Efficient computation of free energy surfaces of chemical reactions using ab initio molecular dynamics with hybrid functionals and plane waves

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Abstract
Ab initio molecular dynamics (AIMD) simulations employing density functional theory (DFT) and plane waves are routinely carried out using density functionals at the level of generalized gradient approximation (GGA). AIMD simulations employing hybrid density functionals are of great interest as it offers a more accurate description of structural and dynamic properties than the GGA functionals. However, the computational cost for carrying out calculations using hybrid functionals and plane wave basis set is at least two orders of magnitude higher than that using GGA functionals. Recently, we proposed a strategy that combined the adaptively compressed exchange operator formulation and the multiple time step integration scheme to reduce the computational cost by an order of magnitude [J. Chem. Phys. 151, 151102 (2019)]. In this work, we demonstrate the application of this method to study chemical reactions, in particular, formamide hydrolysis in an alkaline aqueous medium. By actuating our implementation with the well-sliced metadynamics scheme, we can compute the two-dimensional free energy surface of this reaction at the level of hybrid-DFT. This work also investigates the accuracy of the PBE0 (hybrid) and the PBE (GGA) functionals in predicting the free energetics of this chemical reaction.

KEYWORDS
ab initio molecular dynamics, formamide hydrolysis, free energy calculations, hybrid density functional, plane wave basis set

1 INTRODUCTION

Ab initio molecular dynamics (AIMD) simulations,\textsuperscript{[1–4]} where the atomic forces are computed on the fly using first-principles based quantum mechanical methods, in particular at the level of hybrid density functional theory (DFT) and plane wave basis set, are highly desirable to investigate chemical reactions. Specifically, for computing free energetics and mechanism of chemical reactions in liquids and heterogeneous interfaces, AIMD technique is preferred over the static quantum chemical approaches that rely on finding stationary points on the potential energy landscape. The combination of Kohn Sham density functional theory (KS-DFT) and plane wave (PW) basis sets is the method of choice for carrying out AIMD simulations of periodic and isolated systems.\textsuperscript{[1]} This can be attributed to the fact that PW basis set is free from basis set superposition errors and Pulay forces, and is inherently periodic.

The quality of the results obtained from a KS-DFT calculation critically depends on the chosen exchange-correlation (XC) functional. For the past two decades or more, AIMD using PW KS-DFT is largely restricted to the Generalized Gradient Approximation (GGA)\textsuperscript{[5–7]} level...
of XC functionals. However, it is well known that these functionals suffer from self interaction error (SIE).\textsuperscript{[8–11]} SIE leads to over-delocalization of electron density, resulting in errors in chemical reaction barriers, band gap, and dissociation energy.\textsuperscript{[9,11]} Also, SIE severely affects the electronic structure properties of open-shell systems.

In a hybrid-type XC functional, a portion of the Hartree-Fock exchange energy is added to the GGA exchange energy.\textsuperscript{[8,12–15]} KS-DFT calculations with hybrid functionals are generally known to improve the prediction of energetics, structures, electronic properties, reaction barriers, and band gap of solids.\textsuperscript{[13–20]} Also, hybrid functional based AIMD simulations give an improved description of the structural and dynamical properties of liquids.\textsuperscript{[21–26]} Hybrid functionals reduce SIE and improve the accuracy of KS-DFT computations. Recently, hybrid functional based AIMD simulations in combination with enhanced sampling methods are shown to improve the accuracy of the computed free energy surfaces.\textsuperscript{[27,28]} However, AIMD with hybrid functionals and PW basis set has a substantial computational overhead, which is associated with the evaluation of the exact exchange energy.\textsuperscript{[29]} Thus, free energy calculations of chemical reactions, that requires $\sim 10^6$--$10^7$ force evaluations, in systems containing several hundred or more atoms, are seldom performed employing AIMD.

