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RESEARCH ARTICLE

Metadynamics simulations with Bohmian-style bias potential

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Abstract

Here, we present a parametrization of the metadynamics simulations for reactions involving breaking the chemical bonds along a single collective variable coordinate. The parameterization is based on the similarity between the bias potential in metadynamics and the quantum potential in the de Broglie–Bohm formalism. We derive the method and test it on two prototypical reaction types: proton transfer and breaking of the cyclohexene cycle (reversed Diels–Alder reaction).

KEYWORDS
Bohmian dynamics, bond cleavage, Diels–Alder reaction, metadynamics, molecular dynamics, proton transfer

1 | INTRODUCTION

Metadynamics (MTD) is a powerful molecular-dynamics-based simulation technique that is known to provide the chemical reaction pathways without prior knowledge of the transition states the system goes through.[1-4] MTD is an example of so-called enhanced sampling techniques,[5,6] among which there are such classical schemes as local elevation[7] or conformational flooding.[8] To include the quantum nature of the nuclear motions,[9] the MTD can be combined with the path-integral molecular dynamics.[10,11] In recent years, MTD was also successfully extended to automatic conformational search.[12]

The idea of the MTD is the propagation of molecular dynamics with an effective potential given as[1-4]

$$V_{\mathrm{eff}} = V + V_{\mathrm{MTD}} \,,$$

where V is the potential energy surface (PES) of the nuclei, and the V_{MTD} is the so-called bias potential. The latter marks the previous configurations of the system by increasing their energies, making it less probable for the system to go back, thus forcing the molecule to explore new regions of the PES.

The bias potential is usually formulated using collective variables (CV). These are just functions of the internal coordinates, parametrizing the expected reaction coordinate of the system.[2-4] The classical numerical representation of the bias potential is a sum of Gaussian functions of the user-defined widths and heights. These basic components are added with some periodicity during the MTD simulation, and the centers of these Gaussians are placed at the current values of the CVs. Therefore, at the end of the simulation, $-V_{\mathrm{MTD}}$ represents a coarse and averaged snapshot of the sampled part of the PES.[1-4] The interpretation of this bias potential can also be made through the probability distributions.[13]

In this article, we propose an alternative view of the MTD bias potential. We use its similarity to the quantum potential from the de Broglie–Bohm formalism of quantum mechanics.[14] We discuss the application of this reformulated MTD simulation to a specific class of reactions that involve the breaking of chemical bonds. In particular, we demonstrate the applicability of the proposed approach using the two prototypic reactions: proton transfer in the malonaldehyde[15,16] and the inverse Diels–Alder reaction[17-19] of the cyclohexene. In the end, we provide conclusions and perspectives on the current approach.

2 | THEORETICAL DERIVATION

2.1 | Bias potential shape

To find the building block for the bias potential, let us consider the one-dimensional quantum potential from the De Broglie-Bohm formalism[14,20]:

Abbreviations: MTD, metadynamics; CV, collective variable; PES, potential energy surface.

$$V_{\text{quant}}(q) = -\frac{\hbar^2}{2\mu A}\frac{d^2A}{dq^2}\,, \tag{1}$$

where q is the CV, μ is the effective mass of the molecular motion along the CV, and A is the wavefunction's (ψ) amplitude ($A = |\psi|$). Let us assume that at the current value of the CV, $q = Q$, we have a Gaussian wavepacket centered at the position $q = Q$[20]:

$$A = \mathcal{N}\exp\left(-\frac{(q-Q)^2}{4\sigma^2}\right), \tag{2}$$

where σ is the standard deviation (SD) of the CV q from the mean position Q, and $\mathcal{N} = \left(\sqrt{\sqrt{2\pi}\sigma}\right)^{-1}$ is the normalization factor. Substitution of the Equation (2) into the Equation (3) gives us the quantum potential of the shape

$$V_{\text{quant}}(q) = \frac{\hbar^2}{4\mu\sigma^2}\left(1 - \frac{(q-Q)^2}{2\sigma^2}\right). \tag{3}$$

