



Introducing KICK-MEP: exploring potential energy surfaces in systems with significant non-covalent interactions

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Abstract

Context Exploring potential energy surfaces (PES) is fundamental in computational chemistry, as it provides insights into the relationship between molecular energy, geometry, and chemical reactivity. We introduce Kick-MEP, a hybrid method for exploring the PES of atomic and molecular clusters, particularly those dominated by non-covalent interactions. Kick-MEP computes the Coulomb integral between the maximum and minimum electrostatic potential values on a 0.001 a.u. electron density isosurface for two interacting fragments. This approach efficiently estimates interaction energies and selects low-energy configurations at reduced computational cost. Kick-MEP was evaluated on silicon-lithium clusters, water clusters, and thymol encapsulated within Cucurbit[7]uril, consistently identifying the lowest energy structures, including global minima and relevant local minima.

Methods Kick-MEP generates an initial population of molecular structures using the stochastic Kick algorithm, which combines two molecular fragments (A and B). The molecular electrostatic potential (MEP) values on a 0.001 a.u. electron density isosurface for each fragment are used to compute the Coulomb integral between them. Structures with the lowest Coulomb integral are selected and refined through gradient-based optimization and DFT calculations at the PBE0-D3/Def2-TZVP level. Molecular docking simulations for the thymol-Cucurbit[7]uril complex using AutoDock Vina were performed for benchmarking. Kick-MEP was validated across different molecular systems, demonstrating its effectiveness in identifying the lowest energy structures, including global minima and relevant local minima, while maintaining a low computational cost.

Keywords Potential energy surface · Molecular clusters · Atomic clusters · Electrostatic potential · Density functional theory

Introduction

The exploration of potential energy surfaces (PES) is fundamental in computational chemistry, as it provides detailed insights into the relationship between molecular energy,

geometry, and chemical reactivity. This exploration is essential for identifying optimal molecular geometries, encompassing both local and the global minimum, which are fundamental for understanding and predicting the behavior of molecular systems across a wide range of chemical contexts. Particularly

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in the design of atomic clusters, a deep understanding of the PES is key, as it provides support for the thermodynamic stability of structural configurations (when global minima are found), often comparable to observations from gas-phase experiments designed to favor the presence of thermodynamically stable structures. As molecular size increases, diverse bonding interactions and structural conformations emerge, making the task of mapping the PES increasingly challenging. Each atom adds degrees of freedom, exponentially expanding the PES dimensionality. This results in a landscape filled with numerous local minima and complex transition states, demanding sophisticated computational techniques and significant processing resources for effective PES navigation [1, 2]. Traditional methods for the PES exploration, such as Monte Carlo annealing [3–7], genetic algorithms [8–15], particle swarm optimization [16–18], and basin hopping [19–23], have significantly enhanced our ability to identify low-energy structures and improve our understanding of thermodynamic stability. These methods have been complemented by recent advancements in stochastic approaches, like the Kick method [24–28], which has proven particularly effective for studies involving atomic clusters.

Additionally, techniques such as *ab initio* molecular dynamics, hybrid quantum mechanics/molecular mechanics (QM/MM), and meta-dynamics-based tools, particularly CREST [29], approaches are increasingly utilized to provide more accurate and detailed insights into complex molecular interactions, enhancing our ability to predict and model chemical reactions across a diverse range of systems. However, there remains a notable gap in integrating intuitive chemical models [30], such as Lewis structures or VSEPR theory [31, 32], into the exploration of PES for novel molecular systems. In response, in 2021, we introduced ‘Kick-Fukui’ [33], a hybrid methodology that effectively uses the Coulombic integral between Fukui functions as a descriptor of interaction energy. This approach, combined with the ‘Kick’ process and subsequent local optimizations via a gradient method and density functional theory (DFT) computation [34–39], has proven successful in identifying low-energy configurations across diverse bonding scenarios, including those with pronounced ionic interactions.

Building on the success of ‘Kick-Fukui’, we further developed the ‘Kick-MEP’ methodology to harness molecular electrostatic potential (MEP) [40–57] as a precise tool for mapping PES in systems with significant non-covalent interactions. MEP is pivotal for delineating electrostatic (hard-hard) interactions within molecules, serving as an indispensable tool for identifying potential sites for chemical interactions [58–60]. It effectively pinpoints areas where the electrostatic potential is at its highest and lowest values, corresponding to regions of more positive and negative charges, respectively [61–66]. By visualizing the distribution of electrostatic potentials, MEP plays a crucial role in identifying areas where electrostatic interactions most significantly

impact molecular stability and reactivity [67–74]. In ‘Kick-MEP’, we innovate by using the extreme values of MEP—maximum and minimum [75–77]—identified on isosurfaces of electron density ($1 \times 10^{-3} a_0^{-3}$) [78] of the molecular fragments. These values are used to compute the Coulombic interactions between fragments, which serve as a refined descriptor to estimate interaction energies and select the most promising configurations from a large set generated by the stochastic Kick procedure. Unlike Kick-Fukui, which was proposed for systems where construction fragments are connected by covalent interactions, making the Fukui function a pertinent descriptor, Kick-MEP focuses on MEP, a more suitable descriptor for non-covalent interactions, especially electrostatic ones, as in the systems evaluated in this work.

The effectiveness of ‘Kick-MEP’ has been rigorously tested across various molecular configurations, including atomic clusters and small molecular clusters. This approach utilizes molecular fragments as foundational building blocks, like ‘Kick-Fukui’, but extends the utility by focusing on electrostatic potential extremes to accelerate the search for stable configurations. By strategically selecting fragments to build structures of the target molecule, ‘Kick-MEP’ streamlines the construction and optimization of candidate structures, proving to be highly efficient in swiftly locating the lowest energy structures with reduced computational cost. We have applied ‘Kick-MEP’ in exploring PES for complex systems including silicon-lithium clusters [79], water molecular clusters [80, 81], and host–guest inclusion systems [82], showcasing its versatility and effectiveness in a broad range of chemical environments.