One of the ways to decrease the computational time is by evaluating the exchange integral using localized KS orbitals.\textsuperscript{[19,23–25,28,30–41]} Usage of the multiple time step (MTS) algorithms\textsuperscript{[42–46]} in particular the reversible reference system propagator algorithm (r-RESPA),\textsuperscript{[46]} is a promising alternative. In the r-RESPA algorithm, computationally cheap fast forces are computed more frequently as compared to the computationally costly slow forces. In this way, one obtains the required speed-up using r-RESPA in AIMD simulations.\textsuperscript{[47–54]} In order to apply r-RESPA method in hybrid functional based AIMD simulations, an artificial time scale separation in ionic forces has to be created. In some of the earlier works, time scale separation was introduced by combining the forces from GCA and hybrid functionals\textsuperscript{[49,54]} or forces from different levels of two-electron integral screening.\textsuperscript{[53]} Recently, we proposed an r-RESPA scheme based on the adaptively compressed exchange (ACE)\textsuperscript{[55,56]} operator formulation (r-RESPA+ACE).\textsuperscript{[57]} The implementation of our method in the CPMD code\textsuperscript{[58]} allows us to perform long hybrid functional based AIMD simulations. The r-RESPA+ACE method has been shown to be efficient and accurate in predicting the structural and dynamical properties of bulk water.\textsuperscript{[57]}

Here we use the r-RESPA+ACE operator scheme together with the well-sliced metadynamics (WS-MTD)\textsuperscript{[59]} method to study a prototype hydrolysis reaction in water. In particular, we model the formamide hydrolysis reaction in aqueous alkaline medium and compute the two-dimensional free energy surface for the reaction. The main objective of this work is to demonstrate the applicability of r-RESPA+ACE method for carrying out extensive MD simulations and free energy calculations of chemical reactions. Finally, we compare the accuracy of PBE (GGA) and PBE0 (hybrid) functionals in predicting the free energy surface.

## Methods and Models

### Exact exchange operator

The self-consistent field (SCF) solution of hybrid functional based KS-DFT equations requires the application of the exchange operator on all the occupied KS orbitals at every SCF iteration. The exact exchange operator $V_X$ is defined as

$$V_X = -\sum_{j}^{N_{\text{orb}}} |\psi_j\rangle \langle \psi_j|_{r_{12}},$$

in terms of the set of occupied KS orbitals $|\psi_j\rangle$. Here, $N_{\text{orb}}$ is the total number of occupied orbitals and $r_{12} = |r_1 - r_2|$. The application of $V_X$ on a KS orbital $|\psi_i\rangle$ is given by,

$$V_X |\psi_i\rangle = -\sum_{j}^{N_{\text{orb}}} |\psi_j\rangle \langle \psi_j|_{r_{12}}^{-1} |\psi_i\rangle = -\sum_{j}^{N_{\text{orb}}} v_{ij} |\psi_i\rangle,$$

where

$$v_{ij} = \langle \psi_j|_{r_{12}}^{-1} |\psi_i\rangle.$$

The evaluation of $v_{ij}(r)$ is ideally done in the reciprocal space\textsuperscript{[29,30]} using Fourier transformation. If $N_G$ is the total number of PWs used, the computational cost for doing Fourier transform scales as $N_G^2 \log N_G$ using fast Fourier transform technique. The application of $V_X$ on a single KS orbital requires $N_{\text{orb}}$ times evaluation of $v_{ij}(r)$. Thus, the total computational cost scales as $N_{\text{orb}}^2 N_G^2 \log N_G$\textsuperscript{[29]} as $V_X$ has to be applied on $N_{\text{orb}}$ number of KS orbitals. For typical molecular systems of our interest, $N_{\text{orb}} \sim 10^2$ and $N_G \sim 10^6$, which results in an exorbitant computational time requirement for hybrid functional calculations.

### Adaptively compressed exchange operator

Recently, Lin Lin developed the ACE operator formulation\textsuperscript{[55,56]} to reduce the computational cost of such calculations. In this formalism, $V_X$ operator is approximated by the ACE operator $V_X^{\text{ACE}}$. First, the action of $V_X$ on the set of KS orbitals $|\psi_j\rangle$ is computed as

$$|W_i\rangle = V_X |\psi_i\rangle, \quad i = 1,...,N_{\text{orb}}.$$  \hspace{1cm} (4)

