosecond steps in 1936 using the then available computing power. This was

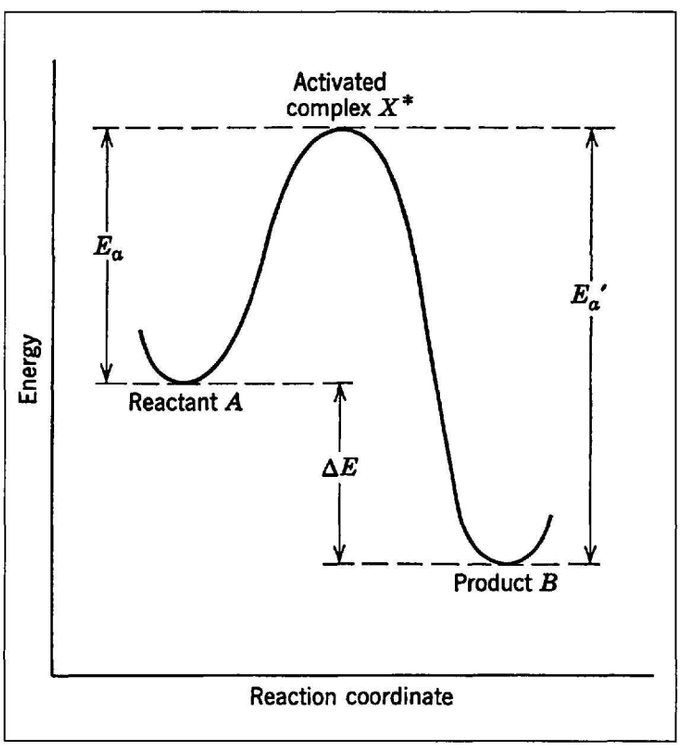


Fig. 1. Relation between the activation energies for the forward (E_a) and reverse (E_a') reactions and the change (ΔE) in internal energy in the reaction.

the birth of 'reaction dynamics', which allowed one to think in terms of potential energy surfaces superimposed by dynamics: the path of a reaction from reactants to products, through valleys and mountains, with the transition state at the saddle point. Around that time, Eyring [4], M.G. Evans and Polanyi [5] formulated the transition-state theory, which gave an explicit expression for the pre-exponential factor A in the Arrhenius equation by invoking statistical mechanics. The theory gave an analytical expression for the rate constant with a 'frequency' for the passage through the transition state. This frequency factor is typically 10^{13} Hertz, the typical value for the frequency of molecular vibrations!

Shortly before these developments, the foundations of quantum mechanics were being laid down. In 1926, Erwin Schrödinger introduced the idea of wave groups in order to make a natural connection between quantum and classical descriptions [6]. A year later, Ehrenfest published his famous theorem [7], outlining the regime for the transition from a quantum to a classical description: the quantum expectation values behave classically in the limit of large quantum numbers. The use of wave groups in physics (and obviously in chemistry) remained limited to a few theoretical examples.

Experimentally it was not possible to synthesize wave groups (now called wave packets). At that time, a temporal resolution of seconds to at best milliseconds was possible in chemistry by means of the stopped-flow technique. The field had to wait several decades in order to reach the required time resolution. The long-standing efforts to improve the latter were the work of many researchers. G. Porter and R. Norrish introduced the flash photolysis technique which allowed millisecond time resolution [8]. By exposing a chemical solution to heat, pressure or an electrical shock, M. Eigen achieved the microsecond temporal resolution [9]. The advent of the pulsed nanosecond laser in the mid 1960s [10] and soon after of the picosecond laser [11] brought about a million times improvement in resolution. However, even on the short picosecond timescale, molecular states already reside in eigenstates (the static limit) and there is only one evolution observable, the change of population with time of that state. Hence, with picosecond spectroscopy employed in numerous applications in chemistry and biology, one is still concerned with kinetics, not dynamics. The advent of femtosecond laser technology, thanks to the work of C.V. Shank and co-workers [12] finally opened the door to femtochemistry, as one was now able to probe molecular motion in real-time. Indeed, as mentioned in the introduction, the vibrational periods of molecules are all larger than ~ 8 fs.

