Constraining molecules at the closest approach: chemistry at high pressure

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The purpose of this *tutorial review* is to illustrate the effects that the application of high pressures can have on chemical reactions involving highly compressible molecular materials. The essentials of the high-pressure technology (generation and in situ control of high pressures) are described with particular attention to the versatile diamond anvil cell (DAC) apparatus. The general effects of pressure on chemical equilibrium, reaction rate and reaction mechanism are discussed. The motivation for application of high-pressure methods (in the 1–300 MPa range) to chemical synthesis and in biochemistry are illustrated focusing the attention on environmental effects and with an excursus on developing biotechnological applications. The peculiarities and the unexpected outcomes of chemical reactions occurring at very high pressures ($\geqslant 300$ MPa) are discussed considering the extraordinary results obtained in polymerization and amorphization of simple molecules and of unsaturated hydrocarbons. The possible connection of the high temperature–high pressure thresholds for chemical reactions with microscopic counterparts (intermolecular distances, molecular orientations) is also discussed.

1 Introduction

Pressure is one of the thermodynamic parameters that control the equilibrium and rate of transformations of materials. In condensed phases, in comparison with the other thermodynamic parameters, temperature and concentration, the effect of pressure on chemical equilibria and on reaction rates has not been explored thoroughly, particularly in the extreme high-pressure regime. One reason is that very high-pressure equipments are not the usual endowment of the chemistry laboratories and have been so far an almost exclusive prerogative of highly specialized laboratories. A second reason originates from the prejudice that liquids and solids are

characterized by a "proper" volume implying that they are incompressible. That this is not the case is known since a long time and many experiments have shown that molecular materials can be compressed with a volume reduction by up to one order of magnitude, a size contraction corresponding to a shrinkage of the intermolecular distances by a factor of two. The consequent severe confinement and overlap of the electron clouds raise the kinetic energy of the electrons and bring the system into a highly repulsive region of the free energy surface. The response of the system to recover a novel free energy minimum will result in a number of phenomena including phase transformations, ionization, condensation, polymerization, amorphization, dissociation and, as an ultimate response to the most extreme conditions, atomization and metallization. The phenomena produced by a marked pressurization exhibit peculiar and unique features since they occur in materials with an electronic structure that is profoundly altered compared to

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ambient conditions:[1] in molecular materials at high pressure the electronic energy levels are drastically shifted, broadened and overlapped and the HOMO–LUMO gaps are reduced or cancelled. Therefore, the chemical reactions occurring at very high pressure can be at complete variance with the familiar laboratory practice. In these circumstances extraordinary transformations have been observed such as the formation from carbon dioxide of an extended tridimensional array where carbon is tetrahedrally coordinated to oxygen atoms giving rise to a material that could possibly be superhard.[2] Similarly, nitrogen molecules, that are characterized by the strongest chemical bond in nature, have been reported to transform at high pressure in an extended non-molecular array reminiscent of the structure of black phosphorus.[3] Among the most strange and exceptional high-pressure phenomena one should mention the insulator-to-metal transition of very simple molecules such as iodine[4] and oxygen.[5]

The interest for high-pressure phenomena is incredibly wide because of the important implications connecting very different research fields. To understand this fundamental aspect it is sufficient to recall the range of pressures that can be encountered in the universe extending over many orders of magnitude: from the 10^{-32} atm of extremely rarified gases in the intergalactic spaces, to the best attainable laboratory vacuum ($\sim 10^{-16}$ atm), to the 10^6 atm at the Earth's center and to $\sim 10^{30}$ atm at the center of a neutron star. Pressures in the 10^{-16}–10^7 atm range can be obtained in the laboratory with the presently available technology. The feasibility of high-pressure laboratory experiments has opened the way to a deeper understanding of many geochemical and planetary phenomena. From another point of view, the investigation of the behaviour of substances at very short interatomic or intermolecular separation is a source of novel information about the fundamental physical and chemical properties of matter. Just the few examples mentioned above show that, relying to the usual classification and variation of properties in the periodic table, unusual chemical and physical behaviours are exhibited by certain elements. For instance, it has been observed that at high pressure the elements tend to behave like the heavier elements of the same group of the periodic table. Furthermore, fundamental research on the properties of matter at high pressures has resulted in important outcomes in applied material science. It has been known since a long time that there are minerals, stable or metastable at ordinary conditions, that can only be obtained at the very high pressures that can be realized in the planet interior. This motivated important research projects with the aim of synthesizing at very high pressures novel materials of technological interest that could be recovered at ambient conditions. The most spectacular example of these attempts has been the synthesis of artificial diamond and of other superhard materials.[6]

One important point is that severe geometrical constraints are imposed on the molecules of any pressurized sample and, in the simplest approach, the reactions occurring with minimum molecular and atomic displacements will be favoured.[7] However the reference frame is far more complicated and actually, at high pressure some reaction pathways are inhibited and others accelerated. This opens the way to a novel selectivity of chemical reactions. The overcoming of the

energy barriers in high-pressure transformations can, as usually, be facilitated by increasing the temperature. The joint control of temperature and pressure enhances the subtleties of the high-pressure phenomena. In fact, while high temperature favors dissociation pressure induces condensation and the balance of the two parameters is an additional control resource. This perspective can be further enlarged. Considering the high pressure as a physical means to activate or inhibit chemical reactions, pressurization can be supplemented by other tools to increase the selectivity of the processes, to increase the reaction rates or to bring the transformation to completion. For instance, it has been reported that laser irradiation and excitation of pressurized reactants in selected excited states can work very efficiently to direct highly selective syntheses.[8,9]

As a whole, a considerable amount of work has already been reported on high-pressure chemical reactions. Yet it appears that this field has not been fully explored. The purpose of this *tutorial review* is to outline the state of the art in this topic and envisage possible perspectives that are made possible by the advancements in high-pressure technology. In the following section the experimental high-pressure devices are briefly reviewed with particular attention to the diamond anvil cell and some fundamentals, regarding the effects of pressure on reaction rates and the principal concepts of solid-state reactivity, are recalled. In sections 3 and 4 applications of high pressure, in some intermediate range, to chemical synthesis and to biochemistry and biotechnology are reviewed. In Section 5 some results concerning with chemical reactions at very high pressure are discussed as test cases to illustrate the full and innovative possibilities offered by carrying the chemistry in the most extreme conditions. The paper is closed by a summary and some concluding remarks.

2 General aspects of high-pressure chemistry

2.1 High-pressure equipment

There are two general approaches, one dynamic and one static, to generate and apply high pressure on a given material for inducing a chemical reaction. The dynamic methods are based on shock wave compression generated by gas guns, pulsed lasers, high pulsed electrical currents and explosives. The accessible pressure range is extremely wide and ranges, depending on the method employed, from few GPa up to thousands of GPa (1 GPa = 1000 MPa = 10 kbar = 9869 atm). However, these pressures are always produced together with temperatures as high as thousands of kelvin making this method a powerful experimental tool in probing high P–T states, such as hot dense plasma, and studying Hugoniot equations of state of geophysical interest. From the chemical point of view this type of experimental studies are limited to the study of the detonation of energetic materials and to the chemical processes occurring in planetary science.[10] Another important limitation of the dynamic compression in chemistry concerns with the very short time of the shock wave propagation (typically in the 10^{-7}–10^{-9} s range) that limits the diagnostic to few fast probing techniques.