We want our bias potential for the MTD to be non-negative. Therefore, we can take only the part of the Equation (3) corresponding to $V_{\text{quant}}(q) \geq 0$ ($(q-Q)^2 \leq 2\sigma^2$), and set the rest of the potential to zero, thus having the following building blocks for the bias potential:

$$V_{\text{b}}(q|Q) = \begin{cases} E_{\text{b}}\left(1 - \frac{(q-Q)^2}{2\sigma^2}\right) & , (q-Q)^2 \leq 2\sigma^2\,, \\ 0 & , (q-Q)^2 > 2\sigma^2 \end{cases}, \tag{4}$$

where notation $(q|Q)$ denotes that the bias component's argument is q and this function is centered at the position $q = Q$, and E_{b} is the bias energy:

$$E_{\text{b}} = \frac{\hbar^2}{4\mu\sigma^2}\,. \tag{5}$$

The total bias potential at a given point of the MTD simulation will thus be

$$V_{\text{MTD}}(q) = \sum_{n=1}^{N} V_{\text{b}}(q|Q_n)\,, \tag{6}$$

where N is the total number of marked CV values Q_n.

2.2 | Collective variable definition

To model the bond breaking in the molecules, the most native coordinate is the distance between the atoms: $R_{ij} = \sqrt{(\mathbf{r}_i - \mathbf{r}_j)^2}$, where i and j are the atomic indexes, and $\mathbf{r}_i$, $\mathbf{r}_j$ denote atomic position vectors. However, since there might be cases when more than two bonds are broken during a reaction, such as the double proton transfer or the breaking of the cycles, we might need more than one distance in the CV definition. Therefore, we will take the following definition of the CV:

$$q = \sum_k c_k R_k\,, \tag{7}$$

where index k enumerates the distances in the definition of CV, $|c_k| > 0$ are the arbitrary coefficients, and $R_k = \sqrt{(\mathbf{r}_{a_k} - \mathbf{r}_{b_k})^2}$ is the distance between atoms number a_k and b_k.

To define the bias energy (Equation 5), we require a reduced mass of the motion. In the case of the $q = R_{ij}$, it is defined simply as the reduced mass of the two atoms forming the bond, that is, as $\mu_{ij} = \frac{m_i m_j}{m_i + m_j}$, where m_i and m_j are the masses of the atoms number i and j, respectively.[21] We will consider a simplified approach based on the classical equipartition theorem[22,23] to define the reduced mass μ_q for the CV coordinate given by Equation (7).

Let us assume that the following equalities hold: $\mu_q\langle\dot{q}^2\rangle = k_{\text{B}}T$ and $\mu_k\langle\dot{R}_k^2\rangle = k_{\text{B}}T$, where k_{B} is the Boltzmann's constant, T is the absolute temperature, and $\dot{x} = dx/dt$ is the velocity of the value x. With the definition of the CV (Equation 7), we can also write:

$$\mu_q\langle\dot{q}^2\rangle = \mu_q\sum_k\sum_l c_k c_l\langle\dot{R}_k\dot{R}_l\rangle = k_{\text{B}}T\,.$$

Assuming that the motions along different bonds are uncorrelated (i.e., $\langle\dot{R}_k\dot{R}_k\rangle = 0$ for $k \neq l$), and noting that $\langle\dot{R}_k^2\rangle = k_{\text{B}}T/\mu_k$, we will get

$$\mu_q\sum_k\sum_l c_k c_l\langle\dot{R}_k\dot{R}_l\rangle \approx \mu_q\sum_k c_k^2\overbrace{\langle\dot{R}_k^2\rangle}^{k_{\text{B}}T/\mu_k} = k_{\text{B}}T\,,$$

which gives the expression for the μ_q:

$$\mu_q = \left(\sum_k\frac{c_k^2}{\mu_k}\right)^{-1}. \tag{8}$$

This expression provides a unique reduced mass value for any CV of the type given in Equation (7). In the standard MTD simulation, the user defines the CV, the width of the Gaussian bias potential, and the height of this potential. However, in this formulation, based on the quantum potential, the user needs to provide a definition of the CV and the width of the bias potential σ to define the MTD simulation because the reduced mass μ_q and the bias energy are computed automatically with Equations (8) and (5), respectively.