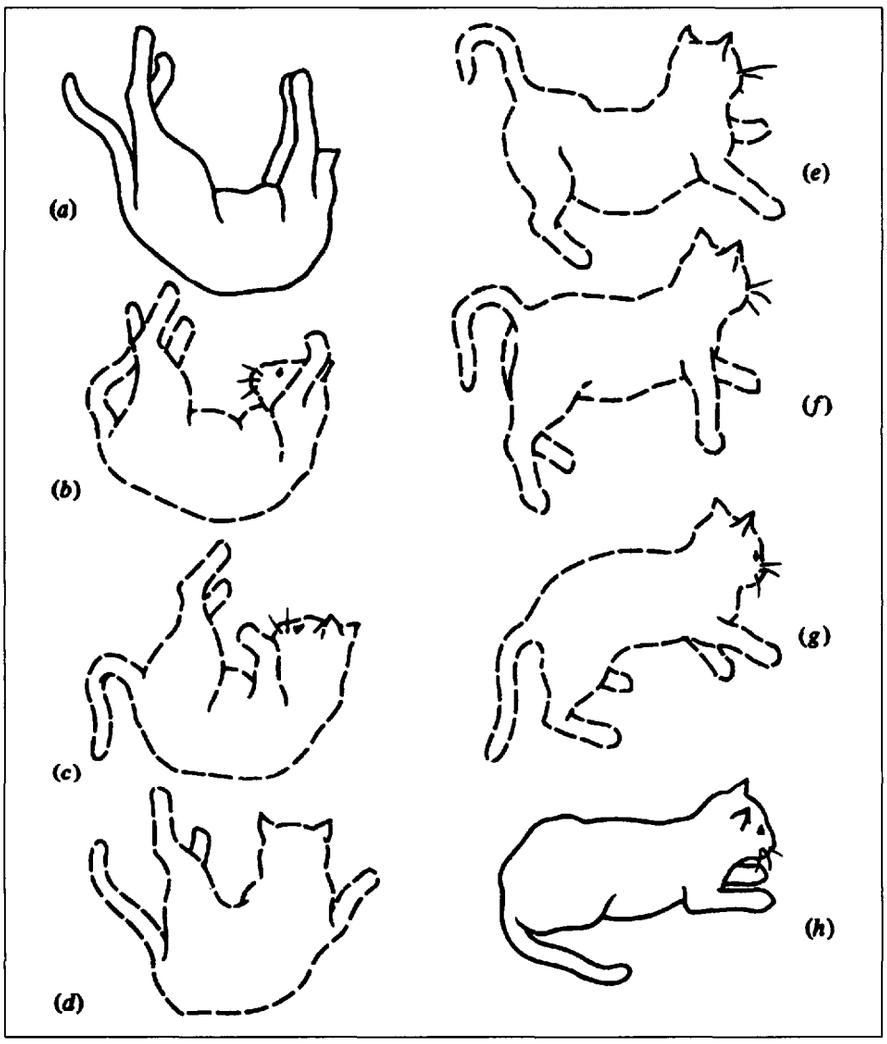


Fig. 2. In 1894, Edouard-Jacques Marey developed a shutter camera to capture the motion of animals. In the above figure, he used a camera with 0.2 sec time resolution to analyse how a cat, released legs up, falls on its feet. While the cat is undergoing translational motion from (a) to (e), it performs a first isomerization process in (c) to (d) followed by a second one from (d) to (e). This double isomerization preserves the symmetry of the cat, that reaches by (g) the ground in an excited state! From (g) to (h), the cat relaxes (similar to vibrational cooling in ground state molecules). The same principle was applied by A.H. Zewail and his group to capture the motion of molecules (or assemblies of molecules) while they undergo chemical change, except that his camera had a resolution of 0.000000000000001 sec! By analogy, the hands releasing the cat correspond to the pump pulse in Zewail's experiments, while the shutter camera taking snap shots of its motion corresponds to the probe pulse.