According to the ACE formalism, $V_X^{\text{ACE}}$ is defined as

$$V_X^{\text{ACE}} = \sum_{i=1}^{N_{\text{orb}}} W_i B_i |W_i\rangle,$$  \hspace{1cm} (5)

where $B = M^{-1}$, and the elements of the matrix $M$ are...
the application of the computation of \( \{ V \} \) for reducing the computational cost of hybrid functional based AIMD calculations.\(^{[57]} \) In that, we made the assumption that the ionic forces, \( \{ F \} \), with \( k = 1, \ldots, 3N \), for a system containing \( N \) particles, can be decomposed into slow and fast components depending on the time scale of their variation as

\[
F_k = F_k^{\text{fast}} + F_k^{\text{slow}}, \quad k = 1, \ldots, 3N. \tag{12}
\]

Now, the Cholesky factorization of \( -M \) is performed as

\[
M = -LL^T. \tag{7}
\]

Here, \( L \) is a lower triangular matrix. Then \( B \) can be computed as

\[
B = -L^{-T}L^{-1}. \tag{8}
\]

The \( V_k^{ACE} \) operator can be rewritten as,

\[
V_k^{ACE} = -\sum_{i=1}^{N_{\text{orb}}} | P_i \rangle \langle P_i |. \tag{9}
\]

Here, the ACE projection vectors \( \{| P_i \rangle \} \) are the columns of the matrix \( P \), which is defined as

\[
P = WL^{-T}. \tag{10}
\]

Now, the evaluation of the action of \( V_k^{ACE} \) operator on KS orbitals can be performed with \( N_{\text{orb}}^2 \) number of simpler inner products as

\[
V_k^{ACE} | \psi_i \rangle = -\sum_{i=1}^{N_{\text{orb}}} | P_i \rangle \langle P_i | \psi_i \rangle, \quad i = 1, \ldots, N_{\text{orb}}. \tag{11}
\]

The advantage of the ACE approach is that the cost of applying the \( V_k^{ACE} \) operator on each KS orbitals is much less as compared to the application of the \( V_k \) operator.

In the scheme proposed by Lin Lin,\(^{[55,56]} \) at the beginning of the SCF iteration, \( V_k^{ACE} \) operator is constructed through the computation of \( | \langle \psi_i | \psi_j \rangle \rangle \) \( \) as described above. Certainly, this step is computationally costly due to \( N_{\text{orb}}^2 \) times evaluation of \( V_k (r) \). As the exchange energy has only a small contribution to the total energy, it is possible to use the same \( V_k^{ACE} \) operator (without updating it) for all the SCF iterations. An outer loop over the SCF calculation updates the \( V_k^{ACE} \) operator till a complete convergence is obtained. It has to be noted that, once the \( V_k^{ACE} \) operator is constructed, its low rank structure allows the easy computation of \( | \langle \psi_i | \psi_j \rangle \rangle \) during the SCF iterations. For example, for a 32 water periodic system, the computational time for the operation of \( V_k^{ACE} \) is \( \sim 240 \) times lesser than that of \( V_k \) (using 120 compute cores).\(^{[57]} \)

### 2.3 Combining ACE operator formalism with r-RESPA

Recently, we took advantage of the properties of the ACE operator to combine it with r-RESPA method\(^{[46,60]} \) for reducing the computational cost of hybrid functional based AIMD calculations.\(^{[57]} \) In that, we made the assumption that the ionic forces, \( \{ F \} \), with \( k = 1, \ldots, 3N \), for the exchange operator \( V_k \) evaluated at every self-consistent field (SCF) cycle. In our implementation, as shown in Figure 1, the \( V_k^{ACE} \) operator is constructed at the beginning of every SCF cycle, based on the initial guess of the wavefunction. The same \( V_k^{ACE} \) operator is used in the
remaining SCF steps, till a convergence in wavefunction is achieved. The initial wavefunction for the SCF cycles is obtained from the Always Stable Predictor Corrector Extrapolation Scheme.\[61\] The converged wavefunction is then used to compute $F_{\text{ACE}}$. For every $n_t$ MD steps, another SCF cycle is executed where the exact exchange operator $V_X$ is computed at every SCF step. The converged wavefunction is then used to compute $F_{\text{exact}}$, and then $\Delta F$.