2.3 | Bias force

The last issue to the MTD simulations with the bias potential given in Equation (6) is the evaluation of the forces. The bias force acting on the atom i with coordinate $\mathbf{r}_i$ is given with the equation[24]

$$\mathbf{F}_i = -\frac{\partial V_{\mathrm{MTD}}(q)}{\partial \mathbf{r}_i} = -\sum_{n=1}^{N} \frac{\partial V_{\mathrm{b}}(q|Q_n)}{\partial \mathbf{r}_i}\,. \tag{9}$$

However, some terms of this sum can be zero because points Q_n can be out of the action range from the current value q (those that fulfill the inequality $(q-Q_n)^2 > 2\sigma^2$, see Equation 4). Thus, we can order the Q_n by their proximity to q, that is, in the increasing order of $|q-Q_n|$, and take only those $\tilde{N} \le N$ values that correspond to nonzero contributions to the potential (i.e., $(q-Q_n)^2 \le 2\sigma^2$ for $1 \le n \le \tilde{N}$, and $(q-Q_n)^2 > 2\sigma^2$ for $n > \tilde{N}$). The derivatives of the components for $1 \le n \le \tilde{N}$ are easy to compute:

$$\frac{\partial V_{\mathrm{b}}(q|Q_n)}{\partial \mathbf{r}_i} = -\frac{E_{\mathrm{b}}}{\sigma^2}(q-Q_n)\cdot\frac{\partial q}{\partial \mathbf{r}_i}\,,$$

which upon substitution to Equation (9) will give

$$\mathbf{F}_i = -\sum_{n=1}^{\tilde{N}} \frac{\partial V_{\mathrm{b}}(q|Q_n)}{\partial \mathbf{r}_i} = \overbrace{\left(\frac{E_{\mathrm{b}}}{\sigma^2}\left[\tilde{N}q - \sum_{n=1}^{\tilde{N}} Q_n\right]\right)}^{F}\cdot\frac{\partial q}{\partial \mathbf{r}_i} = F\cdot\frac{\partial q}{\partial \mathbf{r}_i}\,,$$

where F is the force magnitude and $\frac{\partial q}{\partial \mathbf{r}_i}$ is the direction vector of the force for atom number i. The latter can be computed in a straightforward fashion using Equation (7) as

$$\frac{\partial q}{\partial \mathbf{r}_i} = \sum_k c_k \frac{\partial R_k}{\partial \mathbf{r}_i}\,.$$

The vector $\frac{\partial R_k}{\partial \mathbf{r}_i} = 0$ if atom i is not a part of the distance R_k between atoms a_k and b_k (i.e., $i \ne a_k$ and $i \ne b_k$). In the other case, when, say, $i = a_k$ and $j = b_k$, and thus $R_k = R_{ij} = \sqrt{(\mathbf{r}_i - \mathbf{r}_j)^2}$, then

$$\begin{cases} \dfrac{\partial R_k}{\partial \mathbf{r}_i} = \dfrac{(\mathbf{r}_i - \mathbf{r}_j)}{R_k}\,, \\[2ex] \dfrac{\partial R_k}{\partial \mathbf{r}_j} = \dfrac{(\mathbf{r}_j - \mathbf{r}_i)}{R_k}\,. \end{cases}$$

3 | NUMERICAL DEMONSTRATION

We implemented the proposed MTD routine into the BBBMTD script of the PyRAMD software.[25,26] To demonstrate the algorithm's performance, we chose two prototypical reactions: proton transfer between two oxygens in the enol form of the malonaldehyde and decomposition of the cyclohexene into the 1,3-butadiene and ethylene, which is the inverse of the Diels–Alder reaction. The schematics of these reactions are given in the insets (A) of Figures 1 and 2, respectively.

