Pressure can be used to initiate a plethora of intriguing transformations and chemical reactions. During the past 10 years or so, several quantum chemical methods have been developed that describe the structural and electronic changes in molecules under pressure. This perspective focuses on three of these methods: the extreme pressure polarizable continuum model, the generalized force-modified potential energy surface, and the hydrostatic compression force field approach. The theoretical background of each method is discussed, and several interesting applications are reviewed. The challenges that the field faces, as well as possible routes for future developments, are pointed out.
for the investigation of molecules under pressure that have been developed within the past 10 years or so. In particular, the extreme pressure polarizable continuum model (XP-PCM), the generalized force-modified potential energy surface (G-FMPES), and the hydrostatic compression force field (HCFF) approaches are reviewed from a theoretical and practical perspective. These methods typically focus on the description of single atoms or molecules under high pressures and have only rarely been used for extended systems, thus potentially lending themselves for comparisons to experiments in diamond-anvil cells. To demonstrate the capabilities of these methods, several chemical reactions under pressure that have been studied with the approaches are described as well.

2 | THEORY AND APPLICATIONS

2.1 | Extreme pressure polarizable continuum model

The XP-PCM\(^{29–32}\) is a modification of the implicit solvent model PCM\(^{33,34}\) which allows the application of pressure to a molecule that is surrounded by a uniform solvent. The fundamental idea of XP-PCM is that the space that the electrons in a molecule can occupy is restricted via a pressure-dependent repulsive potential surrounding the molecule.\(^{7}\)

The first step in the XP-PCM protocol is analogous to PCM in that a molecule-shaped cavity is constructed around the solute.\(^{7}\) In many cases, this is achieved by superimposing atom-centered spheres with the element-specific van der Waals radii (multiplied with a scaling factor \(f\), where typically \(f = 1.2\))\(^{30}\) and removing the overlapping regions, which results in the molecular van der Waals surface. Modifications of this approach are possible, leading to the solvent-accessible surface (SAS) or the solvent-excluded surface (SES).\(^{35}\) The external medium is modeled as a continuum with a uniform dielectric permittivity \(\varepsilon\) and an electron density \(\rho\).\(^{7,33}\) The interaction between the solute and the solvent is modeled via electrostatic interaction, that is, the Coulomb interaction between the solute and the surrounding solvent, and Pauli repulsion. The latter contribution emerges from a penetration of the solute’s electrons into the surrounding medium and is modeled as a step potential that is zero inside the cavity and nonzero outside of the cavity. The value of the Pauli repulsion outside of the cavity depends on the electron density of the surrounding medium.

In XP-PCM, pressure enters in two ways.\(^{36}\) First, the size of the solute-shaped cavity is reduced compared to the pressure-free state to account for the experimentally observed reduction in the volume of substances under pressure,\(^{5}\) which leads to decreased mean distances between the solute and the solvent molecules (Figure 1). As a result, a larger part of the electron density of the solute comes into contact with the repulsive Pauli potential that begins at the border of the surrounding medium. Tests have shown that decreasing the scaling factor for the van der Waals radii within the range \(f = 1.2\)-0.9 allows the application of pressures between 1 GPa and 20 GPa.\(^{36}\)

![Figure 1](image-url)
Second, the Pauli repulsion itself is increased by increasing the step potential at the boundary between the solute and the solvent, as well as the density and the dielectric permittivity of the solvent. The main assumptions here are that the scaling factors of these quantities depend on the scaling factor of the van der Waals radii as the external medium experiences a scaling that is closely related to the scaling of the molecular cavity and that the scaling of the Pauli repulsion further depends on a semiempirical parameter \( \eta \).

The pressure that is applied with XP-PCM can be calculated by adjusting the volume of the cavity to different values and calculating the energy in each case. Because the pressure \( P \) can be defined as the negative partial derivative of the electronic energy, \( G_{er} \), with regard to volume,

\[
P = -\frac{\partial G_{er}}{\partial V}.
\]

a subsequent analytic fit yields the applied pressure. The subscript "er" represents the electrostatic and repulsive contributions to the energy. An analytic calculation of the pressure in XP-PCM has been described in detail recently.

The XP-PCM approach has been successfully used to calculate Gibbs energy profiles of the Diels-Alder reaction between cyclopentadiene and ethylene at different pressures (Figure 2). It has been found that the reaction becomes almost barrierless at 3.0 GPa and that the transition state disappears altogether at around 11.2 GPa. This result is chemically intuitive as both the transition state and the product occupy smaller volumes than the reactants.