A wavepacket can now be prepared, as the temporal resolution is sufficiently short to 'freeze' the nuclei at a given internuclear separation, *i.e.* the time resolution is much shorter than the vibrational (and rotational) motions such that the wavepacket is prepared, highly localized, with the structure frozen on the excited-state potential surface. This ultrashort perturbation does not violate the uncertainty principle. On the contrary, a wavepacket is a *coherent* superposition of eigenstates and therefore, the system is coherently prepared. Because of this coherent synthesis, the transition from kinetics to dynamics is possible, and the high temporal resolution implies a spatial resolution, so that one is able to monitor the evolution of the system at atomic resolution!

In *kinetics* one looks at the overall population of substrates before the reaction and of products after the reaction, and conclusions are drawn about the reaction mechanism. Femtochemistry on the other hand is concerned with *dynamics*, as thanks to the atomic-scale resolution, one can think of the molecular system as a set of interaction spheres (the atoms) and reactions can be visualized directly.

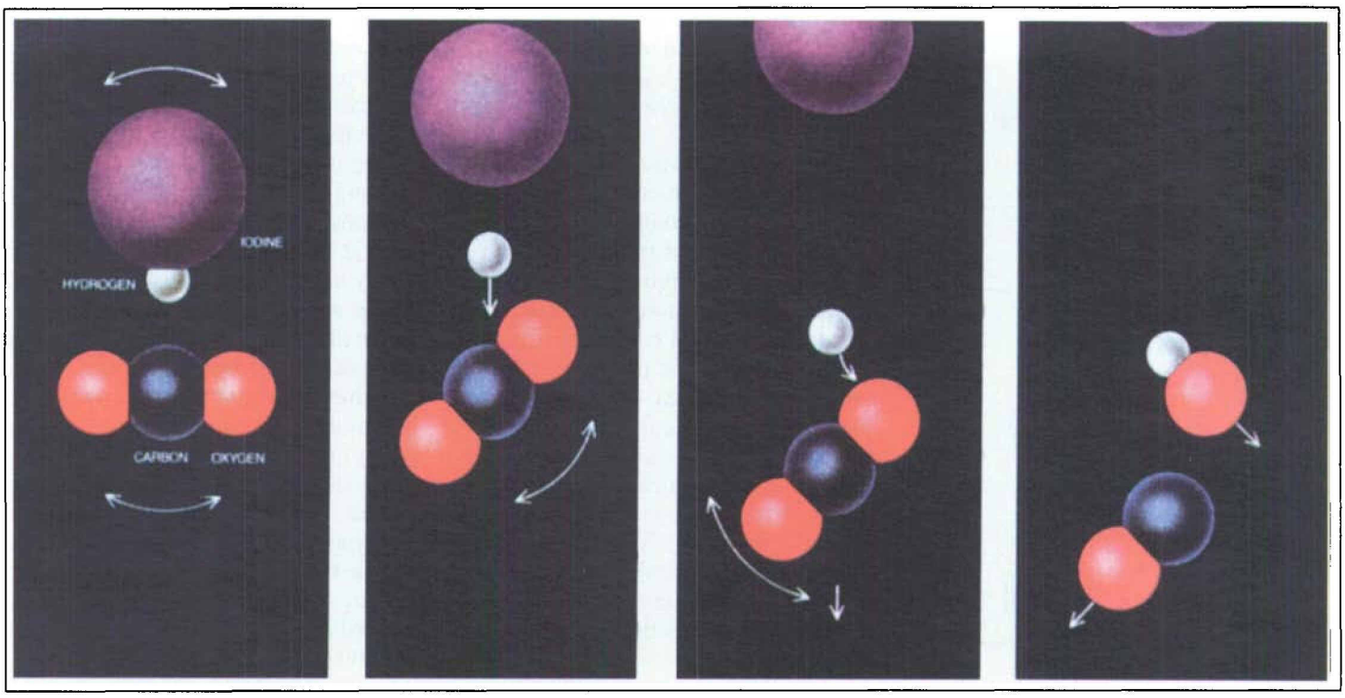


Fig. 3. Example of a bimolecular reaction. In the ground state the IH···CO_2 complex is weakly bound by hydrogen-bonding, the pump pulse dissociates the H atom from the HI molecule. The collision of the hydrogen atom with the carbon dioxide creates carbon monoxide, iodine and hydroxide. This reaction has been observed in real-time by Zewail and co-workers using femtosecond spectroscopy [16].

With this powerful tool in hand, Zewail and co-workers were able to observe the dynamical processes of bond breaking, bond making and of the cornerstone of reactivity, the transition state, with atomic-scale resolution. Swedish researcher S. Forsen of Lund University likened the situation, before the advent of femtochemistry, to an audience seeing only the very beginning and the very end of *Hamlet*: 'the main characters are introduced, then the curtain falls for a change of scenery, and, as it rises again, we see on the stage a considerable number of bodies and a few survivors. Not an easy task for the unexperienced to unravel what actually took place'. Now the stage is set to see the whole action!