To perform quantum-chemical calculations, including the computation of the gradients of the PES in the MTD, we used the ORCA 5 software.[27] The level of theory in all the calculations was BLYP-D3BJ/6-31G.[28-31] First, we optimized the molecular geometries of the malonaldehyde and cyclohexane with subsequent calculations of the harmonic frequencies at the chosen level of theory. From these equilibrium geometries, we started the MTD simulations, generating initial velocities of the atoms from Maxwell–Boltzmann distribution at the temperature of 300 K,[22] and then this temperature was kept by a Berendsen thermostat[32] with a relaxation time of 100 fs. The time step in every MTD simulation was 1 fs.

The MTD simulations for malonaldehyde had the following settings. The CV was

$$q = \frac{(r(\mathrm{O-H}) - r(\mathrm{O\cdots H}))}{2}\,, \tag{10}$$

where $r(\mathrm{O-H})$ and $r(\mathrm{O\cdots H})$ denote the distances between oxygens and hydrogen, corresponding to the O–H covalent and O···H hydrogen bonds in the equilibrium geometry, respectively (see Figure 1). The reduced mass of this CV was thus $\mu_q = 1.9$ a.m.u. The width of the bias potential σ was 0.2 Å, which subsequently gave the bias energy E_{b} (Equation 5) of 111 cm^{-1}. The bias potential was updated with the current value of CV every 30 fs. We accumulated 16 MTD trajectories in total, each 2 ps in duration.

In the case of cyclohexene, the CV was

$$q = r_1(\mathrm{C-C}) + r_2(\mathrm{C-C})\,, \tag{11}$$

where $r_1(\mathrm{C-C})$ and $r_2(\mathrm{C-C})$ the distances corresponding to the two C–C bonds broken in the reaction (see the inset (A) of Figure 2). This definition gave the μ_q of 3.0 a.m.u. Nine MTD trajectories with the bias potential update time of 10 fs and width $\sigma = 0.1$ Å, resulting in bias energies $E_{\mathrm{b}} = 281$ cm^{-1}, with total simulation duration of 5 ps. To prevent the dissociation of the ethylene and 1,3-butadiene, an artificial constraining potential was applied. It was defined as

$$V_{\mathrm{c}} = \sum_i k_{\mathrm{B}} T f(r_i)\,,$$

where k_{B} is the Boltzmann's constant, $T = 300$ K is the temperature of the MTD simulation, r_i is the distance of the ith atom to the center of mass of the system, and $f(r)$ is defined as

$$f(r) = \begin{cases} 0,\ r < r_{\mathrm{sph}} \\ \left(\dfrac{r - r_{\mathrm{sph}}}{L}\right)^2,\ r \ge r_{\mathrm{sph}} \end{cases},$$

with parameters $r_{\mathrm{sph}} = 4$ Å and $L = 0.05$ Å, that regulate the radius and softness of the constraining spherical harmonic potential for the atoms. Within the sphere of radius r_{sph} from the center of mass of the system, atoms do not feel any constraints, but outside this sphere, they are being pushed back toward the center of mass by a harmonic potential of V_{c}.

The results for MTD simulations of the proton transfer in malonaldehyde and cycle breaking in cyclohexene are given in the insets (B), (C), and (D) of Figures 1 and 2, respectively. In insets (B), we can see the representations of the MTD trajectories as the atomic density distributions computed with the CubeTheMD script[33,34] using an