Static pressures are produced through the application of a mechanical force perpendicularly to the surface of the sample

placed in a vessel capable to contain the substance once it is compressed. A piston sliding into a cylinder, with the sample squeezed between the piston and the bottom of the cylinder, is the simplest way to realize such a mechanism. Final pressures ranging from 0.1 up to some GPa can be obtained with this method and consequently piston-cylinder based devices have been widely employed in studying under moderate high-pressure conditions chemical processes such as additions (Wittig, Michael), cycloadditions (Diels–Alder, 2 + 2, dipolar), ionogenic, substitution and polymerization reactions.[11] The piston-cylinder principle is also at the basis of many large volume hydrostatic high-pressure apparatuses. Instruments based on this principle are able to generate pressures up to 1 GPa on cm^3 sized samples. On the piston-cylinder principle is based the opposed anvils device. Here the sample is compressed between massively supported tapered pistons (tungsten carbide in the Bridgman anvil device) and the lateral containment is ensured by a metallic gasket. Large volume solid samples can be compressed by using multianvil systems. In these cases several identically shaped pistons pushed one against each other squeeze the sample whose shape is determined by their number, usually a regular polyhedron. On the opposed anvil concept is based also the diamond anvil cell (DAC)[12] that highly widened the accessible pressure range for static measurements and consequently enlarged the type and the number of substances to be investigated. In the DAC case the anvils are made of diamonds, the hardest known material that allows to reach pressures higher than any other material. Furthermore, their transparency, from the far infrared to the X-ray region, makes the optical investigation of the sample possible. This device allows the continuous tuning of the pressure up to pressures exceeding 100 GPa, of the temperature from 4 up to 1000 K, and the employment of a large number of probing techniques for *in situ* measurements (see ref. 13 and references therein). All the spectroscopic techniques have been successfully adapted to the studies of micrometric samples contained in the DAC taking advantage of focalized laser or synchrotron beams. For these reasons the DAC in spite of the small sample volume (50–300 μm in diameter, and 10–50 μm thickness) is the most reliable tool to study the matter under pressure. From a chemical point of view the great advantage of using the DAC is represented by the possibility to maintain the required *P–T* conditions for the desired time allowing the kinetic, and then thermodynamic, study of a chemical reaction. Many types of DAC have been developed but all are based on the opposed anvil system differing in the way the diamonds are pushed one against the other. Both mechanical, where pressure is generated through lever-arms, threads, clamps and screws, and pneumatic driven systems, where the force on the diamond is applied by inflating a metallic membrane, diaphragm or bellow by means of a fluid medium, usually helium, are in use. The cell type choice depends mainly on the experiment. In the case of chemical reactions optical techniques are commonly employed to monitor the changes in the sample. In this case the use of a mechanical cell requires for every pressure change its removal from the optical path of the instrument. Moreover, when constant thermodynamic conditions are required, as in the case of kinetic studies, these devices prevent any instantaneous

adjustment of the pressure as required in any reaction where a denser material forms. These limitations can be overcome by employing a pneumatic system where a fine pressure regulation is obtained by a remote control of the helium pressure in the membrane. This is a significant advantage when performing low- and high-temperature experiments, when monitoring kinetic evolutions, or simply when the cell is contained in an evacuated apparatus. Furthermore, the fine tuning of the pressure can be crucial in studying phase transitions, equilibrium processes, crystal growth.

The principle of the DAC operation is very simple: two opposing diamond anvils press the sample which is laterally contained by a metal gasket (see Fig. 1). The pressure applied on the large face of the diamond, and the ratio between the area of this face and that of the smaller flat tip in contact with the sample, determines the pressure to which the sample undergoes. Typically facet diameters are 4 mm for the larger surface while the smaller culet diameter ranges between 50 and 700 μm, depending on the desired attainable pressure.

Diamonds for high-pressure experiments are selected on the basis of the experiment to be performed. Broad fluorescence bands due to defects and impurities are common in natural diamonds and can affect Raman and Brillouin measurements interfering with the signal from the sample. In the infrared spectrum an absorption band, due to two phonon modes, is present near 2000 cm^{-1}. Nitrogen impurities are responsible for the activation in the infrared spectrum of another strong phonon band in the region between 1100 and 1300 cm^{-1}. These impurities determine the classification of the diamonds in Ia and IIa,[14] the latter being nitrogen free and therefore preferred for IR spectroscopy experiments (see Fig. 2).

The sample between the two diamonds is laterally contained by a metallic gasket that also provides the lateral support for the tips of the anvils. The gasket is produced from a metallic foil having an initial thickness of 100–250 μm that is
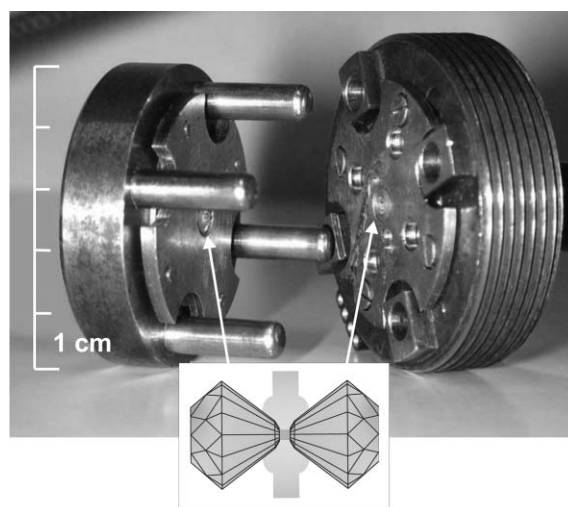

Fig. 1 Diamond anvil cell of the membrane type employed for studying high-pressure chemical reactions. The two parts of the cell are pushed one against the other allowing the sample, which is laterally contained by a metallic gasket, to be sealed between the two diamonds. In the inset a schematization of this operation principle is shown. Pressure is applied by inflating an external membrane not visible here.
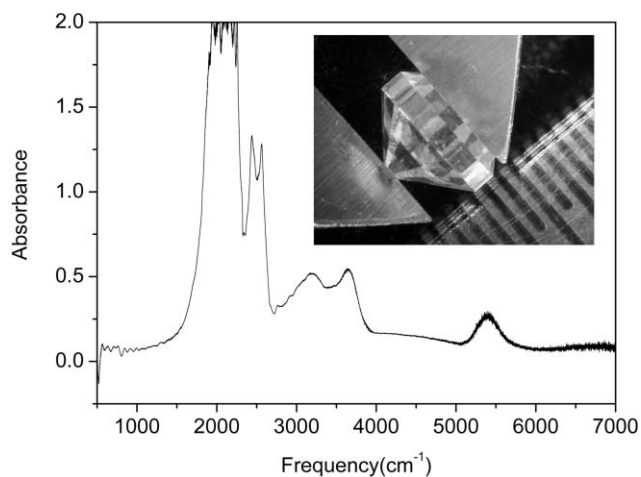
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Chem. Soc. Rev., 2007, **36**, 869–880 | 871

Fig. 2 IR absorption spectrum of a 2.6 mm thick 16 sided standard cut IIa diamond having a 400 μm culet. An anvil of the same type, typically employed in high-pressure experiments, is shown in the inset.

preindented to a typical thickness of 50–30 μm by applying pressure to the diamonds and then drilled at the center of the crater left by the diamonds. The hole produced will be the sample chamber and from its diameter will depend the final pressure, the larger the hole, the lower the pressure. The materials for the gasket are chosen on the basis of their mechanical strength, of a large friction coefficient on the diamond and, considering their employment in chemical studies, they must be inert with respect to the sample in order to avoid unwanted reactivity. High-strength stainless steel and rhenium are commonly employed, the latter being preferred at very high pressure and also for high-temperature studies.