As XP-PCM is the oldest and most established of the methods described here, many applications have been reported in literature. Examples include several chemical reactions under high pressures, for example, pericyclic reactions, other Diels-Alder reactions, the retrocycloaddition of the anthracene photodimer, in addition, pressure-induced changes in vibrational frequencies, electronic excitation energies, and lattice parameters in crystals as well as electronic changes in all elements of the periodic table have been reported. The examples demonstrate the wide applicability of XP-PCM when describing diverse pressure-induced processes.

### 2.2 | Generalized force-modified potential energy surface

As its name suggests, the G-FMPES approach has its origins in mechanochemistry. As pressure is conveniently defined as the normal component of the force, \( F_\perp \), per area \( A \),

\[
P = \frac{F_\perp}{A}.
\]

the connection between pressure and mechanical forces is patently obvious and has been appreciated by other authors as well. The original FMPES scheme was proposed as one of the fundamental methods in mechanochemistry to apply constant external stretching forces to
molecules, thereby allowing the calculation of various force-dependent quantities in mechanochemical processes. In essence, the constant external force is added to the nuclear gradient within a geometry optimization along the connecting line between two atoms, and convergence is achieved when the external force cancels the internal restoring force of the molecule.

The G-FMPES approach generalizes this idea to spatially varying forces and has been used to apply pressure to molecules. The G-FMPES $\tilde{V}(R)$ is given by adding a path-independent integral to the Born-Oppenheimer PES, $V(R)$,

$$\tilde{V}(R) = V(R) + \int F_{\text{ext}}(R) \, dR.$$  

Practically, in the G-FMPES model, the external force applied to the $j$th atom of the molecule, $f_{j_{\text{ext}}}$, is given by

$$f_{j_{\text{ext}}} = P_{\text{HP}} \cdot \left| r_j - c \right|,$$  

where $P_{\text{HP}}$ is a scalar “pseudo-hydrostatic pressure” that is defined by the user, $r_j$ is the position vector of the $j$th atom, and $c$ is the vector of the molecular centroid. Scaling the forces according to Equation (4) means that atoms further away from the geometric centroid of the system experience higher compressive forces than atoms that are closer to the centroid (Figure 3). This approach is equivalent to placing all atoms in the same parabolic potential, centered at the molecular centroid, which leads to a compression of the molecule. This compression is more pronounced if larger values of $P_{\text{HP}}$ are chosen.

In general, $P_{\text{HP}}$ is not the real macroscopic pressure that is applied to the system. Instead, the macroscopic pressure, $P_{\text{G-FMPES}}$, is estimated in the G-FMPES scheme as

$$P_{\text{G-FMPES}} = \frac{\langle |f| \rangle}{\langle A \rangle},$$

where $\langle |f| \rangle$ is the average of all external forces calculated via Equation (4), and $\langle A \rangle$ is the average area of the spheres on which the atoms are located. These spheres are again centered at the geometric centroid of the system (cf. Figure 3). Hence, it is not possible for the user to input precisely the pressure that is applied to the system in the calculation.

Using the G-FMPES methodology, it was found that new minima can be introduced in the potential energy surface by using pressure, and minima that exist in the pressure-free state can disappear when pressure is applied. Calculations of the Diels-Alder reaction between butadiene and ethylene in the pressure range between 68 MPa and 1410 MPa yielded the intuitive result that the activation energy barrier for this reaction decreases with increasing pressure. Equally intuitively, pressure has been found to increase the reaction barrier for the decomposition of RDX (hexahydro-1,3,5-trinitro-s-triazine), a propellant and explosive. Moreover, vibrational frequencies of molecules are affected by pressure. Similar effects have been observed before in the case of mechanical forces that deform molecules, which emphasizes the mechanical character of pressure.

### 2.3 Hydrostatic compression force field

The HCFF model is a modification of the G-FMPES approach. It uses the same basic ideas as the original protocol in that all atoms are located within the same parabolic potential, which compresses them toward the molecular centroid. In contrast to G-FMPES, however, the maximum force that acts on the atoms, $f_{\text{max}}$, is calculated as

![FIGURE 3](https://example.com/figure3.png)
where $P_{\text{guess}}$ is a user-defined guess for the pressure applied to the system, and $A_{\text{vdW}}$ is the molecular van der Waals surface. The choice of using $A_{\text{vdW}}$ was made because the pressure is applied to the molecule through the solvent at the surface of the molecule. In principle, the areas of the SAS or the SES can be used instead of $A_{\text{vdW}}$.\(^{[35]}\) Unlike XP-PCM, the sizes of the van der Waals spheres are not shrunk in the HCFF approach when pressure is applied. As in G-FMPES, the forces acting on the atoms are scaled according to their distances to the geometric centroid, which means that $f_{\text{max}}$ acts on the outermost atom. Subsequently, the physical pressure applied to the system is calculated via\(^{[58]}\)

$$P_{\text{HCFF}} = \frac{\langle |f| \rangle}{A_{\text{vdW}}}. \quad (7)$$

Again, $\langle |f| \rangle$ is the average of the forces acting on the atoms. While $P_{\text{guess}}$ is an upper bound to $P_{\text{HCFF}}$,\(^{[58]}\) the values are typically reasonably close to each other, which is a profitable feature of the HCFF approach as the user-defined parameter $P_{\text{guess}}$ is closely connected to the physical pressure that is applied to the system via this mechanical model.