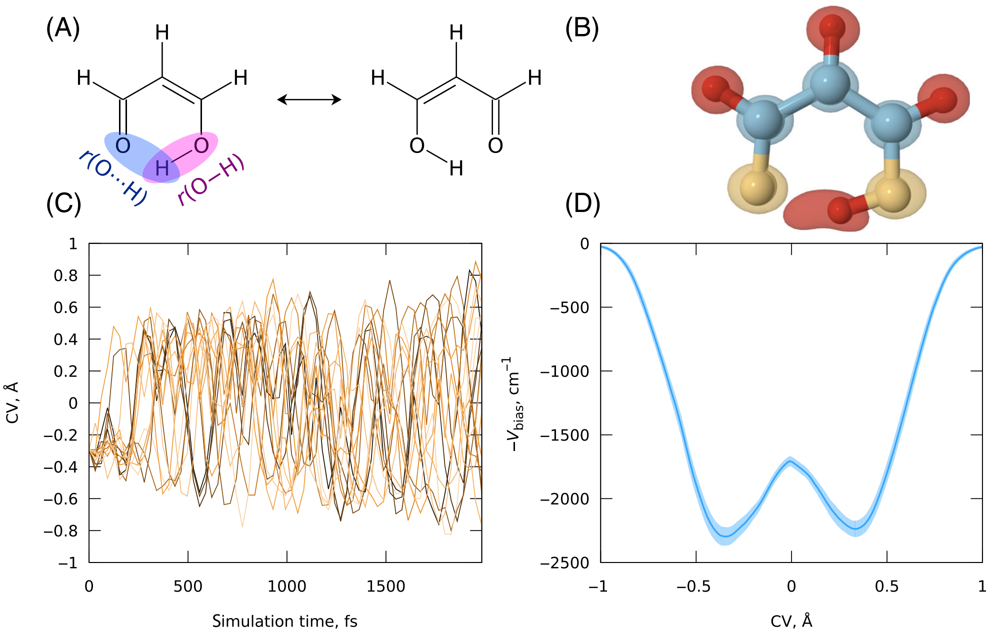

FIGURE 1 Results of the metadynamics (MTD) simulations of the proton transfer in malonaldehyde. (A) The formal reaction and the components of the collective variable (CV). (B) The averaged nuclear probability distribution from all MTD trajectories, where red atoms denote hydrogens, yellow—oxygens, and blue—carbons. (C) The positions of the saved CV values along the MTD trajectories. (D) The resulting mean bias potential from the MTD simulations. The semi-transparent area around the curve in (D) indicates the ± SE range.

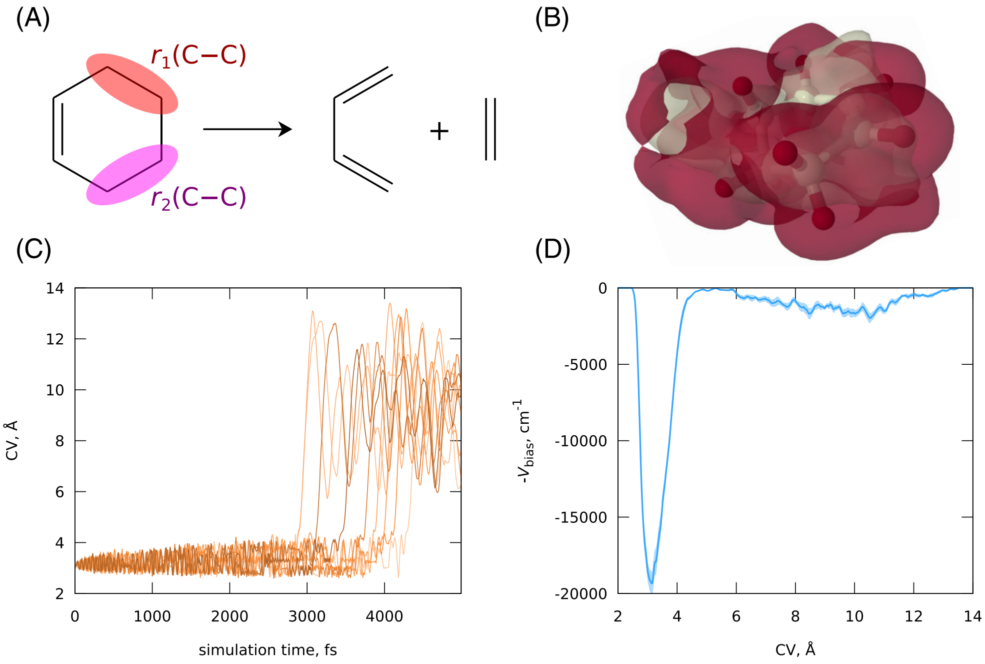

FIGURE 2 Results of the metadynamics (MTD) simulations of the decomposition of the cyclohexene. (A) The formal reaction and the components of the collective variable (CV). (B) The averaged nuclear probability distribution from all MTD trajectories, where red atoms denote hydrogens and yellow—carbons. (C) The positions of the saved CV values along the MTD trajectories. (D) The resulting mean bias potential from the MTD simulations. The semi-transparent area around the curve in (D) indicates the ± SE range.