Methodology

Electron density, $\rho(r)$, and electrostatic potential, $V(r)$, are fundamental molecular properties interconnected through Poisson’s equation:

$$\nabla^2 V(r) = 4\pi \sum_A Z_A \delta(r - R_A). \quad (1)$$

Here, Z_A and R_A represent the charge and spatial position of nucleus A , respectively, and $\rho(r)$ the electron density. For an atom, the electrostatic potential at a point is also defined as the work done to move a unit of positive charge from infinity to point r :

$$V^{at}(r) = \frac{Z}{r} - \int \frac{\rho(r')}{|r' - r|} dr' \quad (2)$$

Similarly, for a molecule the MEP is

$$V(r) = V_{Nuc}(r) + V_{Elec}(r) = \sum_A \frac{Z_A}{|r - R_A|} - \int \frac{\rho(r')}{|r - r'|} dr'. \quad (3)$$

The values that the electrostatic potential takes on significant molecular surfaces offer detailed insights into molecular interactions. Following Murray and Politzer [83], we will call $V_s(r)$ the MEP on the surface defined by the points where $\rho(r) = 1 \times 10^{-3} \text{ a}_0^{-3}$. These reveal regions of positive and negative values critical for understanding interactions using quantities such as the most negative $V_{s,\min}$ and most positive $V_{s,\max}$ values. In this way, $V_s(r)$ analysis, calculated for an isolated molecule A, could effectively predict preferential interaction regions (with a B molecule), acting like a ‘key-lock’ (A—B) mechanism.

In our hybrid strategy to the PES, we employ the Marching Tetrahedra (MT) [84, 85] algorithm, which precisely localizes the maximum (positive) and minimum (negative) critical points of the molecular electrostatic potential (MEP) on isodensity surfaces. MT allows further refined surface analysis by eliminating inaccurately distributed vertices from earlier implementations [86–89]. Our hybrid algorithm aims to swiftly identify key PES conformations, including local and global minima. We start by generating a large initial population of molecular structures through the random combination of molecular blocks A and B using the Kick algorithm. From this initial population, we select the most promising candidates based on an electrostatic interaction descriptor that quantifies A-B interactions via electrostatic potential analysis. The descriptor proposed and implemented in this work aims to efficiently screen the best structures by providing a simple yet effective representation of molecular interactions, with significant computational efficiency. Our descriptor establishes an electrostatic interaction model between the critical values of $V_s(r)$ of fragments A and B in the confronted areas. Since these values are discrete, the descriptor is summarized in a sum as described below:

$$\begin{aligned} \langle JV \rangle_{AB} = & \sum_{i \in A} \sum_{j \in B} \frac{V_A^+(i) \cdot V_B^+(j)}{r_{ij}} + \sum_{k \in A} \sum_{l \in B} \frac{V_A^-(k) \cdot V_B^-(l)}{r_{kl}} \\ & + \sum_{i \in A} \sum_{l \in B} \frac{V_A^+(i) \cdot V_B^-(l)}{r_{il}} + \sum_{k \in A} \sum_{j \in B} \frac{V_A^-(k) \cdot V_B^+(j)}{r_{kj}} \end{aligned} \quad (4)$$

where $V_{A,B}^\pm$ denotes the values of the critical points of $V_s(r)$ identified in fragments A or B, and i, j, k , and l denote the positions of these critical points. Our aim is to find configurations where favorable interactions (opposite signs values, $V_{A,B}^\pm$) manifest in close spatial proximity, while unfavorable interactions (same sign) are spatially distant. This descriptor aids in quantifying the electrostatic complementarity between fragments A and B, facilitating the selection of configurations that promote effective molecular interactions.

The Kick-MEP algorithm involves multiple procedures, as schematized in Fig. 1 and summarized below:

1. Independently compute and analyze the MEP for fragments A and B to identify the critical values of $V_s(r)$ on the 0.001 a.u. electron density isosurface.
2. Generate an initial population of candidate structures using the Kick algorithm. This algorithm constructs structures by randomly combining A and B molecular fragments. In this study, we only consider two building fragments. Details on the Kick algorithm can be found elsewhere [27].
3. Evaluate the $\langle JV \rangle_{AB}$ descriptor for each structure of the Kick-generated initial population. To compute this descriptor, only ‘reactive critical points’, which are within chemically significant distances, are considered. To simplify this process, a spherical constraint algorithm is proposed. Each critical point is enclosed within a sphere with a radius equal to the covalent radii of the atoms close to the critical point in its molecular fragment, and Eq. 4 terms are then calculated by considering interactions only with points inside the sphere from the other fragment.
4. Use the values $\langle JV \rangle_{AB}$ to screen the most promising candidate structures based on their best (most negative) values.
5. Optimize the most promising candidate structures using DFT computations to locate the lowest energy isomers.

Computational details

Geometry optimizations were performed at the PBE0-D3/Def2-TZVP level [90–92], as well as employing Tight-Binding GFN2-xTB within both Gaussian 16 (version B.01) [93] and the xTB [94] software.