With his ultrafast camera, Zewail and co-workers were able to capture each instant in the evolution of a molecular system and generate a 'molecular movie'. The principle is very similar to that used more than a hundred years ago in the then-nascent photography when shutter cameras with sub-second time resolution were developed by E. Muybridge and by E.-J. Marey to record the motion of animals (see Fig. 2).

To take a picture of a simple chemical reaction, Zewail and co-workers used two beams of femtosecond pulses and a fluorescence spectrometer. A first pulse of light (called the pump pulse) strikes the molecule and energizes it. If the photon energy is sufficient, it eventually breaks the molecule apart (dissociation). Out of this process, new chemical species (the fragments) are created. In order to clock their birth and to determine their order of appearance, another pulse travelling just a few femtoseconds behind the first, hits the fragments to give rise to emission of light which will thus be detected by the fluorescence spectrometer. The second pulse, called the probe pulse, can be timed precisely at different intervals to reveal how long it takes for various chemical species to appear and in what order they do so.

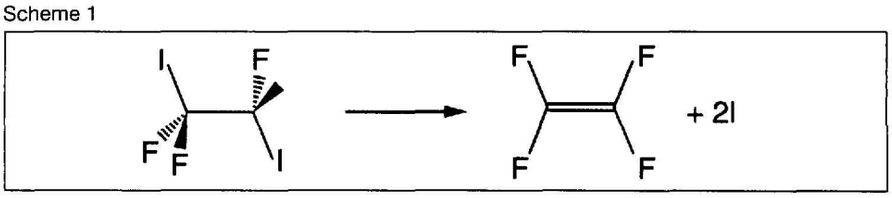
2. From Small Molecules to Complex Organic Molecules

The first age of femtochemistry was marked by the study of simple molecular systems, in order to establish the experimental methods and the theoretical concepts [13]. The experiment that gave birth to femtochemistry was carried out by Zewail and co-workers in 1987 on the dissociation of cyanogen iodide (ICN), in which the appearance of a free CN fragment was found to occur in about 200 fs [14].

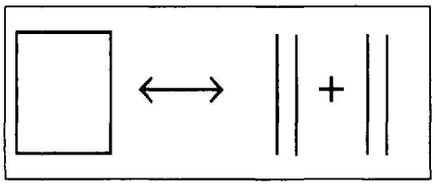
In another experiment, Zewail and co-workers addressed an issue that had occupied chemists for many years, without reaching a clearcut answer. That is: why are certain chemical bonds more reactive than others? What happens if a molecule has two equivalent bonds? Will they break simultaneously or sequentially? To tackle this problem, they studied the dissociation of diiodotetrafluoroethane ($C_2F_4I_2$) into tetrafluoroethane and two iodine atoms (Scheme 1) and found [15] that the two C–I bonds break sequentially: the first bond cleavage takes about 200 fs, while the second follows on a timescale a 100 times longer.

