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Editorial

Special Issue: Biomolecular systems under extreme environmental conditions

Decades of calorimetric studies have contributed invaluable insight into the nature of the heat capacity of proteins and their response to changes in temperature. Understanding of the effects of hydrostatic pressure in contrast, has lagged behind for a long time. This is unfortunate as with other problems in chemical thermodynamics, the solution to the most important problems in biomolecular science will require a complete description of the energy landscape of their conformations and interactions. To this end, pressure depended studies are able to contribute significantly. Interest in high hydrostatic pressure as a thermodynamic and kinetic variable has been dramatically growing in physical–chemical studies of biological materials in recent years. Pressure acts on the structure and dynamics of biomolecular systems through changes in volume that are largely due to changes in hydration or packing efficiency. Thus, high hydrostatic pressure is uniquely well suited for studying the role of solvation in folding, conformational dynamics, and interactions of proteins and other biomolecules. Pressure is also ideal for characterizing spontaneous conformational fluctuations, because fluctuations involve a change in volume, and high-energy conformers that are normally not easily accessible experimentally can be stabilized by pressure. Moreover, the balance between hydrogen bonding, electrostatic and hydrophobic interactions can be changed in a controlled way by pressure perturbation. Hence, from a physical–chemical point of view, studying pressure effects on solutions of biomolecules are able to reveal important mechanistic information on fundamental biomolecular processes and reactions. A few reasons are listed below:

- Changing temperature of a system at atmospheric pressure produces a simultaneous change in thermal energy and volume. Therefore, to separate thermal and volume (density) effects, one must carry out also pressure-dependent experiments.
- Studies on model systems have shown that pressure (i.e., density) effects often determine the mechanism, whereas temperature often changes the frequency of the motions, only.
- Because noncovalent interactions play a primary role in the stabilization of biochemical systems, the use of pressure allows one to change, in a controlled way, the intermolecular interactions without the major perturbation often produced by changes in temperature or cosolvent concentration.
- Pressure affects chemical equilibria and reaction rates. Le Châtelier's principle predicts that the application of pressure shifts a chemical equilibrium towards the side that occupies a smaller volume, and processes for which the transition state has a smaller volume than the ground state are accelerated. For example, if a reaction is accompanied by an activation volume, $\Delta V^{\#}$, of −50 mL/mol, it is enhanced more than 3000-fold by applying pressure of 4 kbar at ambient temperature. With the knowledge of the reaction and activation volumes, ΔV^{o} and $\Delta V^{\#}$, respectively, one can draw additional valuable conclusions about the nature of the reaction and its mechanism.
- As the characteristic time for the transmission of pressure approaches the speed of sound, the high pressure application can be considered as instantaneous.
- The viscosity, dielectric constant, and many other properties of the solvent can be changed continuously by pressure.
- High pressure may increase the population of so far undetected, (low-lying) excited states (e.g. conformational and functional substates, folding and aggregation intermediates of proteins, or intermediate states during lipid phase transitions).
- High pressure allows modulating intermolecular interactions (e.g., it weakens hydrophobic interactions and strengthens H-bonding).
- High pressure can reveal different pathways of aggregation and can dissociate protein aggregates, which holds several biotechnological implications.
- High pressure is a good disturber and stressor of cellular physiology (e.g., for modulation of signaling and metabolic processes).

So far, pressure-dependent studies have mainly focused on the study of simple biomolecular systems, including monomeric and oligomeric proteins, DNA, one-, two- and three-component lipid bilayers and model biomembranes, and a few reconstituted membrane-protein systems. Furthermore, the use of high pressure to refold proteins and dissolve protein aggregates has been explored, and several biotechnological processes (e.g. high pressure food processing) have been initiated. Enzyme-catalyzed synthesis of pharmaceuticals under mild conditions has already proved to be possible, as well as the enantioselective synthesis of esters such as ibuprofen esterification by lipases. By operating in the presence of stabilizing cosolvents or in organic media, it may even be possible to increase the thermobarostability of industrial enzymes. A molecular-level understanding of pressure effects on enzymatic processes is largely lacking, however. The application of high pressure to perturb and modulate biochemical processes and reactions and its molecular level understanding is largely terra incognita as well, but is on the agenda of several laboratories worldwide.

Besides this physical–chemical and biotechnological interest in the pressure parameter, pressure is a well-known parameter also in the biological context. Although hydrostatic pressure significantly influences the structural properties and thus functional characteristics of cells, this has not prevented life from invading high pressure habitats of marine depths. Psychrophilic–piezophilic (cold- and pressure-adapted) species, which live at ~4 °C, are found on the deepest ocean floor (~11,000 m) in the Mariana Trench and in deep sea sediments, the so-called deep biosphere. The piezophilic microbiota living there are adapted to these pressures or even obligately require them for their

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life. Furthermore, close to hydrothermal vents, generally several thousand meters under the sea surface, even organisms far more complex than bacteria can be found at conditions of elevated hydrostatic pressure (~300 bar) and high temperature (up to ~120 °C).

Hence, there are also extraordinary prospects for using the pressure variable to deepen our understanding of life, including deep sea biology, prebiotic chemistry, and astrobiology (e.g., the search for life in the deep crust of the Earth, in permafrost regions of extraterrestrial planets or on moons like Europa and Titan). The field of high-pressure biology, specifically the temperature–pressure limits of life in general, has been controversial. Claims of evidence for viability of *Escherichia coli* and *Shewanella oneidensis* to 14 kbar (1.4 GPa) at room temperature were met with initial skepticism, but have been supported recently. Directed evolution has been used to reveal the potential of the model bacterium *E. coli* to develop the ability to survive exposure to high temperature and pressure. While heat resistance could only be marginally increased, piezoresistance could readily be extended into the 10 kbar range, thereby greatly exceeding the currently recognized maximum for growth or survival. Major cutting-edge questions concern the nature of the biological activity at these conditions and why those that survived did so. Pressure studies can also help elucidate what happened in the first stages of the emergence of life on Earth. RNA may have emerged from an earlier world under extreme conditions of pressure, temperature and pH. This hypothesis presents double-helix molecules as crucial building blocks. It has been noticed that these molecules might be able to acclimate to harsh conditions, such as those found in the deepest sea trenches, in Earth's interior or under the impact of a meteorite. A molecular understanding of the physical and chemical properties as well as elementary reactions of these molecules under high-pressure conditions is lacking, however.

The wide range of topics covered in this special issue of Biophysical Chemistry is reflective of the broad range of perspectives in high pressure bioscience. It is hoped that the articles in this special issue will foster interest in pursuing this still rather novel area of research. High pressure is shown to allow us to peek into the hidden structures, dynamical properties and interactions of biomolecules, and, in turn, enables us to control the function of biomolecules in practical applications. We may expect a boost of pressure applications in the near future in finding active conformations that selectively bind to other biomolecules or drugs, in steering enzymatic reactions, and in modulating metabolic and signaling processes. The incentive to understand the effects of pressure on biological systems and the search for applications in novel biotechnological processes will bring together amazingly different fields of expertise, including molecular biosciences, systems biology, biotechnology, food science, biomedicine, pharmacology, deep sea research, and astrobiology. This may be expected to generate novel ideas and a multitude of cutting-edge research collaborations.

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