The $V_s(r)$ values were visualized by plotting them onto a predetermined molecular surface (see Figures S1–S4 in the SI), defined at a density threshold of $\rho(r) = 0.001 \text{ a.u.}$ We selected the 0.001 a.u. electron density isosurface for electrostatic potential mapping because it closely approximates the Van der Waals surface, effectively capturing relevant non-covalent interactions while representing a significant portion of the electron density [76, 95]. The $V_s^+(r)$ and $V_s^-(r)$ values were identified through quantitative analysis of $V(r)$ utilizing the marching tetrahedra (MT) method, which was implemented in the Multiwfn 3.36 [84, 96] program. MT provides pdb files, which summarize the atomic coordinates of the molecular geometry, the coordinates of the vertices of the surface, and coordinates and values of the minimum and maximum points in $V_s(r)$.

After generating 100,000 initial conformations using the Kick-MEP process, the top 100 configurations (structures) were chosen based on their most negative $\langle JV \rangle_{AB}$. These preliminary structures for $(\text{H}_2\text{O})_n$, $\text{OCS}-(\text{H}_2\text{O})_m$, and $\text{Li}_{12}\text{Si}_{10}$ clusters were optimized at the PBE0-D3/SDDAll level theory [90, 97, 98]. Subsequently, a higher level of theory was employed for refinement at the PBE0-D3/Def2-TZVP level. In the case of thymol@cucurbit[7]uril, the optimization was performed with the tight-binding quantum chemical method at the GFN2-xTB level (see Figure S5 in the SI).

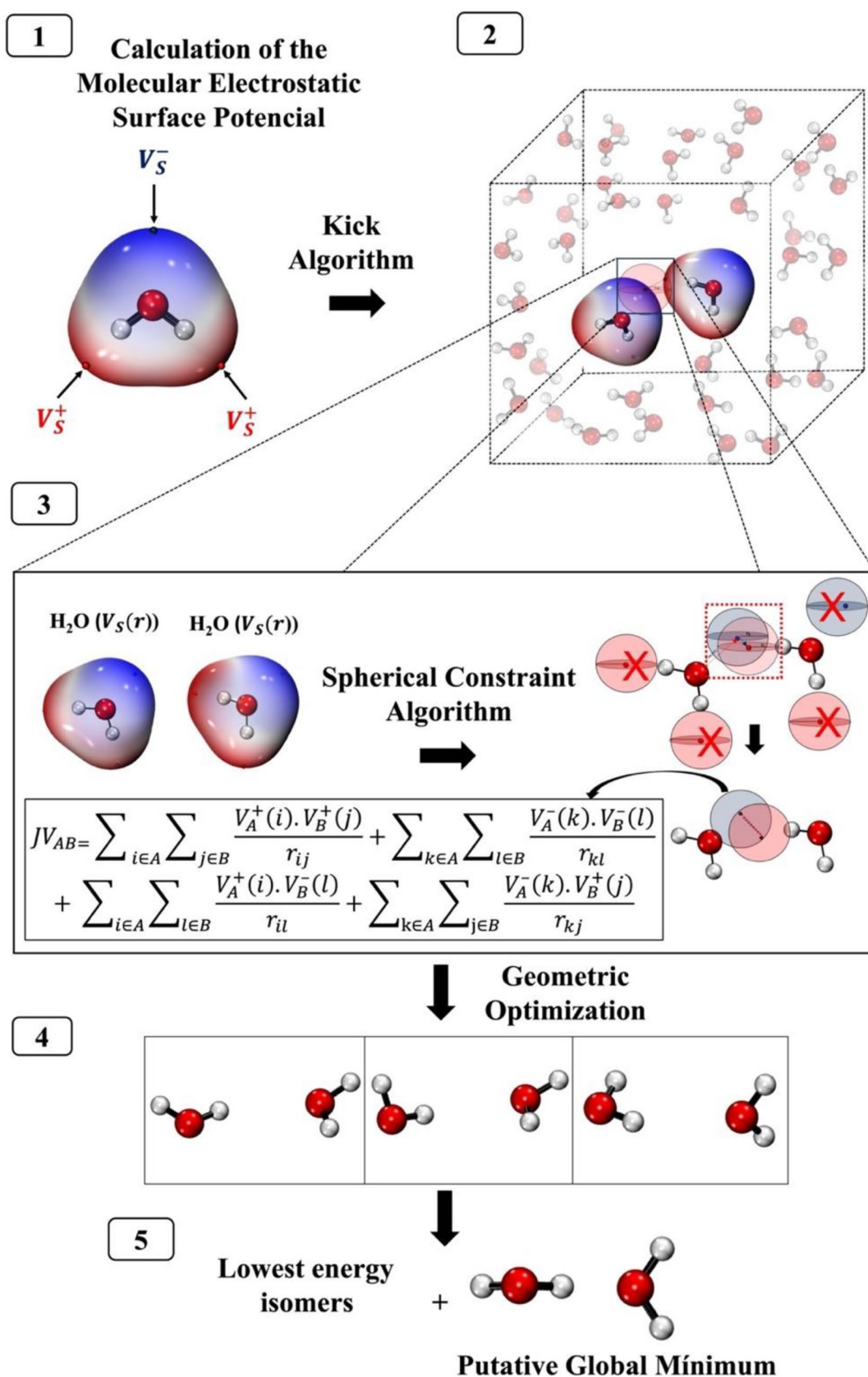


Fig. 1 Schematic representation of the Kick-MEP algorithm outlining key procedures for structure generation, screening, and geometry optimization

For comparison, molecular docking simulations for thymol and Cucurbit[7]uril were carried out employing AutoDock Vina [99, 100], a widely recognized computational tool in medicinal chemistry for predicting the preferred orientation of small molecules to their protein targets. The Lamarckian genetic algorithm underpinned the search strategy, simulating an evolutionary process to optimize the thymol conformations. Initial conditions included a diverse population of 150 random individuals, with the algorithm permitted to iterate over 2.5×10^7 energy evaluations and 27,000 generations, subjected to a mutation rate of 0.02 and a crossover rate of 0.80, to converge on the energetically favorable binding poses.