The most widely used technique in optical experiments to measure *in situ* the sample pressure in the DAC is the ruby fluorescence method.[15] A few milliwatt of a green or blue laser emission are sufficient to excite the fluorescence of a micro ruby chip placed in the sample chamber. The strong and narrow R_1 ruby fluorescence line at 694.25 nm (300 K and ambient pressure) presents a remarkable pressure shift that has been carefully calibrated up to pressures exceeding 1 Mbar.[16] The empirical equation correlating the pressure and the ruby wavelength for quasi-hydrostatic conditions is:

$$P = \frac{A}{B}\left[\left(\frac{\Delta\lambda}{\lambda_0}+1\right)^B - 1\right] \quad (1)$$

where P is expressed in GPa, A and B are parameters whose values[17] are 1904 GPa and 7.665, respectively, and λ_0 is the wavelength expressed in nm of the R_1 ruby fluorescence line at ambient pressure and at the reference temperature, typically the room temperature. $\Delta\lambda$ is the R_1 line shift with respect to the ambient pressure wavelength. A correction for the temperature dependence of the wavelength can be applied by including a correction term $\Delta\lambda_T$ in the expression of $\Delta\lambda$. The ruby fluorescence method allows to perform pressure measurements in a very short time scale ($1-10^{-3}$ s) if compared to that of many solid-state chemical processes, a prerequisite in studying kinetic processes. In these last cases it is also important to minimize the laser power used for measuring the ruby

fluorescence in order to avoid undesired photochemical effects on the sample. In the case of IR absorption studies, that are commonly used for kinetic purposes, vibrational pressure gauges have been used to replace ruby in order to avoid these risks of unwanted photochemical reactivity.[18]

2.2 Effect of pressure on equilibrium and reaction rate

The equilibrium constant K of a chemical reaction is given by the ratio between the product and the reactants activities a_i of the system at the equilibrium, condition realized when the Gibbs free energy ΔG^0 is minimum. The free energy ΔG^0 is the difference between the chemical potentials μ_i^0 of the products and the reactants in their standard state (to be defined as the pure state of the component at the T and P of the reaction). Since the chemical potentials μ_i^0 depend on pressure through:

$$\left(\frac{\partial\mu_i^0}{\partial P}\right)_T = V_i^0 \quad (2)$$

where V_i^0 is the molar volume in the standard state, and the basic thermodynamic relation for the equilibrium is:

$$\Delta G^0 = -RT \ln K \quad (3)$$

it follows that the dependence of the equilibrium constant on pressure is given by:

$$\left(\frac{\partial RT\ln K}{\partial P}\right)_T = -\Delta V^0 \quad (4)$$

where ΔV^0 is the difference of the molar volumes in the standard state between the products and the reactants. Eqn (4) shows that for reactions involving a volume contraction the equilibrium constant increases exponentially with pressure at constant temperature. This extremely large variation shows the fundamental role of pressure as a regulatory tool for chemical equilibrium.

These basic considerations also apply to the particular class of chemical reactions occurring in the solid state. The mechanism of such a type of reactions can be understood once the sequence of its elementary steps is known. In general, the overall reaction rate coincides with that of the slowest elementary reaction, also referred to as the rate determining step. Studies of the pressure dependence of the reaction rate can give very useful information on the rate determining step and then on the reaction mechanism. According to the transition state theory determination of the rate constant as a function of temperature at constant pressure provides the activation energy E_a:

$$\left(\frac{\partial\ln k}{\partial T}\right)_P = -\frac{E_a}{RT} \quad (5)$$

and as a function of pressure at constant temperature the activation volume $\Delta V^{\neq}$, *i.e.* the volume difference between the transition state complex and the reactants:

$$\left(\frac{\partial\ln k}{\partial P}\right)_T = -\frac{\Delta V^{\neq}}{RT} \quad (6)$$

Reactions of associative type, where the rate determining step involves the formation of a covalent bond, give rise to

negative $\Delta V^{\neq}$, while dissociative type reactions, *i.e.* involving the breaking of a covalent bond, present a positive $\Delta V^{\neq}$. A review of experimentally determined $\Delta V^{\neq}$ for organic reactions in solution are reported in ref. 19. Experimental determination of $\Delta V^{\neq}$ for a reaction requires the rate constant k to be determined at different pressures. k is obtained as a fit parameter by reproducing with a suitable model the reactants, or products, concentration evolution as a function of time. The choice of a kinetic model for a solid-state chemical reaction is not trivial because many steps, having comparable rates, may be involved in the process. Furthermore, beside the strictly chemical transformations, also the diffusion (transport of matter to and from the reaction center) and the nucleation processes should be taken into account. A general expression accounting for these processes, and having a form equal to that derived by Avrami for describing the growth of a crystal from a liquid phase,[20] is:

$$\ln \frac{1}{1-x} = kt^n \qquad (7)$$

where x is the fraction of the product formed at time t relative to the total amount formed at equilibrium, k is the reaction rate, and n is a parameter related to the nucleation rate and to the spatial evolution of the reaction and increases with the dimensionality of the growth. The n value can provide in some cases unambiguous information to understand the microscopic evolution of the process. Specifically, when $n < 1$ a linear diffusion controlled growth takes place. This is for instance the situation encountered in the pressure induced polymerization of acetylene and ethylene,[18,21] where the diffusion control should be interpreted in terms of the lattice phonon activity (translational and librational motions) that regulates the nucleation and the chain growth steps by tuning the distances of the reacting molecules.[22]