The HCFF model has been used to model pressure-induced spin crossover in octahedral transition metal complexes (Figure 4A).\(^{[58]}\) Upon application of pressure, the average metal-ligand distance decreases as the ligands are pushed toward the metal center, thus leading to an increase in the ligand field splitting energy. If the spin state of the metal is high spin at zero pressure, a sufficiently high pressure leads to a low spin configuration. This is the basic idea of pressure-induced spin crossover\(^{[61]}\) and opens the avenue toward novel and efficient ways to store, separate, and activate various gases or to tune the optical and magnetic properties of materials by using pressure.

As an example of this effect, the pressure-induced spin crossover process in $[\text{Fe(II)(H}_2\text{O)}_6]^{2+}$ has been investigated (Figure 4B).\(^{[58]}\) In this system, spin crossover occurs at approx. 1.20 GPa. However, it has been found that the pressure required for spin transition is a function of the position of the ligand in the spectrochemical sequence (cf. Table 1).\(^{[58,62]}\) With strong field ligands requiring less pressure to induce spin crossover in the central metal ion, which paves the way for a rational design and precise tailoring of transition metal complexes that show spin transition at a desired pressure. Following up on this idea, it was possible to decrease the pressure required for spin transition by an order of magnitude by tuning the ligand field.\(^{[58]}\)

Interestingly, nitrogen ligands were found to flip from end-on coordination to side-on coordination if sufficiently high pressures are applied, which is a result of the concentric nature of the forces applied in HCFF (in analogy to G-FMPES) and the resulting effort of...
the molecule to minimize its surface area. Hence, the mechanochemical models of pressure are expected to work best if the molecule’s symmetry is close to spherical. In most cases, the octahedral ligand fields described in ref. [58] were found to be unproblematic in this regard. Moreover, the electronic changes during spin transition have been investigated with energy decomposition analysis using absolutely localized molecular orbitals.[63] It was found that the unfavorable Pauli repulsion between the metal and its surrounding ligands increases with increasing pressure, thus confirming one of the basic assumptions of XP-PCM, and that—at the same time—the favorable charge-transfer contribution increases due to an increased overlap between the metal and the ligands. The delicate interplay of these energetic contributions determines the electronic response of a given system when exposed to pressure.

3 | OUTLOOK

In this perspective, three recently developed quantum chemical methods for the application of pressure to molecules have been discussed: the XP-PCM, the G-FMPES, and the HCFF approaches. While XP-PCM models a solute in a uniform dielectric medium and applies pressure through the variation of various parameters of the solvent and the cavity, the other two methods originate from mechanochemistry and apply compressive forces to model pressure. These three methods have been used successfully to model various physicochemical processes and chemical reactions under pressure.

On the methodological side, several challenges remain. Future extensions of the mechanochemical models of pressure will likely include effects that are beyond the pure application of compressive forces to nuclei, that is, important contributions such as the increase in kinetic energy of the electrons in a molecule under pressure need to be included,[58] and the contribution of the surrounding medium needs to be modeled realistically. Expanding on this idea, all approaches described here at least partially neglect important changes in the surrounding of the solute, for example, increased viscosity of the solvent, packing effects, and the overall statistical nature of pressure-induced changes in the geometric and electronic properties of the solutes. Moreover, it would be highly desirable for the user to be able to input precisely the pressure that is modeled in the calculation, without the need to specify indirect parameters from which the applied pressure is calculated. Some of these questions have been addressed in the context of ab initio molecular dynamics simulations,[28] but it is highly desirable to extend the static, purely quantum chemical approaches described here to incorporate these effects.

Furthermore, extensive testing and benchmarking against experiments is necessary to judge the reliability and scope of each method. Such data would potentially allow the prediction of experiments at high pressure, for example, in diamond-anvil cells, and the establishment of synergistic relationships between experimental and theoretical high-pressure chemistry. In the context of pressure-initiated chemical reactions, an interesting perspective is provided by an analysis of the strain due to the deformation of the molecules,[64] which potentially allows rationalization and optimization of the occurring bond rupture and formation events.

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