Results and discussion

In our assessment of the Kick-MEP algorithm, we selected three series of systems to comprehensively evaluate its performance. The first group focused on scrutinizing interactions among water molecules within clusters (H_2O)_n,

$n = 2-5$. Additionally, it investigated interactions between carbonyl sulfide and water clusters, $\text{OCS}(\text{H}_2\text{O})_m$, $m = 1-5$. These systems represent fundamental interactions within aqueous environments, offering insights into hydrogen bonding and solvation phenomena. The second group examined interactions within lithium-silicon molecular clusters, particularly focusing on the structures of $\text{Li}_{12}\text{Si}_{10}$. These systems represent complex alkali metal-silicon interactions, providing valuable insights into cluster stability and coordination behavior. Finally, the third group consists of complexes between Thymol and Cucurbit[7]uril, two organic molecules known for their host-guest chemistry. By examining their binding interactions, this group aimed to assess the algorithm's capability to predict non-covalent interactions within molecular recognition processes.

Through the systematic analysis of these benchmarking groups, the efficacy of the Kick-MEP algorithm in predicting and facilitating the formation of molecular clusters governed by non-covalent interactions could be rigorously evaluated, thereby enhancing our understanding of its applicability and potential in diverse molecular assembly scenarios.

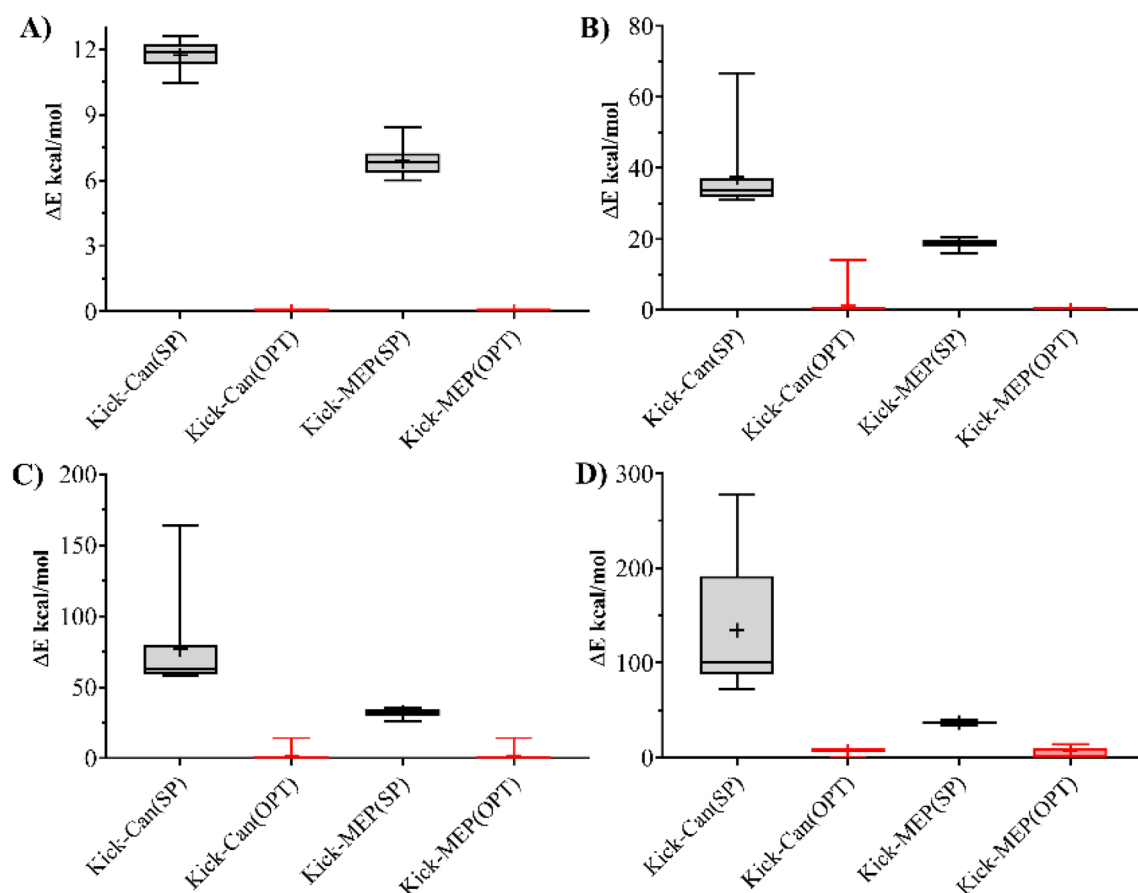


Fig. 2 Boxplots comparing the relative energy distribution of water cluster candidates for the **A** dimer, **B** trimer, **C** tetramer, and **D** pentamer. Comparisons are made between Kick-Canonical and Kick-

MEP selections from an initial population of 100,000 individuals. Gray boxes show single-point energies, while red boxes represent energies after geometry optimization

$(\text{H}_2\text{O})_n$ and $\text{OCS}(\text{H}_2\text{O})_m$ molecular clusters ($n=2-5$ and $m=1-5$)

Since we are only considering the energy descriptor for two fragments (A and B) in this evaluation, the smallest system is searched first and then used as a fragment for the next system. For example, for $(\text{H}_2\text{O})_2$, both fragments A and B

are H_2O ; for $(\text{H}_2\text{O})_3$, fragment A is $(\text{H}_2\text{O})_2$, and fragment B is H_2O , and so on. It is important to note that this is a restriction in the search process from the initial population generation and could be the reason for not finding the best minima. However, this is not a deficiency of the descriptor we are evaluating. Since the comparisons are made from the same starting populations, this restriction should equally