As already mentioned, a general effect of compression is the change of the molecular electronic structure that becomes particularly relevant in proximity of the instability threshold thus driving the chemical reaction. Experimentally, these remarkable changes can be monitored through the shift and the broadening of the absorption bands with increasing pressure. In general a red shift is observed as a consequence of two different contributions.[1,23] A relative vertical shift of the ground and excited states which can change the configuration interaction to a considerable extent and give rise to a thermal population of the excited state even at room temperature, thus having important consequences for the chemical reactivity. The second contribution corresponds to a change of the relative position of the ground and excited states along an appropriate configuration coordinate, and can be viewed as arising from a different compressibility of the two electronic states. Among the important consequences, for their chemical implications, of the mixing of the electronic states with increasing pressure, the possible buildup of an electric dipole moment even in non-polar centrosymmetric molecules, as it has been calculated for butadiene,[24] should be mentioned. Among the possible transitions the $\pi \rightarrow \pi^*$ are generally the most sensitive to pressure. Given that these transitions are usually the lowest in energy for unsaturated compounds, it results that these systems are particularly reactive at high

pressure. The energy shift with pressure of the $\pi \rightarrow \pi^*$ transitions has been reported for several conjugated systems[25] also above the reaction threshold pressure, such as in the case of benzene[26] and furan.[27]

We have already recalled that a general effect of the increased density realized at high pressure is the creation, as a consequence of the larger intermolecular interactions, of steep energy barriers around the molecule. These barriers are particularly relevant in the solid state so that the reacting molecules are arranged with rather fixed molecular orientations and intermolecular separation. Therefore, reactions requiring a high mobility of the reacting units can be completely prevented unless the high potential barriers are overcome by high temperatures. On the other hand, the relative orientational confinement of the molecules can selectively favor some particular reaction pathways. This behavior is rationalized through the topochemical principle which states that reactions in solids take place with a minimum of atomic and molecular movement.[7] The polymerization of crystalline hydrogen cyanide,[28] acetylene[18] and ethylene[21] are enlightening examples concerning the topochemical principle. HCN molecules are aligned in the crystal in linear chains by hydrogen bonds and compression produces only one of the several possible polymers that are obtained in solution under different catalysis and solvent conditions. Acetylene polymerizes in the *trans* form reacting along the diagonal of the *bc* plane of the orthorhombic cell, where the intermolecular distances are smaller and the relative orientation resembles the polymer structure. The same happens in solid ethylene along the *a* axis of the monoclinic cell. An extension of the topochemical principle is represented by the reaction cavity concept where also the role of the molecules surrounding those participating to the chemical reaction is taken into account.[29] According to this principle the reaction occurring with minimal change or distortion of the surface of the reaction cavity will be favored. Given that the surrounding molecules enter in the reaction dynamics and since all the molecules of an ordered crystal are connected through collective motions, the lattice phonons, it is not difficult to imagine that the influence of the environment on the reaction itself is not limited to the nearest neighbor molecules. As a matter of fact, the lattice phonons transmit the perturbation represented by the reaction seed by site to site and modify the relative distances and orientations among the molecules, therefore representing a mechanical analogue of the solvent effect. The fact that reactions in molecular crystals could be activated by low-frequency phonon modes involved in the reaction coordinate was first proposed by Prasad and co-workers.[30] The amplitude increase of molecular translations or rotations, revealed by the softening of a phonon mode, was suggested to be a possible way to bring neighboring molecules close enough for a reaction to occur. This is a critical point in high-pressure reactions. Even if the compressibility of molecular condensed systems is rather large, the static (structural) nearest neighbors distance that can be realized at the reaction threshold pressure is not short enough to account for the occurrence of the reaction itself. Recently, the basic role of zone boundary acoustic and lattice phonons in triggering the ring disruption of benzene has been demonstrated[22]

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Chem. Soc. Rev., 2007, **36**, 869–880 | 873

and a more detailed resume will be presented in the last section.

3 Applications to organic synthesis

The application of high pressure to organic synthesis has several facets. An important issue, that is not specifically the object of the present paper but is nonetheless worth of mention, is the use of supercritical fluids as solvents in chemical synthesis.[31] Considering the most commonly used supercritical solvents, carbon dioxide and water, reactions are carried at pressures above the critical points of 7.38 and 22.1 MPa, respectively. Above the critical point the supercritical solvent shares the properties of the liquid and of the gas phase. From this the several advantages of the supercritical solvents are derived and among these are the increased solvating power compared to normal liquids, the higher diffusivity approaching the gas phase behaviour, the change of density, viscosity and dielectric constant. However, the main resource is that by changing the pressure and temperature the solvent properties can be finely tuned between the liquid and gas phase extremes and adjusted for the reaction of interest. For instance, the dielectric constant of supercritical water can be varied continuously from 1 (a typical value for non-polar solvents) to 30. In addition, in supercritical water the ionic product can be increased by three orders of magnitude and the H^+ concentration increased by 30 times compared to normal conditions. A major interest in supercritical solvents derives from the fact that they can be easily removed and recovered and are environmentally benign as substitutes of unfriendly organic solvents. An additional advantage is that separation procedures are simplified in supercritical solvents. For the purpose of the present tutorial review, the mode of action of supercritical solvents reveals a basic feature of all high-pressure operations, and mainly the fundamental importance of the environment on the equilibrium and kinetics of chemical reactions.

Chemical reactions at high pressure are mostly carried in solution.[32] This sets an upper limit to the pressures that can be encountered in the practice of high-pressure chemical synthesis, a limit that is defined by the freezing point of the solvent and that can be partly extended with a control of the temperature variable (typically the melting point increases by 10–20 °C per 0.1 GPa). On the other hand, the realization of high-pressure conditions limits the sample volumes that can be dealt with in the range from 1 to 100 ml. Therefore, these experiments are carried in apparatuses of the piston-cylinder type, in some cases with pressure intensifiers or with continuous flow devices. For all these reasons the pressure used in chemical synthesis experiments is mostly in the range of up to 1000 MPa, even though there are several examples of organic reactions studied at higher pressures. In the pressure range considered the changes of the electronic structure are not dramatic and the chemical reaction can be studied and controlled with the help of the thermodynamic and kinetic equations described in the previous section.

The basic information to rely on, or to extract from studies as a function of pressure, is the volume profile of the reaction that encompasses the activation and the reaction volumes.

According to the thermodynamic and kinetic eqns (4) and (6) both the equilibrium constant and the reaction rate increase exponentially with pressure. However, high pressure has been mainly exploited for a kinetic control of chemical reactions. In fact there are various classes of reactions (such as electron exchange, symmetric exchange, isomerizations) where the reaction volume is zero or nearly zero while the activation volume can be significant.

Fig. 3 shows the enhancement of the reaction rate with pressure for a reaction with an activation volume $\Delta V^{\neq}$ ranging from -50 to -10 cm^3 mol^{-1} at 300 K. As an example, it can be seen that when $\Delta V^{\neq} = -30$ $\Delta V^{\neq}$ only above 200 MPa the enhancement factor becomes extremely high. The trend shown in the figure corresponds to the assumption that the activation volume is pressure independent, but this does not apply at higher pressures, and the profile is actually smoother also as a consequence of the environmental effects to be discussed later. It is evident that only when the activation volume is significantly large the use of pressure is justified to accelerate or to retard the reaction. The kinetic analysis of chemical reactions as a function of pressure is nonetheless of primary importance for mechanistic applications through the obtainment of the activation volumes. If the reaction can be studied both in the forward and in the reverse direction both the activation and reaction volumes can be obtained from kinetic studies. In general the activation volume is the basic piece of information to identify the structure of the transition state and to clarify the reaction mechanism. This knowledge can be of great practical importance. Whenever the reaction can develop along different pathways associated to transition states with distinct activation volumes the pressure variable offers the opportunity to control the selectivity of the reaction. This is also the case when the reaction proceeds as a multistep process and the pressure has a different effect on the various intermediates.