As the $V_{\text{ACE}}$ operator closely resembles the $V_X$ operator, the differences in the ionic force components of $F_{\text{exact}}$ and $F_{\text{ACE}}$ are very small. In our earlier work,\[57\] we demonstrated that the magnitude of $\Delta F$ is $\sim 100$ times smaller than that of $F_{\text{ACE}}$. It was also shown that $\Delta F$ computed at every $n_t = \Delta t/\delta t$ steps is slowly varying as compared to $F_{\text{ACE}}$. In this way, r-RESPA+ACE scheme allows us to compute computationally costly $\Delta F$ (or $F_{\text{exact}}$) less frequently than the computationally cheaper $F_{\text{ACE}}$. As a result, we get a substantial speed-up. For a periodic system containing 32 water molecules, we obtained a speed-up of 7 with $n_t = 15$; See Figure 2 and Mandal and Nair.\[57\]

In the r-RESPA+ACE scheme, the efficiency of the method critically depends on the choice of $n_t$. Larger the value of $n_t$, better is the speed-up, as the evaluation of computationally costly forces has to be carried out less frequently. However, usage of a large $n_t$ value could deteriorate the quality of integration of the equations of motion and could result in total energy drift. The choice of $n_t$ is restricted by the resonance,\[62\]-\[64\] which arises when the update frequency of the slow forces is proportional to its natural frequency. In r-RESPA schemes, an optimal choice of $n_t$ is determined by monitoring the total energy drift. In our earlier study,\[57\] we identified the optimal value of $n_t$ for the r-RESPA+ACE method as 15. Stochastic thermostats, such as that proposed by Leimkuhler et al.\[63\] can be employed for using higher values of $n_t$, which will be explored in a future work.

2.4 | Computational details

For modeling the chemical reaction, a cubic periodic simulation cell with a side length of 10 Å was chosen, which contained one formamide molecule, one hydroxide ion, and 29 water molecules. A homogeneous positive background charge was added to maintain the charge neutrality in the system. All the calculations were carried out employing the CPMD program\[58\] wherein the r-RESPA+ACE method was implemented by us. The PBE0\[16\] XC functional was used together with the norm-conserving Troullier-Martin type pseudopotentials\[65\] and a PW cutoff energy of 80 Ry was taken. We carried out Born-Oppenheimer molecular dynamics simulations to
perform MD simulations at canonical (NVT) ensemble for $T = 300$ K. Here, r-RESPA+ACE scheme with $\Delta t = 0.48$ fs and $\Delta t = 7.2$ fs (i.e., $n_t = 15$) was considered and Nosé–Hoover chain thermostats were used.\textsuperscript{[66]} During the SCF (see Figure 1), we converged the wavefunctions till the magnitude of the maximum wavefunction gradient was below $1 \times 10^{-6}$ au. Always Stable Predictor Corrector Extrapolation Scheme\textsuperscript{[61]} of order 5 was used to obtain initial guess of wavefunction.

We employed the WS-MTD approach\textsuperscript{[59]} to compute the free energy surface of the base-catalyzed formamide hydrolysis reaction. The WS-MTD method is designed to achieve a controlled sampling of coordinates and efficient exploration of high-dimensional free energy landscape. This method is ideal for investigating the formamide hydrolysis reaction, since we would like to sample the distance between a reactive water molecule and the formamide in a controlled manner, while ensuring exhaustive sampling of the protonation state of the attacking water. We chose two collective variables (CVs), $s = \{s_1, s_2\}$, to explore the free energy surface of the reaction. The first CV ($s_1$) is the distance, $d[C-O_2]$, between the carbon atom (C) of the formamide and the oxygen atom (O$_2$) of the attacking water molecule, as shown in Figure 3. This CV was sampled using the umbrella sampling\textsuperscript{[67]} like bias potential

$$W_h(s_1) = \frac{1}{2} \kappa_h (s_1 - d_h^{(0)})^2, \quad h = 1, \ldots, M$$

which ensures a controlled sampling along this coordinate. Here, $M$ is the total number of umbrella windows used, while $\kappa_h$ and $d_h^{(0)}$ are the restraining force constant and the equilibrium value of the $h$-th umbrella restraint, respectively.