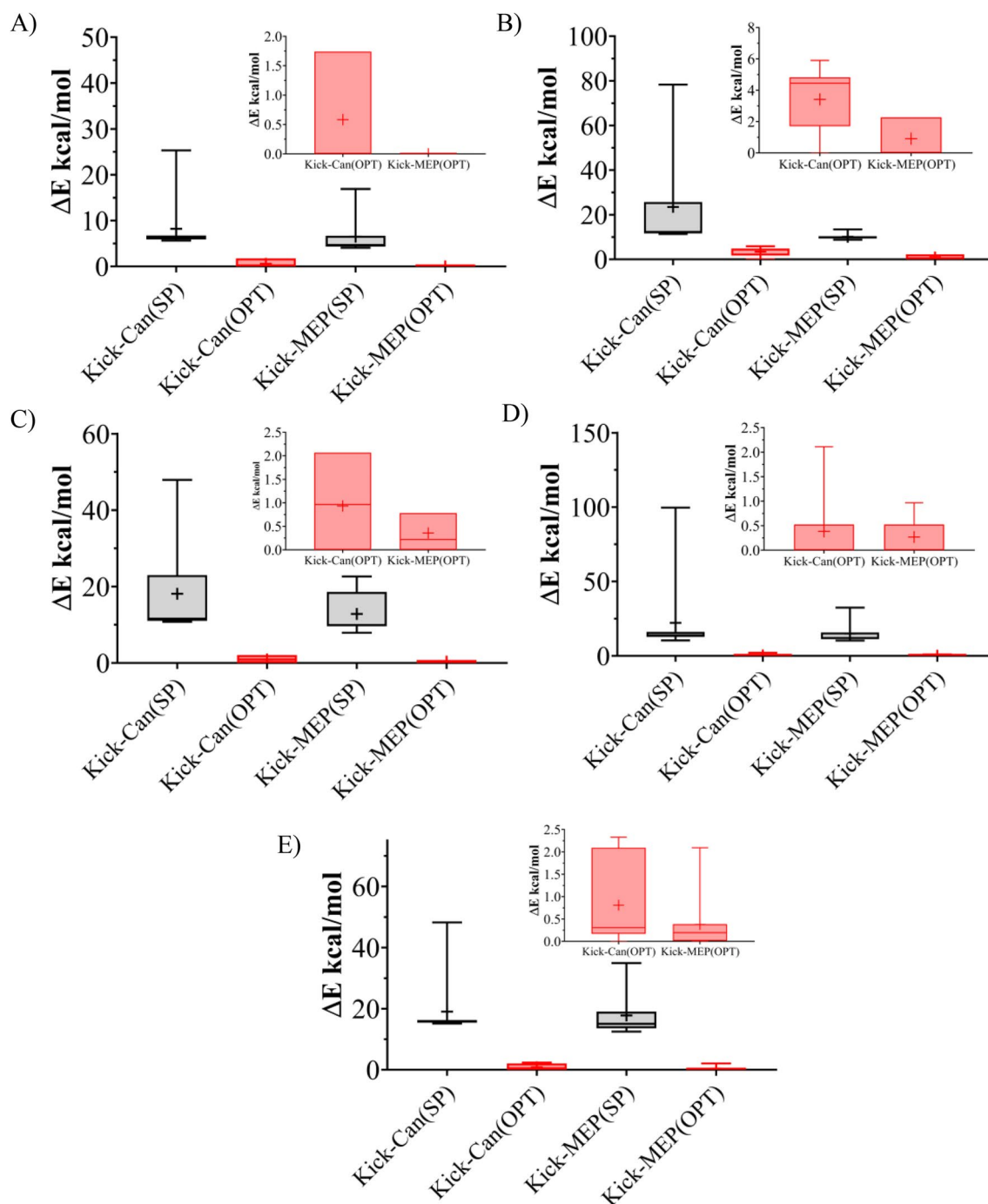


Fig. 3 Boxplots comparing the relative energy distribution of $\text{OCS}(\text{H}_2\text{O})_m$ ($m=1-5$) cluster candidates for the **A** monomer, **B** dimer, **C** trimer, **D** tetramer, and **E** pentamer. Details are similar to those in Fig. 2

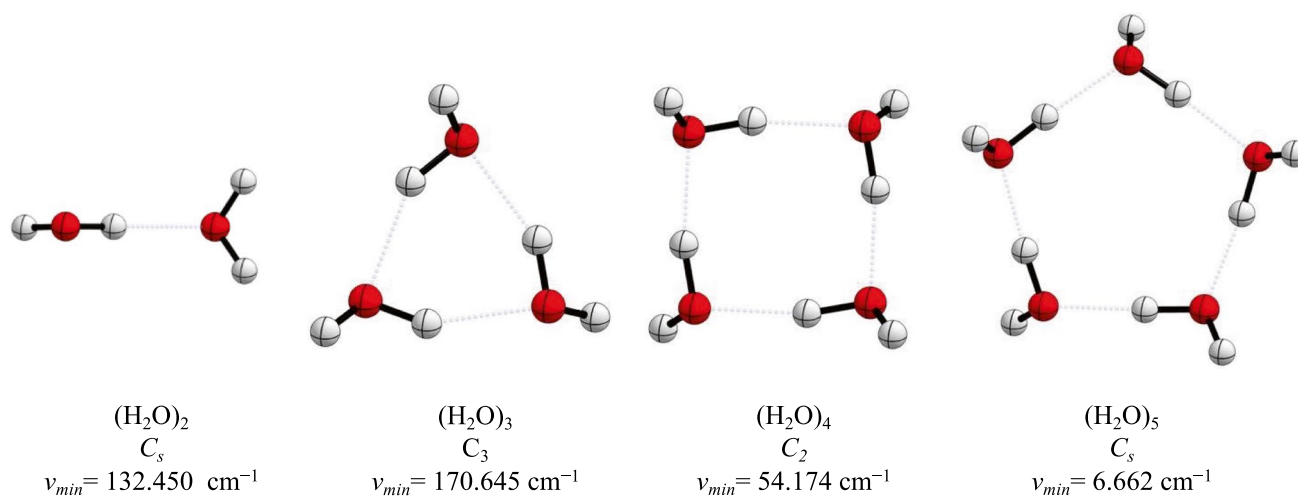


Fig. 4 Global minimum structures of water clusters, $(\text{H}_2\text{O})_{(n=2-5)}$, their point group symmetries, and smallest vibrational frequencies ($\nu_{\min}$) at the PBE0-D3/Def2-TZVP level