The volume profile is not simply defined in terms of the reactants, transition state and products properties, since environmental and solvent effects play an important and, at times, dominant role. The intrinsic contribution to the activation volume can be estimated from quantum mechanical calculations or from the knowledge of the structure of the reactants and transition complexes and of the atomic van der
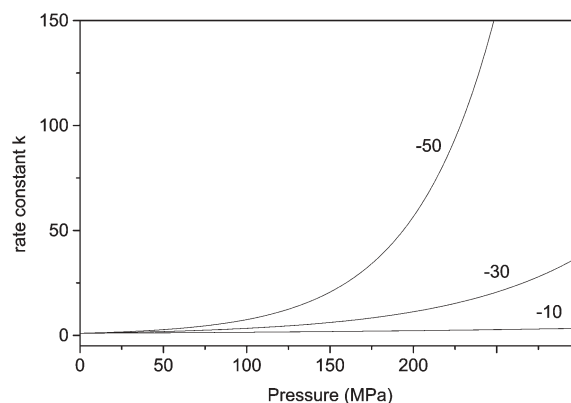

Fig. 3 Room-temperature pressure dependence of the rate constant for different activation volume values (in cm^3 mol^{-1}).

Waals radii. However, the actual volumes occupied by the reactants and transition complex differ from these intrinsic estimates because of the packing of the molecules that will include voids depending also on the thermal motion. The presence of voids will obviously be of considerable importance for the pressure effects. As a rule of thumb, the formation of an additional bond in the transition state, contributes a negative activation volume of the order of $-(10–15)$ cm^3 mol^{-1}. For instance, exchange reactions may occur through an associative or dissociative intermediate state and will correspondingly be accelerated or retarded at high pressure. In general condensation reactions correspond to negative activation volumes and are therefore kinetically favoured at high pressures. Cyclizations, cycloadditions and Diels–Alder reactions fall in the category of pressure accelerated processes. Extensive collections of experimental activation volumes for many kinds of chemical reactions are available. In Table 1 the range of activation volumes for typical chemical reactions is reported.[19]

The total activation volumes can considerably differ from the simple intrinsic estimates because of several environmental effects. The role of the medium in organic synthesis at high pressure has been reviewed in detail recently.[33] The medium can affect the reaction rates in two different ways. First, increasing the pressure the physical properties of the solvent can change considerably. This can be the case for diffusion controlled reactions since at high pressure the viscosity of the medium increases and the dynamics of the solvent cage around the reactants slows down considerably. However, the most important effect is related to the packing of the solvent molecules around the reactants and around the transition state complex. Pressurization can affect both the medium–medium and the medium–reactant interactions. If the transition state has a higher polarity or is ionic compared to the reactants the packing of a polar solvent around the transition state will be more efficient (electrostriction) and the medium contribution to the activation volume can be larger or even of opposite sign with respect to the intrinsic contribution. A significant contribution to the activation volume is associated with steric hindrance or overcrowding in the transition state.

The essential of high-pressure applications to organic chemistry can be illustrated by considering the simplest cycloaddition reactions (see Fig. 4).[32]

In the first instance these reactions can occur as [4 + 2], [2 + 2] or, depending on the nature of the R groups, as [4 + 4] cycloadditions. Correspondingly, there is a variety of
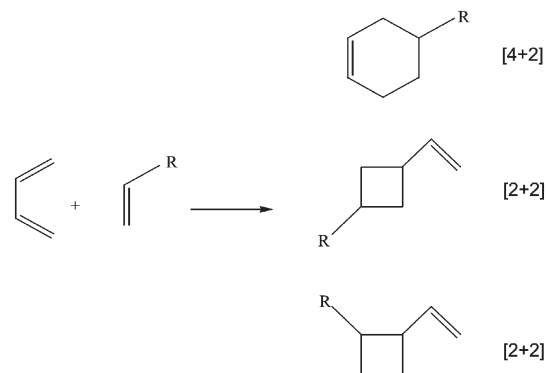

Fig. 4 Typical cycloaddition reaction involving a butadiene (diene) and a substituted ethylene (dienophile).

transition states. The [4 + 2] cycloaddition may result from a concerted reaction where the transition state is cyclic. The concerted mechanism can be synchronous or asynchronous (see Fig. 5) corresponding to the simultaneous or non-simultaneous formation of the two partial σ bonds. The [4 + 2] cycloaddition can also occur with a stepwise mechanism where one bond is first formed (in a rate determining step) followed by the fast formation of the second bond. In this case the intermediate is a diradical (or a zwitterion).

The [2 + 2] and [4 + 4] cycloadditions certainly occur though a stepwise process. The complexity of these reactions is further increased when the dienophile and the diene are substituted because of the possibility of *endo* or *exo* approach. This will affect the stereochemistry of the products as reported in Fig. 6.

The structure and the volume of the transition states will be different in the various cases outlined above and, therefore, the determination of the activation volumes from kinetic studies as a function of pressure will help in determining the reaction mechanism. As the reverse of the medal, pressure increase will
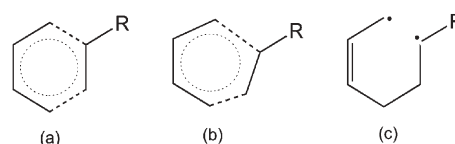

Fig. 5 Intermediates for a concerted synchronous (a), concerted asynchronous (b) and a stepwise (c) Diels–Alder cycloaddition.

Table 1 Activation volume values (cm^3 mol^{-1}) for various kinds of reactions[19]

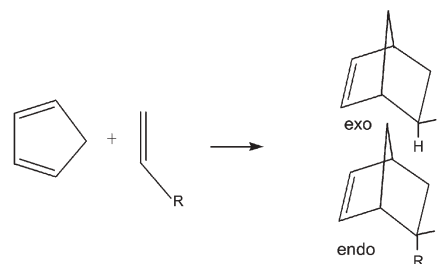| Reaction	$\Delta V^{\neq}$
Homolysis	5 to 20
Polymerization (radical propagation)	~ -20
Cycloadditions	
Diels–Alder	-25 to -40
intramolecular	-25 to -30
dipolar	-40 to -50
(2 + 2)	-40 to -55
Ester hydrolysis	-10 to -15 (basic), > -10 (acid)
Epoxide-ring opening	-15 to -20
Wittig reactions	-20 to -30

Fig. 6 Cycloaddition reaction of a substituted ethylene to cyclopentadiene. This classification concerns the relative position of the R substituent, reflecting the approach geometry, with respect to the one-carbon bridge: *cis* for the *exo* product, *trans* for the *endo*.
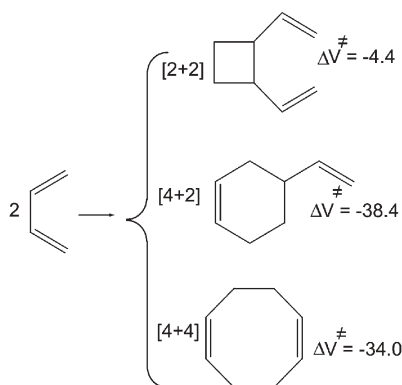
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Chem. Soc. Rev., 2007, **36**, 869–880 | 875

Fig. 7 Activation volumes for the dimerization reaction of butadiene leading, from top to bottom, to 1,2-divinylcyclobutane, 4-vinylcyclohexene, 1,4-cyclooctadiene, respectively.

favor reaction pathways corresponding to more negative activation volumes.