Femtosecond spectroscopy has also been used to examine analogues of the activated complex involved in bimolecular reactions (see Fig. 3). In an experiment [16], that has now become a textbook example, Zewail and co-workers used molecular beams to produce a weakly bound IH···CO_2 complex between HI and CO_2, which is held together in the ground state by weak hydrogen bonding (Fig. 3). The HI bond can be dissociated by a femtosecond pulse, and the H atom is ejected

Scheme 1



Scheme 2



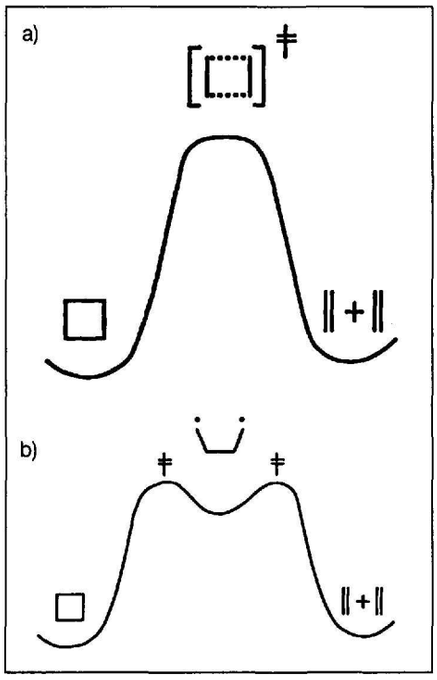


Fig. 4. A classic case for a Woodward–Hoffmann description of concerted reactions. The reaction may proceed in two ways. In a) the reaction proceeds directly through a transition state at the saddle point of an activation barrier. In b) it proceeds by a two-step mechanism, beginning with the breakage of one σ-bond to produce tetramethylene as a diradical intermediate.

towards the O atom of the neighboring CO_2 molecule to form HOCO. Hence, the van der Waals molecule is a source of a species that resembles the activated complex of the reaction:

$$H + CO_2 \rightarrow [HOCO]^{\ddagger} \rightarrow HO + CO$$

The study of large molecules has opened up new and fascinating horizons in physical-organic chemistry and has already changed our view of fundamental reactions, in a way that was unthinkable just a few decades ago. A good example is the case of the diradical hypothesis in organic chemistry. For the past 60 years, the concept of diradicals as intermediates of reactions has been considered the archetype of chemical transformation in many classes of thermally activated, as well as photochemical reactions. For example, a classic case of such a reaction is the ring opening of cyclobutane to yield ethylene or the reverse process (Scheme 2).

This provides a case study of a Woodward–Hoffman reaction. The reaction may proceed directly through a transition state at the saddle point of an activation barrier (Fig. 4a) or, it may proceed by a two-step mechanism, starting with the breakage of one σ-bond to yield tetramethylene (Fig. 4b). The heart of the problem lies in the competition between these two mechanisms: a concerted one-step process *versus* a two-step process with an intermediate. Such intermediates are expected to be longer lived than transition states, such that the dynamics of their nuclear motion (vibration and rotation), unlike a concerted motion (translation), determine the outcome of the reaction. An Arrhenius type treatment of the reaction is unable to distinguish between the two schemes, and one actually only sees an activation barrier (Fig. 4a). By combining femtosecond spectroscopy with time-of-flight mass spectrometry and molecular beams, Zewail and co-workers clearly established the existence of the diradical (Fig. 4b) as a distinct molecular species on a sub-picosecond timescale [17].