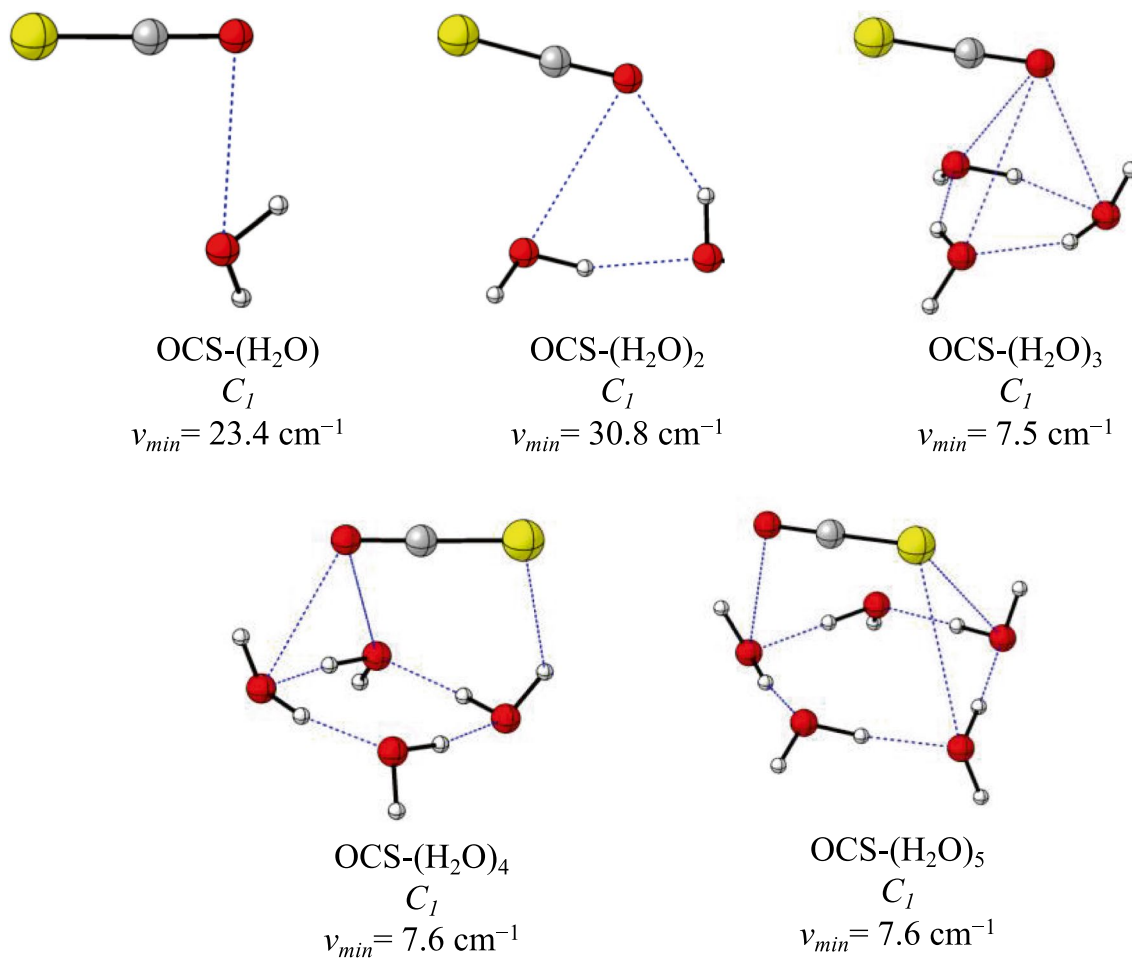


Fig. 5 Global minimum structures of $\text{OCS}-(\text{H}_2\text{O})_{(m=2-5)}$, their point group symmetries, and smallest vibrational frequencies ($\nu_{\min}$) at the PBE0-D3/Def2-TZVP level

affect all approximations being compared. Figure 2 compares the relative energy distribution (with respect to the most stable isomer) of candidate water cluster structures. This comparison is performed by constructing boxplots of the relative energies of these structures, selected in two ways: from an initial population of 100,000 initial individuals generated by the Kick procedure, 100 individuals are selected at random (Kick-Canonical) or by their minimum values of the descriptor $\langle JV \rangle_{AB}$ (Kick-MEP). For all clusters, the energies of the individuals selected by Kick-MEP show narrower interquartile ranges (height of the boxes) compared to Kick-Canonical, suggesting a more compact distribution of the lower energy configurations. However, more importantly, they are lower-energy systems, so they should converge faster in the subsequent geometry optimization process, saving computational resources. Also, when comparing the relative energies of the optimized systems, the structures chosen by Kick-MEP converge to the lowest energy structure more frequently, while Kick-Canonical has higher dispersion. However, the lowest energy structures are eventually found in both cases, mainly due to the optimization procedure included in our methodology, albeit at a higher computational cost in Kick-Canonical approach. For the OCS-(H₂O)_m cluster, whose comparative plots are shown in Fig. 3, the behavior is very similar. This is evidence that the approach of using this energy descriptor to perform a preliminary screening of the best structures is effective and allows us to choose lower energy structures that converge to the best minima in an optimization process in fewer cycles than if this screening is not performed.