The second CV ($s_2$) is the coordination number (CN) of the oxygen atom (O$_1$) of the attacking water with all the hydrogen atoms ($H_w$) of the solvent molecules (including that of itself):

$$\text{CN}[O_1: H_w] = \sum_{i=1}^{N_w} \frac{1}{1 + (d_{i1}/d_0)^2}$$

with $d_0 = 1.30$ Å. Here, $N_w$ is the total number of $H_w$ atoms and $d_{i1}$ is the distance between the O$_1$ atom and the $i$-th $H_w$ atom. Well-tempered metadynamics (WT-MTD) bias potential\textsuperscript{[68]} $V^\delta$, was employed to sample $s_2$:

$$V^\delta(s_2, t) = \sum_{i=t} w(r) \exp \left( - \frac{(s_2 - s_2(r))^2}{2(\delta s)^2} \right).$$

Here, $\delta s$ is the width of the Gaussian function and the height of the Gaussian $w(r)$ is given by,

$$w(r) = w_0 \exp \left( - \frac{V^\delta(s_2, r)}{k_B T} \right).$$

Table 1. Umbrella sampling parameters: Here, $d_h^{(0)}$ is in Å and $\kappa_h$ is in Hartree·Bohr$^{-2}$

| $h$ | $d_h^{(0)}$ | $\kappa_h$ | $h$ | $d_h^{(0)}$ | $\kappa_h$ |
|-----|-------------|-------------|-----|-------------|-------------|
| 1   | 1.51        | 0.4         | 16  | 2.43        | 0.4         |
| 2   | 1.60        | 0.2         | 17  | 2.50        | 0.2         |
| 3   | 1.63        | 0.4         | 18  | 2.60        | 0.2         |
| 4   | 1.70        | 0.4         | 19  | 2.70        | 0.2         |
| 5   | 1.76        | 0.4         | 20  | 2.80        | 0.2         |
| 6   | 1.81        | 0.4         | 21  | 2.90        | 0.2         |
| 7   | 1.86        | 0.4         | 22  | 3.00        | 0.2         |
| 8   | 1.93        | 0.4         | 23  | 3.10        | 0.2         |
| 9   | 1.99        | 0.4         | 24  | 3.20        | 0.2         |
| 10  | 2.05        | 0.4         | 25  | 3.30        | 0.2         |
| 11  | 2.10        | 0.2         | 26  | 3.40        | 0.2         |
| 12  | 2.21        | 0.4         | 27  | 3.50        | 0.2         |
| 13  | 2.25        | 0.4         | 28  | 3.60        | 0.2         |
| 14  | 2.30        | 0.2         | 29  | 3.70        | 0.2         |
| 15  | 2.39        | 0.4         |     |             |             |

In total, 29 umbrella windows were used for sampling $d[C-O_2]$ in the range from 1.51 to 3.70 Å. The parameters of the umbrella bias potentials, $\kappa_h$ and $d_h^{(0)}$, were taken according to our earlier study\textsuperscript{[28]} and given in Table 1. The time-dependent WT-MTD bias acting along $\text{CN}[O_1:H_w]$ was updated every 19.4 fs. The WT-MTD bias parameters...
$w_0$, $\delta s$ and $\Delta T$ were chosen to be 0.59 kcal/mol, 0.05 and 4,000 K, respectively. After carrying out 2–3 ps of equilibration for each umbrella window, we performed 15 ps of production run for every window. Thus a total of $29 \times 15 = 435$ ps long production run was carried out at the level of hybrid-DFT. The initial structure for an umbrella window was taken from the equilibrated structure of the adjacent window.

3 | RESULTS AND DISCUSSION

The hydrolysis of formamide in aqueous basic medium is one of the important reactions in the field of chemistry and biochemistry. In particular, it serves as a model for the hydrolysis of peptide bonds in enzymes. The reaction has been well studied experimentally$^{[70]}$ and theoretically,$^{[71–74]}$ and it is an ideal prototype reaction in liquid water to demonstrate the application of r-RESPA+ACE method.

We launched WS-MTD simulations to investigate this reaction. The hydrolysis reaction proceeds through the nucleophilic attack of the hydroxide ion on the carbon atom of the carbonyl group to form a tetrahedral intermediate ($P$) as shown in Figure 3. The rate limiting step of the hydrolysis is the formation of the tetrahedral intermediate ($P$)$^{[72,73]}$

The computed free energy surface is given in Figure 4. The minimum energy pathway on this surface was used to extract the mechanism and free energy barrier. Convergence of free energy barriers as a function of simulation time is shown in Figure 5 and the converged free energy barrier is listed in Table 2. For comparing with PBE data, we have taken the results from our earlier work$^{[28]}$