The prototype Diels–Alder cycloaddition of ethylene to butadiene is reversible and the activation volume for the direct reaction (-32 cm^3 mol^{-1}) is more negative than for the reverse reaction (-2 cm^3 mol^{-1}). These activation volume values represent a good evidence for a concerted mechanism. In the dimerization of butadiene the [4 + 2] cycloaddition leading to vinylcyclohexene is in competition with the [2 + 2] and [4 + 4] cycloadditions leading to 1,2-divinylcyclobutane and 1,4-cyclooctadiene, respectively (see Fig. 7).

Only vinylcyclohexene may result from a concerted mechanism (corresponding to the more negative activation volume) while all the three isomers can be obtained by the stepwise process. The activation volumes data show that the selectivity of the reaction can be considerably increased at high pressure.

In the dimerization of cloroprene five different isomers are formed as illustrated in Fig. 8. From the activation volume data it is argued that two of the [4 + 2] cycloadducts are formed through a concerted mechanism while the third [4 + 2] and the two [2 + 2] adducts are formed through a stepwise process.
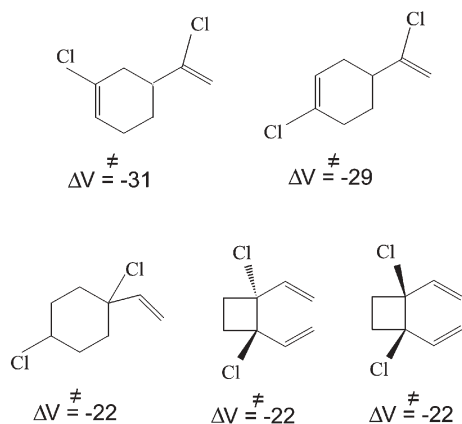

Fig. 8 Activation volumes for the dimerization reaction of cloroprene. The three cyclohexene and the two cyclobutane derivatives are formed through [4 + 2] and [2 + 2] cycloaddition reactions, respectively.

4 Applications to biochemistry and biotechnology

The general motivations for applications of high-pressure methods to biomolecules and biosciences are not dissimilar from those described for chemical reactions. The basic point is that the use of the pressure variable alone allows for a study of pure volume effects on the structure, properties, function and dynamics of biomolecules. It is more difficult to sort out pure volume effects from changes of temperature since this will alter the energetics of the system as well. Variable-pressure experiments are therefore particularly useful since they allow to finely tune the intermolecular interactions of the biomolecules within themselves and with the environment, without the more drastic changes that are brought about by the usual probe methods, such as chemical changes and alteration of the solvent polarity or of the pH. On the other hand the definition of the volume changes occurring in biomolecules are intrinsically more complex than considered in the previous section. In the pressure range generally encountered in biosciences (up to few hundreds MPa) it can be safely assumed that the proper volume of a biomolecule (for instance of a protein) is constant. However, the overall volume of the system will include voids that are obviously very sensitive to pressure and should be taken into account. In addition pressure can considerably alter the permeability of complex biochemical structures to small molecules, such as water, and in general have an effect on the hydrophilic and hydrophobic interactions. All these effects of pressure will influence the function of biological systems. Therefore, there is a wide range of basic biochemical and biophysical properties that can be explored when pressure is used as a perturbation tool in addition to temperature and chemical probing. Widening the perspective, the study of biomolecules and biosystems at high pressures is a preliminary step to understand the problem of life adaptation to extreme conditions and hostile environments. While several types of extremophiles (microorganisms that can tolerate or favourably grow in extreme environments) such as anaerobes, hyperthermophiles, acidophiles, have been studied in fair detail the search for piezophiles (microorganisms that grow more favorably at high pressures) is less advanced. However, extreme pressure conditions are encountered in many instances such as at deep see level and in the subsurface biosphere. High-pressure studies can therefore be of importance in the issue of exobiology and extraterrestrial life. Early applications of high-pressure to biomolecules revealed interesting phenomena such as protein denaturation at room temperature or the inactivation of microorganisms, enzymes and viruses. These have been the seminal findings that have led to a number of developing biotechnological applications.[34] An important and consolidated field of application is the pressure processing of foods since high pressure can produce sterilization, gel formation, protein denaturation, coagulation, very much as can be obtained with temperature treatments, but with a more favorable preservation of the organoleptic properties. Important applications are also developing in the field of medicine and pharmacology exploiting the sterilization and improved separability ensured at high pressures.

For the several aspects of application of high-pressure methods in fundamental and applied studies in biochemistry and biophysics the reader is referred to an extensive collection of review articles published by Banly, Masson and Heremans.[35] In this section we will only address the important issue of folding–unfolding of proteins because this best illustrates the potentialities of high-pressure methods in the biosciences and the role of proteins and of their three-dimensional structure and dynamics is of primary importance in molecular biology.

Protein denaturation can be accomplished by heat, by cold, by chemical denaturants and also by application of pressure. Pressure and temperature effects should be considered in a unified picture since both involve volume changes. Considering denaturation as a two-step process (*i.e.* as the transition between the native and denatured existing states of a protein) the Gibbs free energy difference can be expanded to second order in the pressure and temperature variables. The projection of the free energy surface on the P–T plane ($\Delta G = 0$) gives an elliptical phase diagram defining the stability region of the native state.[36] Deformation of the elliptical phase diagram can be produced by higher order terms in the expansion. For the behaviour of the protein what really matters is the orientation, the size and the origin of the elliptic stability region in the P–T plane, parameters that are determined by the specific heat, the thermal expansion and the compressibility differences between the two forms. The molecular and structural interpretation of the unfolding process goes beyond the phenomenological thermodynamic model. The already mentioned different contributions to the volume of pressure (and temperature) should be considered, together with the response to pressure of the various components of the intermolecular interactions, with hydrogen bonding and aromatic stacking interactions stabilized and hydrophobic interactions, tertiary structure and protein–protein association destabilized at high pressure. The overall structure of the protein (whether monomeric or oligomeric) is also of considerable importance since this is of relevance for the reversibility of the folding–unfolding process. From a practical point of view kinetic effects, arising from the existence of energy barriers opposing the crossing of the phase boundaries, should be taken into account. A limitation of this thermodynamic model arises from the consideration of only the native and denatured states but in many instances, and in particular in the case of oligomeric proteins, there is evidence of the existence of intermediate states. The elliptic form of the P–T phase diagram is characteristic of proteins but is not necessarily the appropriate form for other biopolymers. For instance, different linear phase diagrams have been observed for nucleic acids and biomembranes. The ellipticity character found for the pressure inactivation process of bacteria can be taken as an evidence of the role of proteins in bacterial inactivation. The range of pressure that can be used in studies of proteins unfolding can be extended coupling the pressure with chemical denaturants. It appears that the effects of pressure and chemical denaturants are concurrent according to a scheme such as

Protein (native) → Protein-A → Protein (denatured)

where the intermediate step denotes either the binding of the chemical denaturant to the protein or the water penetration in the case of the pressure induced process.