The water dimer, the simplest water cluster, is the cornerstone of our understanding of hydrogen bonding. Theoretical calculations predict its structure as non-linear and curved, characterized by a lone hydrogen bond and an O...O interatomic distance of approximately 2.98 Å. The transition to the water trimer (H₂O)₃ features a planar cyclic arrangement with three hydrogen bonds forming a six-membered ring. These bonds alternate in length, with an average O...O distance ranging from 2.8 to 2.9 Å. The tetramer (H₂O)₄ has a planar square conformation with an equal number of hydrogen bonds. The cyclic pentamer (H₂O)₅ has a planar motif characterized by a five-membered ring architecture. Kick-MEP allows the identification of all global minima of these water molecular clusters, with their structures reported in Fig. 4.

Carbonyl sulfide (OCS) forms molecular clusters with water, a process well-studied through computational methods, revealing intricate structures and properties. For OCS monohydrate, the most stable configuration involves a water molecule interacting non-covalently with the sulfur end of OCS through an S...H₂O interaction, with a bond distance of approximately 3 Å. In OCS dihydrates, optimal structures feature one water molecule interacting with the sulfur end

(S...H₂O) and another with the oxygen end (O...H₂O) of OCS, forming interwater hydrogen bonds. OCS trihydrates prefer a cyclic water trimer engaging OCS through O...H₂O and S...H₂O interactions. For OCS tetra- and pentahydrates, the first solvation shell around OCS is completed by four water molecules, with additional water molecules forming interwater hydrogen bonding networks. These clusters are stabilized by various non-covalent interactions, including S...H₂O, O...H₂O, and weaker C...H₂O interactions. Water molecules organize into cyclic hydrogen-bonded networks around the OCS core, illustrating the interplay between molecular geometry and intermolecular interactions. The Kick-MEP method successfully identified all global minima for these OCS(H₂O)_m molecular clusters ($m=1-5$), as shown in Fig. 5.

Lithium-silicon clusters

Previously, we assessed Kick-MEP in molecular clusters where hydrogen bonding, a specific type of dipole–dipole interaction, played a significant role. Now, we evaluate it in exploring the PES of a system characterized by significant Li–Si ionic interactions. The global minima structure of Li₁₂Si₁₀ is characterized by the presence of two aromatic pentagonal Si₅ ring units. Interestingly, these rings maintain the aromatic character and bonding patterns of the C_{2v}-Li₆Si₅ cluster. For this reason, we have chosen it as a study system, using this cluster as an assembly block to generate the initial structures.

Figure 6 shows the comparative analysis, like that performed with the previously discussed molecular clusters. The Kick-Canonical distribution shows a negatively skewed pattern with a pronounced whisker towards lower energies. After geometry

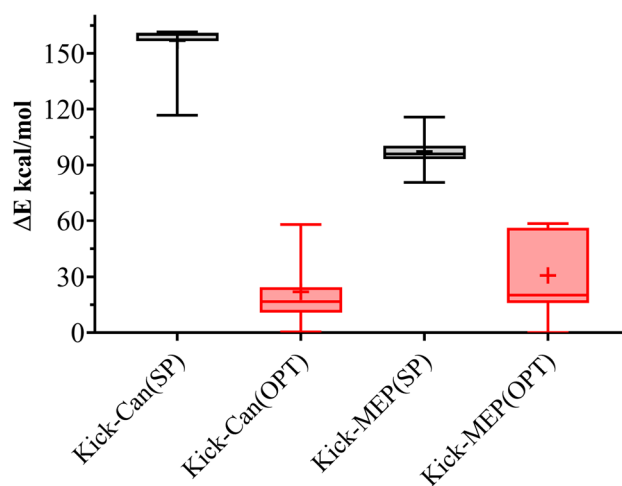


Fig. 6 Boxplots comparing the relative energy distribution of Li₁₂Si₁₀ cluster candidates. Details are similar to those in Fig. 2

optimization, the distribution becomes less skewed, and outliers are reduced at very low energies. This suggests that the optimization process rearranges the geometries of the selected candidates to low-energy isomers, consistent with observations in water clusters. On the other hand, the Kick-MEP guided selection presents a single-point energy distribution similar to the Kick-Canonical one, characterized by negative asymmetry and outliers at low energies. However, the selected candidates are appreciably lower in energy, ensuring a faster optimization process. After optimization, the optimized energy distribution in red shows a higher median compared to Kick-Canonical, with noticeably fewer outliers at low energies. This verifies

that Kick-MEP allows for effective pre-screening without additional computational cost, extending the approach's capabilities to evaluate atomic clusters with strongly ionic bond-forming characteristics.

Figure 7 shows the minimum energy structures identified by Kick-MEP, including the global minimum in agreement with previous reports. It should be noted that the Kick-Canonical method also provides structures that, after the optimization process, result in very low-energy structures, including the GM. However, this optimization process is slower since it starts from structures much higher in energy than those selected by Kick-MEP.