algorithm similar to that used in the Trajectory Analyzer and Visualizer (TRAVIS) software.[23] From there, we can see that during the MTD simulation, the only major change in the malonaldehyde was the proton transfer, whether, in the case of cyclohexene, it was the dissociation of the C_2H_4 to form a complex. The same can be inferred from the trajectories of the CVs, mapping out the bias potential, which is given in the insets (C) of Figures 1 and 2.

The resulting bias potentials of the individual simulations are given in insets (D) of Figures 1and 2. The individual bias potentials from different simulations were averaged to produce a single curve with the standard errors (SE), showing the agreement between different individual results. The bias potential for the malonaldehyde (Figure 1) resembles the expected double-well potential of the symmetric proton transfer.[15,16] The estimated barrier height was found to be 590 ± 60 cm^{-1}. We also computed the electronic activation energy ($\Delta E^{\neq}$) at the chosen level of theory for the same reaction as a reference value for comparison. We used a nudged elastic band with the transition state optimization afterward (NEB-TS) to find the transition state molecular geometry.[35] The resulting value of $\Delta E^{\neq} = 623\ \text{cm}^{-1}$ is within the uncertainty of the estimated value from the MTD simulations.

In the case of cyclohexene, the estimated activation energy from the fine MTD simulations was 19,300 ± 500 cm^{-1}. For comparison, the $\Delta E^{\neq}$ of the inverse Diels–Alder reaction was also computed. The initial guess for the transition state of the Diels-Alder reaction was taken from Reference 19. Then, this structure was readjusted at the BLYP-D3BJ/6-31G level of theory. A difference from the electronic energy of the cyclohexene at the same level of theory was taken as $\Delta E^{\neq}$. The resulting value was 17,932 cm^{-1}, similar to that obtained from the MTD simulations.

4 | CONCLUSIONS

Here, we presented an alternative approach to constructing the metadynamics algorithms based on the formal similarity of the bias potential with the quantum potential in the de Broglie–Bohm formalism of quantum mechanics. This parametrization requires fewer parameters than the standard metadynamics approach with the Gaussian-shaped bias potential components. We derived and implemented the proposed approach in the case of a single collective variable in the form of a linear combination of the chosen interatomic distances. The numerical tests of two prototypical chemical reactions (proton transfer and the inverse Diels–Alder reaction) show that the proposed approach works. Although our derivations were done in the case of a single collective variable, the same principle can be expanded into a multidimensional case.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in Data S1.

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REFERENCES

[1] A. Laio, M. Parrinello, *Proc. Natl. Acad. Sci.* **2002**, *99*(20), 12562.

[2] A. Barducci, M. Bonomi, M. Parrinello, *WIREs Comput. Mol. Sci.* **2011**, *1*(5), 826.

[3] O. Valsson, P. Tiwary, M. Parrinello, *Annu. Rev. Phys. Chem.* **2016**, *67*(1), 159.

[4] G. Bussi, A. Laio, *Nature Rev. Phys.* **2020**, *2*(4), 200.

[5] Y. I. Yang, Q. Shao, J. Zhang, L. Yang, Y. Q. Gao, *J. Chem. Phys.* **2019**, *151*(7), 070902.

[6] J. Hénin, T. Lelièvre, M. R. Shirts, O. Valsson, L. Delemotte, *Living J. Comput. Mol. Sci.* **2022**, *4*(1), 1583.

[7] T. Huber, A. E. Torda, W. F. van Gunsteren, *J. Comput. Aided Mol. Des.* **1994**, *8*(6), 695.