5 Chemical reactions at very high pressure

An extended review of the chemical reactions that have been studied at very high pressures (typically in the range of 1 GPa or above) has been reported recently[13] and in this Section we will focus only on a small number of test cases appropriate to illustrate the perspective and motivations of these studies. We shall first discuss the reaction of carbon dioxide at high pressure (and high temperature) that is related to the search of new superhard materials. Then we shall report on the high-pressure transformation of nitrogen that falls in the field of attempts to obtain energetic materials. The other case study that will be discussed is hydrocarbon polymerization at ultrahigh pressures, an issue that is of general interest in the context of formation of carbonaceous aggregates in planetary and astrophysical environments. The polymerization of ethylene and of *trans*-butadiene will be considered since these reactions illustrate the extremely high selectivity that can be attained at high pressures, particularly when pressurization is accompanied by photochemical activation induced by appropriate laser irradiation. Finally, we shall report on some recent results on the mechanism of the aromatic benzene ring disruption since these experiments reveal the microscopic counterpart of high pressure (and high temperature) thresholds of chemical reactions and in addition reveal the subtleties of the experimental conditions that are important in high-pressure chemistry.

The behaviour and the reaction of carbon dioxide at high pressures has been the object of considerable attention. Beside the already mentioned use of supercritical carbon dioxide as a solvent in organic chemistry, solid carbon dioxide is of interest for its occurrence in planetary environments. Superhard materials are mostly associated with tridimensional networks of light elements (such as is the case for diamond and boron nitride). In this respect it has been intriguing to explore if at high pressures (and temperature) carbon dioxide could be transformed in a non-molecular structure. The P–T phase diagram of solid CO_2 is rather complex and on increasing the pressure the low-temperature ambient-pressure $Pa3$ structure changes to lower symmetry (orthorhombic) phases still maintaining the inversion center. Iota first reported that at 40 GPa and at an approximate temperature of 1800 K a further transformation occurs from phase III to a new crystalline phase denoted as CO_2-V.[2] A number of experimental evidences (including second harmonic generation, disappearance of Raman and infrared vibron bands, X-ray diffraction, optical band gap and bulk modulus estimates) show that a reaction has occurred and that in CO_2-V the carbon atoms are tetrahedrally coordinated to the oxygen atoms in a general arrangement similar to silica. The estimated bulk modulus was reported to be close to the boron nitride value but this datum, not confirmed by calculations, could be possibly altered also by the presence in the sample of diamond formed during the reaction.[37] The reaction product could be quenched at 10 K and 10 GPa. However, attempts to recover a

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Chem. Soc. Rev., 2007, **36**, 869–880 | 877

new potentially superhard material at ambient conditions failed and the high-pressure reaction product reversibly transformed back to molecular CO_2. The exact structure of non-molecular CO_2 has not been identified with certainty. Several silica analogues have been suggested based on X-ray diffraction and *ab initio* molecular dynamics simulations but it has been also proposed that, owing to the different electronegativity of carbon and silicon and different polarities of the C–O and Si–O bonds, there no guarantee that the structure of CO_2-V is actually an analogue of one of the many phases of SiO_2. Very recently it has been reported that CO_2 transforms from phase III into a three-dimensional amorphous network similar to a-SiO_2 and a-GeO_2 at much lower temperature conditions, the reaction being activated above 40 GPa already at room temperature.[38] The question arising from these results is if the analogy among the oxides of the IV group elements at high pressure can be extended in such a way that also for carbon dioxide the incredible variety of SiO_2 polymorphs can be expected. A very important aspect of this surprising reaction that has not been fully clarified concerns the microscopic mechanism of the linear to tetrahedral structure transformation. From spectroscopic evidences (and in particular from the Raman activity of the bending mode) it has been argued that in some intermediate crystal phase the carbon dioxide molecules are bent, thus favoring the transformation from the sp to the sp^3 hybridization. However, a more accurate spectroscopic analysis has shown that in all crystal phases carbon dioxide remains linear,[39] therefore suggesting an abrupt collapse of the molecular crystal phases, from which the extended non-molecular phase is obtained, at definite threshold conditions.

The bond dissociation energy of molecular nitrogen N≡N (226 kcal mol^{-1}) largely exceeds three times the dissociation energy of the single N–N bond ($\sim$38 kcal mol^{-1}). Therefore, clusters of nitrogen atoms, if metastable and quenchable at ambient conditions, could be promising high-energy-density materials. The observed nitrogen dissociation in shock wave experiments[40] and the theoretical prediction that a single bonded polymeric form of nitrogen is the stable high-pressure structure of nitrogen[41] stimulated a search for a non-molecular form of the element at high pressure and temperature as a possible energy storage system. An amorphous non-molecular modification of this element was first obtained at pressures above 150 GPa.[3] The non-molecular character of the new allotrope was demonstrated by the disappearance of the nitrogen vibron and of the lattice modes. The sample however was found to have a band gap of $\sim$0.7 eV and turned black at pressures above 150 GPa: these findings and the broadness of the infrared and Raman bands implied that the new form was disordered and did not appear appropriate for an extended array of triply coordinated nitrogen atoms. On the basis of more recent experiments it has been suggested that this form of nitrogen is actually a mixture of atomic clusters of different dimensions and it been found that by heating at temperatures above 2000 K the disordered form changes further, the sample becomes transparent and new sharp Raman bands develop.[42] X-ray diffraction experiments have clearly shown that the transparent form of the compound is actually the cubic gauche form of nitrogen first hypothesized

by Mailhiot as the polymeric nitrogen structure, with a N–N bond length of 1.346 Å. The bulk modulus of the new compound (300–340 GPa) is in the range expected for a covalent crystal. This non-molecular allotrope of nitrogen is metastable at lower pressures (down to 42 GPa) but so far it has not been possible to recover it at ambient conditions.