In both PBE and PBE0 free energy surfaces, the deep minimum corresponding to the reactant state $R$ is nearly at the same location: $s_1 \in [2.9, 3.5] \text{Å}, s_2 \in [1.8, 2.0]$ (unitless). The state $P$ is the tetrahedral intermediate, and the locations of $P$ are also nearly the same for both the functionals: $s_1 \sim 1.5(\text{Å}), s_2 \sim 1.0$ (unitless). Similarly, the positions of the saddle point (TS) on the landscapes are also matching: $s_1 \sim 1.9$ (Å), $s_2 \sim 1.3$ (unitless). However, the passage through the TS state is narrower on the PBE0 surface than on the PBE surface. This observation is consistent with the difference in the curvature of the potential

![Figure 4](https://example.com/figure4.png)  
**FIGURE 4** Free energy surfaces computed using (a) PBE,$^{[28]}$ and (b) PBE0 density functionals for the $R \rightarrow P$ reaction are presented. Contour lines are drawn every 2 kcal/mol. A representative snapshot of the TS state is shown in (c). The indicated bond distances here are in Å. Atom colors: red (O); blue (N); black (C); white (H) [Color figure can be viewed at wileyonlinelibrary.com]

![Figure 5](https://example.com/figure5.png)  
**FIGURE 5** Convergence of the free energy barrier ($\Delta F^\ddagger$) of $R \rightarrow P$ reaction with simulation time (per umbrella window) using PBE,$^{[28]}$ and PBE0 density functionals. The experimentally determined value of $\Delta F^\ddagger$ is shown as dotted black line [Color figure can be viewed at wileyonlinelibrary.com]

| Method     | $\Delta F^\ddagger$ (kcal/mol) |
|------------|----------------------------------|
| PBE$^{[28]}$ | 18                              |
| PBE0       | 20                              |
| Experiment$^{[70]}$ | 21.2 ± 0.2                      |

![Table 2](https://example.com/table2.png)  
**TABLE 2** Free energy barriers ($\Delta F^\ddagger$) of the reaction $R \rightarrow P$ (Figure 3) using PBE and PBE0 functionals are compared with the experimental measure.
energy landscape along vibrational modes between the two functionals. For instance, the C–O stretching frequency of CH$_3$OH is higher for PBE0 (1,065 cm$^{-1}$) compared to PBE (1,013 cm$^{-1}$). As expected, in the TS structure, the attacking water molecule has dissociated one of its protons, and a weak covalent bond between O$_1$ and the carbon atom is formed (see Figure 4c). This mechanism is in agreement with the previous work.[73]

Although the topology of the free energy surfaces is qualitatively similar for the two functionals, the free energy barrier differs substantially. The free energy barrier for PBE is 18 kcal/mol, while that for PBE0 is 20 kcal/mol. The PBE0 free energy barrier is about 2 kcal/mol higher than that of PBE. Most importantly, the barrier computed from PBE0 is closer to the experimentally determined free energy barrier of 21.2 ± 0.2 kcal/mol at 298 K.[75] For the same reaction, similar trend in PBE and PBE0 free energies was noticed in our earlier work,[28] in which the PBE0 calculations were carried out using a Noise Stabilized Molecular Dynamics approach and localized KS orbitals.

4 | CONCLUSIONS

By combining r-RESPA and ACE formalism, an effective speed-up of seven was obtained in AIMD simulations using hybrid functionals and plane waves. With this speed-up, we are able to perform free energy calculations for chemical reactions in water from extensive AIMD simulations. We demonstrated this by studying the base catalyzed hydrolysis of formamide in water. Although the system contained ~100 atoms, we could perform 29 × 15 ps long WS-MTD simulations with PBE0 functional. Based on these calculations, the two-dimensional free energy surface for the chemical reaction was computed. We find that PBE (GGA) functional underestimates the free energy barrier by ~3 kcal/mol as compared to the experimental result. On the other hand, PBE0 (hybrid) functional is able to predict the free energy barrier more accurately—it is only ~1 kcal/mol lower than the experimental measure of the free energy barrier. In conclusion, we have demonstrated that free energy computations of chemical reactions are now computationally affordable with hybrid functionals and plane wave basis set employing the r-RESPA+ACE approach. We believe that this work will aid in using our implementation of r-RESPA+ACE in the CPMD program for the free energy calculations of chemical reactions at the level of hybrid DFT.

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