[8] H. Grubmüller, *Phys. Rev. E* **1995**, *52*, 2893.

[9] T. E. Markland, M. Ceriotti, *Nature Rev. Chem.* **2018**, *2*(3), 0109.

[10] R. Quhe, M. Nava, P. Tiwary, M. Parrinello, *J. Chem. Theory Comput.* **2015**, *11*(4), 1383.

[11] S. D. Ivanov, I. M. Grant, D. Marx, *J. Chem. Phys.* **2015**, *143*(12), 124304.

[12] S. Grimme, *J. Chem. Theory Comput.* **2019**, *15*(5), 2847.

[13] M. Invernizzi, M. Parrinello, *J. Phys. Chem. Lett.* **2020**, *11*(7), 2731.

[14] D. Bohm, *Phys. Rev.* **1952**, *85*, 166.

[15] S. L. Baughcum, R. W. Duerst, W. F. Rowe, Z. Smith, E. Bright Wilson, *J. Am. Chem. Soc.* **1981**, *103*(21), 6296.

[16] D. S. Tikhonov, *Struct. Chem.* **2022**, *33*(2), 351.

[17] O. Diels, K. Alder, *Justus Liebigs Ann. Chem.* **1928**, *460*(1), 98.

[18] B. Briou, B. Améduri, B. Boutevin, *Chem. Soc. Rev.* **2021**, *50*, 11055.

[19] Y. Song, H. M. de Bruijn, D. Svatunek, T. A. Hamlin, F. Matthias Bickelhaupt, *ChemistryOpen* **2018**, *7*(12), 995.

[20] L. D. Landau, E. M. Lifshits, *Quantum Mechanics (Non-Relativistic Theory)*, 3rd ed., Vol. III, Butterworth-Heinemann, Oxford **1981**.

[21] Y. V. Vishnevskiy, D. Tikhonov, *Theor. Chem. Accounts* **2016**, *135*(4), 88.

[22] L. D. Landau, E. M. Lifshitz, *Statistical Physics*, Vol. 5, Elsevier Science, Oxford **2013**.

[23] A. Jain, I.-H. Park, N. Vaidehi, *J. Chem. Theory Comput.* **2012a**, *8*(8), 2581.

[24] L. D. Landau, E. M. Lifshitz, *Mechanics. Course of Theoretical Physics*, 3rd ed., Vol. 1, Butterworth-Heinemann, Oxford **1976**.

[25] D. S. Tikhonov. Pyramd manual. **2021a** https://confluence.desy.de/display/CFA/PyRAMD (accessed: April 5, 2023).

[26] D. S. Tikhonov. Pyramd. **2021b** https://stash.desy.de/projects/PYRAMD/repos/pyramd/browse (accessed: April 5, 2023).

[27] F. Neese, F. Wennmohs, U. Becker, C. Riplinger, *J. Chem. Phys.* **2020**, *152*(22), 224108.

[28] A. D. Becke, *Phys. Rev. A* **1988**, *38*, 3098.

[29] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785.

[30] S. Grimme, S. Ehrlich, L. Goerigk, *J. Comput. Chem.* **2011**, *32*(7), 1456.

[31] W. J. Hehre, R. Ditchfield, J. A. Pople, *J. Chem. Phys.* **1972**, *56*(5), 2257.

[32] H. J. C. Berendsen, J. P. M. Postma, W. F. van Gunsteren, A. DiNola, J. R. Haak, *J. Chem. Phys.* **1984**, *81*(8), 3684.

[33] D. S. Tikhonov. (madschumacher)Clouds of atomic vibrations (in russian). **2022a** https://habr.com/ru/post/684990/ (accessed: April 5, 2023).

[34] D. S. Tikhonov. (madschumacher)Cubethemd. https://gitlab.com/madschumacher/cubethemd, 2022b (accessed: February 2023).

[35] V. Ásgeirsson, B. O. Birgisson, R. Bjornsson, U. Becker, F. Neese, C. Riplinger, H. Jónsson, *J. Chem. Theory Comput.* **2021**, *17*(8), 4929.

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