Nearly all types of reactions in organic chemistry (Diels-Adler [18][19], Norrish type [20], Bodenstein type [21] and many others [22–28]) have been scrutinized by Zewail's group. They allow us to define the mechanistic concepts crucial to the understanding of the nature of chemical bond changes.

3. From Condensed-Phase Chemistry to Biology

Most of chemistry, in particular preparative chemistry, takes place in the condensed phase. Therefore, any chemical change is affected by the motion of the surrounding species. Because of collisions with solvent molecules, the time and energy barrier of a reaction may change with respect to those in free (*i.e.* gas phase) conditions. The competition between solvent fluctuation times and the timescale of a reactive motion is crucial if one wants to avoid randomization of energy along a specific reactive coordinate in the condensed phase. The interplay between these timescales (coherent *versus* diffusive) is now being addressed with unsurpassed precision by femtosecond spectroscopy. This concerns all possible reactions ranging from barrier-crossing events [26], over rotation of molecules [28] to bond-breaking events [29]. Contrary to the expectation of an ultrafast energy randomization, coherent nuclear motion in the retinal chromophore [30], in a membrane protein [31] and for molecules in solutions or in crystals [29][32–34] has been observed, making it possible to localize the energy along specific reactive coordinates for a sufficiently long time in the condensed phase.

The very first event in a chemical reaction is the change of binding forces that originates from a redistribution of charge. Therefore, in solvents, there is the need to understand the dynamics of electronic solvation processes, whereby the environment adapts to the new distribution of charges – a step that uses up part of the energy available for the reaction process. Ultrafast pump-probe spectroscopy has recently been applied to pinpoint the details of solvation dynamics in polar [35][36], non-dipolar [37][38] and non-polar media [39]. Recently, the simplest of all solutes, the solvated electron, has been used [40], and some of these studies were carried out using the ultimate time resolution of 5 fs!

The various steps of a biological function can now be followed as the time resolution is bridged from seconds to femtoseconds. Major breakthroughs have recently been achieved in our understanding of primary biochemical processes in proteins by a combination of femtosecond spectroscopy and site-directed mutagenesis. Molecular biology methods take the role of chemical synthesis and many protein systems can be manipulated at will and obtained in a reproducible and unique way. This has greatly contributed to make several biological systems the testing grounds of elementary reaction mechanisms and dynamics. Such combinations of techniques are unraveling details of fundamental processes in biological phenomena such as vision, photosynthesis, *etc.* [30][31][41–43].

Elementary chemical reactions like *cis–trans* isomerizations and dissociations are the basis of the function of many biological photoreceptors (retinal in vision and in bacteriorhodopsin; linear tetrapyrroles in phytochrome; *p*-comaric acid in the photoactive yellow protein, *etc.*) and enzymes (myoglobin, hemoglobin, cytochrome, *etc.*). Ultrafast spectroscopy is providing detailed insight [30][31][41][42] into the function of such systems. Indeed, the ability to visualize vibrational motion in a protein enables studies of the relation between nuclear motion and biological function. As an example, it is known that hydrogen bonds bind the double-stranded

DNA helix and determine the complementary of the pairing. Until recently the dynamics of hydrogen bonds and the ensuing tautomerization, which is thought to disturb the genetic code, was not well understood. By carrying out femtosecond pump-probe studies on model base pairs (*e.g.* 7-azaindole), Zewail's group [43] identified different timescales of the structural relaxation in the initial pair, vibrational relaxation and cooling of the tautomer. These studies have yielded a detailed molecular picture of the nuclear dynamics and are providing us with the fundamentals of chemical reactivity in biological functions.

4. From Spectroscopy to Imaging

Structure is at the heart of biology and of chemical sciences. F. Crick, co-discoverer of the double-helix DNA structure used to say 'If you want to understand function, study structure'. Femtochemistry has added the dimension of time to structure and we should now speak of 'time-dependent structures'.