Polymerization is a common response of materials to high pressurization and this is particularly the case for unsaturated hydrocarbons where the double and triple bonds are substituted by singly bonded arrays favored by the overall volume contraction. This is quite intuitive on grounds of the Le Chatelier principle. However, the practical occurrence of polymerization reactions may require the overcoming of significant potential energy barriers in the pressurized reagent. This has already been encountered in the carbon dioxide and nitrogen transformations where high temperatures are required for the reaction completion. Two additional major issues are of interest in high-pressure polymerization reactions. The first is concerned with the possibility of obtaining, in the absence of catalysts and solvents, conformationally pure, stereoregular and crystalline polymers, *i.e.* polymers with interesting mechanical, physical and chemical properties. To this purpose, considering pressurization as a physical activation method, it could be supplemented by additional activation means including temperature control, photochemical activation or even mechanochemical methods. The second issue is the definition of a microscopic counterpart of the observed polymerization thresholds. This information would, on the one hand, help in understanding the reaction mechanisms and, on the other, would be important to plan appropriate experiments to obtain high-quality polymers.

Recent experiments have shed some light on these issues. In the case of ethylene, a mixture of amorphous and crystalline polyethylene is normally obtained when the monomer is compressed at 0.3–0.5 GPa in the presence of catalysts or radical initiators that trigger the chemical reaction. On the contrary, when at 0.7 GPa liquid ethylene is laser irradiated in the visible or in the near ultraviolet, a high-density polyethylene is obtained.[9] Angle-resolved X-ray diffraction with monochromatic synchrotron radiation and the infrared and Raman spectra show that the optically catalyzed reaction product is a fully crystalline polymer with no detectable traces of amorphous domains. The photophysical activation of the reaction is induced by a two-photon absorption in the $^1B_{1u}$ antibonding state. Participation of excited states is an usual feature of high-pressure reactions. In purely pressure induced processes this is ensured by the enhanced configuration interaction favoured by the shift of the molecular orbital energies and by the broadening of the electronic density of states. The coupling with excited states is facilitated by photochemical activation and this leads to a decrease of the pressure threshold for the reaction (down to 0.2 GPa in the case of ethylene), a feature that can be of relevance in view of practical synthetic applications. It is seen that, in many respects, the increase of pressure and the selective laser irradiation can be thought as alternative and equivalent reaction activation tools. This has most clearly been demonstrated in the benzene amorphization reaction[43] to be discussed in the following. Ethylene polymerization has also

been studied at higher pressures in the solid phase.[21] In this case the condensation of the monomers can involve ethylene molecules on equivalent or on non-equivalent crystal sites with the former process favoured below 4 GPa and giving rise to a highly crystalline polymer. On the contrary, above 5 GPa the molecules located on non-equivalent sites are also involved, on account of the anisotropic compressibility of the crystal, in the chain growth and the degree of branching and the amount of conformational defects accordingly increases.

The selectivity that can be achieved in very high-pressure condensation reactions has been nicely demonstrated in the reaction of *trans*-butadiene in the liquid phase.[8] It has been found that at room temperature and at 0.7 GPa butadiene dimerizes into vinylcyclohexene. From the analysis of the infrared spectrum of the reaction product it is found that vinylcyclohexene is the only dimer formed and that traces of a polymer are hardly detectable. When in the same pressure regime the liquid sample is laser irradiated at 488 nm the dimerization reaction is completely inhibited and a conformationally pure *trans*-polybutadiene polymer is formed with no traces of the *cis* isomer generally present in commercial samples. The linear growth of the polymer is also evident from the kinetic analysis of the reaction. The photochemical activation of the polymerization is induced by a two-photon absorption in the 2^1A_g excited state that, being a π antibonding state, determines a lengthening of the molecule and reduces the molecular rigidity facilitating the head-to-tail condensation of the monomeric units.

The elucidation of the very high pressure reaction mechanisms is not an easy job. In fact the exact structure of the reactant (molecular orientations, intermolecular distances, electronic distribution) is in general not known. The kinetic analysis of the reaction, the identification of the excited states participating in the reaction and of the phonon modes assisting the reaction are obviously important pieces of information. Experimentally, interesting conclusions have been reached as a result of extensive investigation of the amorphization reaction of benzene in the solid state. It has been found that the reaction is greatly facilitated by the selective pumping of the pressurized sample in the S_1 first excited electronic state.[26] Pumping in the S_1 state reduces the room-temperature reaction threshold pressure of an unannealed sample from 25 to 15 GPa but the reaction seems to occur according to the same mechanism and the same product of the purely pressure induced reaction is obtained. It is thus apparent that the mixing of the ground and the S_1 state is fundamental in driving the benzene ring opening. From a mechanistic point of view, a basic information on the microscopic mechanism of the benzene amorphization has been obtained by the determination of the precise reaction pressure threshold at various temperatures.[22] These studies have shown that an accurate annealing of the samples is necessary to ensure reproducible reaction threshold conditions. Impurities due to an incomplete elimination of the metastable low-pressure crystal phase appreciably reduce the pressure reaction thresholds. Furthermore, at these ultrahigh pressures the deformation of the metal gasket produces shear forces able to induce the reaction at lower pressures. Operating with pure high-quality crystals the extraordinary stability of the benzene molecular edifice in quasi-hydrostatic compression conditions is unveiled, and the amorphization reaction at room temperature only occurs above 40 GPa. From the knowledge of the lattice parameters evolution with pressure,[44] the intermolecular shortest C–C contacts have been obtained along various crystallographic directions for all the different pressures (between 14 and 41 GPa) where the reaction has been induced by adjusting the temperature. To these distances have been subtracted the amplitudes of out of phase translational and acoustic modes at the different reaction temperatures (298–643 K). It turns out that for all the P–T conditions experimentally studied the onset of the reaction invariably occurs when the C–C intermolecular separation along the a axis becomes lower than 2.6 Å. This is a sharp demonstration of the fundamental role played by the lattice phonons that regulates a type of molecular diffusion realizing the instantaneous configurations for the reaction to occur. When, such as in glassy phases, collective motions are missing the occurrence of the chemical reaction can be prevented also at very critical values of temperature and pressure. This is actually what has been observed in propene[45] where the reaction is observed from the fluid at 4 GPa and 270 K but not from the glassy solid at the same temperature but up to pressures exceeding 11 GPa.

6 Summary and conclusions

In this *tutorial review* the peculiarities of chemical reactions occurring in the high-pressure regime have been discussed. The experimental equipment used in high-pressure science have been introduced with particular attention to the versatile diamond anvil cell. The general effects of pressure on chemical equilibria and reaction rates have been recalled with mention of the general environmental effects and of the mechanisms of solid-state chemical reactions. In an intermediate range high-pressure methods have been found to be very useful for mechanistic studies of organic and inorganic reactions particularly through the determination of activation volumes. At high pressures the selectivity of chemical reactions can be significantly enhanced. Perspectives for fundamental and applied studies in the biosciences are presented. Novel phenomena observed at ultrahigh pressure in the chemical reactions of simple molecules and of unsaturated hydrocarbons have been reviewed showing that the pressure–temperature thresholds of the transformations can be correlated with microscopic reaction conditions such as intermolecular distances, molecular orientations and phonon assistance. As a whole, it has been shown that high-pressure activation of chemical reactions offers ample possibility for fundamental studies of reaction mechanisms and for many applications to obtain novel products. Through simplification and versatility of high-pressure equipments, and in particular the availability of the DAC, it can be foreseen that high-pressure studies of chemical reactions can be developed more extensively in the near future.

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