In an optical pump-probe experiment, both the excitation and the probing rely on an *a priori* knowledge of the spectroscopy (energy, intensity and lineshape of bands) of the system under study. Unfortunately, spectroscopic data are not easy to translate to atomic coordinates, except in a few rare cases such as small molecules for which potential curves or potential surfaces are available. On the other hand, techniques such as X-ray or electron diffraction have proven to be powerful tools for the structural determination of condensed matter and biological molecules with a high spatial resolution. Therefore, one could in principle combine the direct inversion advantages of these techniques and their high spatial resolution with the high temporal resolution of femtosecond laser pump-probe techniques, provided sufficiently short duration electron or X-ray pulses can be generated. Time-resolved X-ray diffraction was for a long time limited to the second to nanosecond timescales [44]. Recently, picosecond and femtosecond resolution has been reached but only in experiments describing the melting of materials and the recovery of an ordered structure [45]. On the other hand, using time-resolved electron diffraction, Zewail's group managed a 'tour de force' by imaging for the first time, a chemical reaction as it evolves from reactants to products. He used an ultrashort laser pump pulse to trigger the dissociation of diiodotetrafluoroethane ($C_2F_4I_2$) and an ultrashort electron bunch to record its time-evolving diffraction pattern [46].

Electrons have low penetration depths into matter, so that one is mainly limited to gas-phase reactions, at least for the time being. Another approach that delivers local structural information is X-ray absorption (*via* EXAFS, the Extended X-ray Absorption Fine Structure) which has the advantage of being applicable to disordered as well as ordered media. In combination with ultrashort X-ray pulses it is now being implemented to probe dynamical processes in condensed-phase chemical media [47].

These dynamical structural approaches, based on X-ray diffraction and X-ray absorption, are opening the way to an imaging of time-evolving biological systems or chemical systems in the course of a biological function or a chemical transformation.

5. Outlook and Conclusions

Femtochemistry has opened new avenues in chemistry, biology and material sciences that could not have been foreseen 20 years ago. In particular, the ability to view molecular dynamics also suggests new ways of controlling reactions. The outcome of a chemical reaction is an interference of molecular pathways and the prospect exists now for fine-tuning the motion and reactivity of molecules, so that laser-customized chemistry may be developed [48][49]. This fine tuning can be achieved by appropriately shaped femtosecond pulses which can drive a system along a well-defined reaction channel. A complementary approach is the use of high intensity pulses which, because of their high electric fields, can perturb the molecular system in such a way that intramolecular couplings are created in the system, which otherwise do not exist in the unperturbed system [50]. These couplings open new routes to the outcome of a chemical reaction.

Are we at the end of the race against time? In March 1993, at the Berlin Conference on Femtochemistry, the 1967 Nobel Laureate Sir George Porter observed: 'The study of chemical events that occur in the femtosecond timescale is the ultimate achievement in half a century of development and, although many future events will be run over the same course, chemists are near the end of the race against time'. If this is true as far as nuclear dynamics is concerned, sub-femtosecond pulses or attosecond pulses (1 attosecond = 10^{-18} seconds) may prove useful to probe the motion of the electron and of valency, that play such a crucial role in chemistry. The generation of attosecond pulses is in principle feasible [51]. When it becomes reality, we will be at the threshold of a new era in the study of atomic and molecular systems.

The field of femtochemistry has undergone a real explosion since its birth in 1987. There is no doubt that Ahmed Zewail's personality has played a crucial role in this respect. His ability to communicate with strength and conviction the essence and the beauty of the new physics and chemistry he was unraveling with his ultrafast camera, has been decisive to the evolution of the field. The far-reaching discoveries he made, matched by his charisma and his enthusiasm have marked the field throughout the world. There is no doubt that the scientific community will experience many new discoveries and the emergence of new concepts from his group. Ahmed Zewail has been a regular visitor to Switzerland. His achievements have been recognized by the Honorary Doctorate of the University of Lausanne in 1997 and the Paul Karrer Medal in 1998.

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