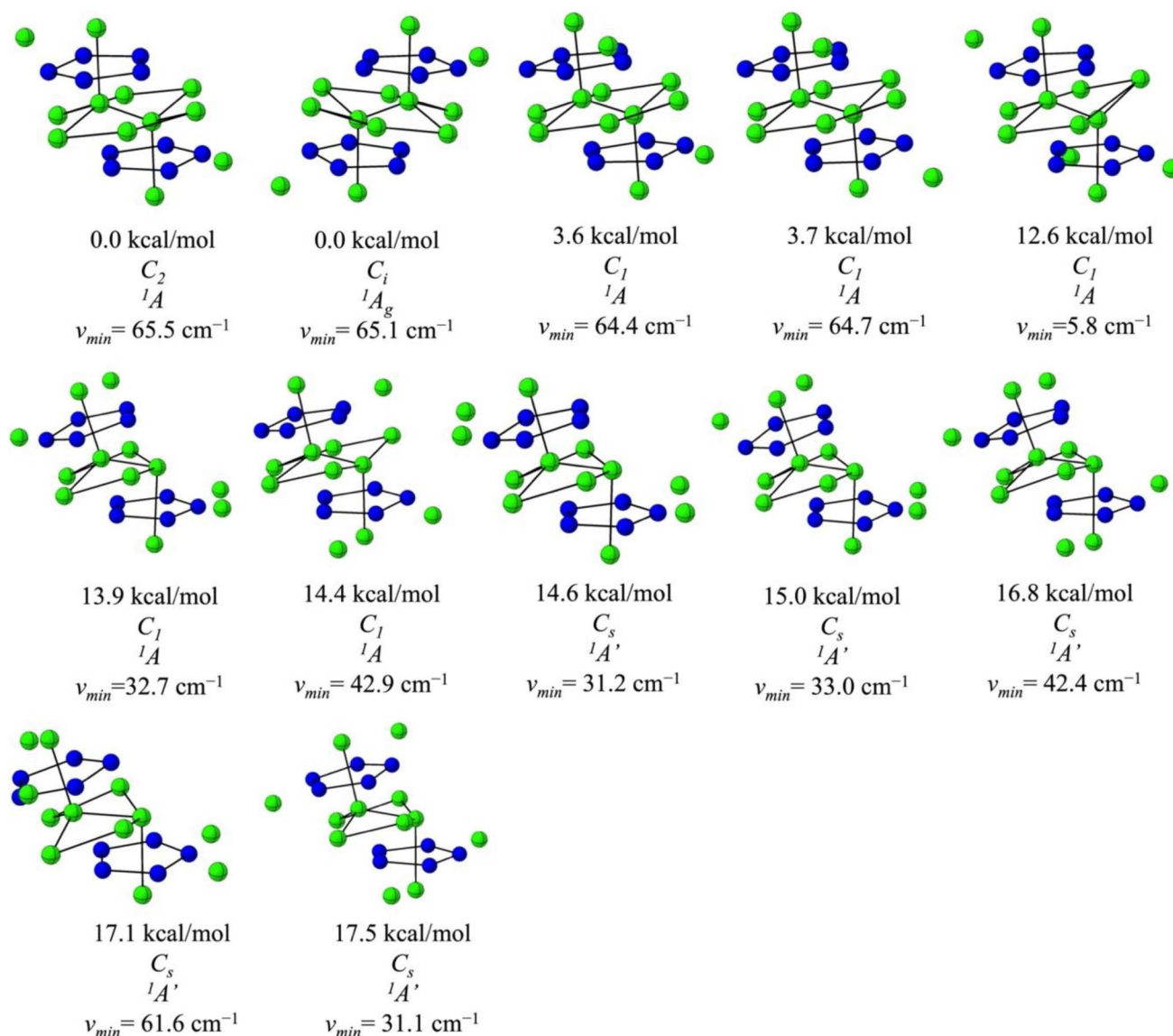


Fig. 7 Optimized structures of the lowest energy isomers identified (Kick-MEP) for $\text{Li}_{12}\text{Si}_{10}$, showing point group symmetries, spectroscopic states, and smallest vibrational frequencies (ν_{min}) at the PBE0-

D3/Def2-TZVP level. Relative energies are listed in kcal mol^{-1} with zero-point energy (ZPE) corrections

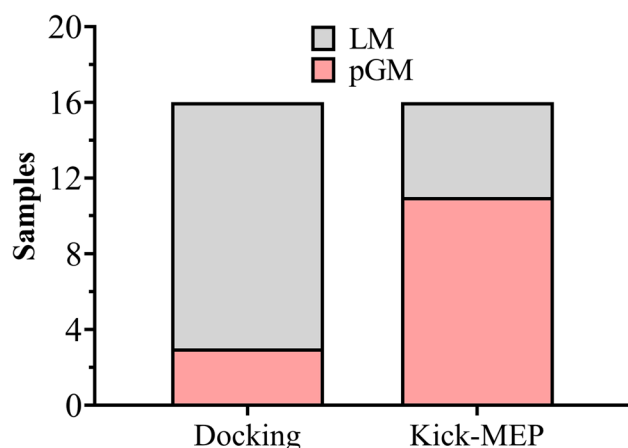


Fig. 8 Stacked barplot comparing the number of putative global minima and local minima (LM) of thymol@cucurbit[7]uril inclusion found by molecular docking and Kick-MEP guided selection. The pink bars represent the frequency of putative global minima, while the gray bars represent the frequency of LM among the 16 selected structures

Inclusion of thymol in cucurbit[7]uril

This system has been chosen to evaluate Kick-MEP's performance in identifying the most stable conformations in a host–guest system. The encapsulation of thymol in cucurbit[7]uril exemplifies molecular recognition driven by hydrophobic interactions, hydrogen bonding, and size and shape complementarity. Previous computational molecular docking studies [82] have provided valuable information on the inclusion process of the natural monoterpene thymol into the cucurbit[7]uril host cavity. The isopropyl group of thymol is located in the cucurbit[7]uril cavity, while the hydroxyl group forms hydrogen bonds with the carbonyl groups.

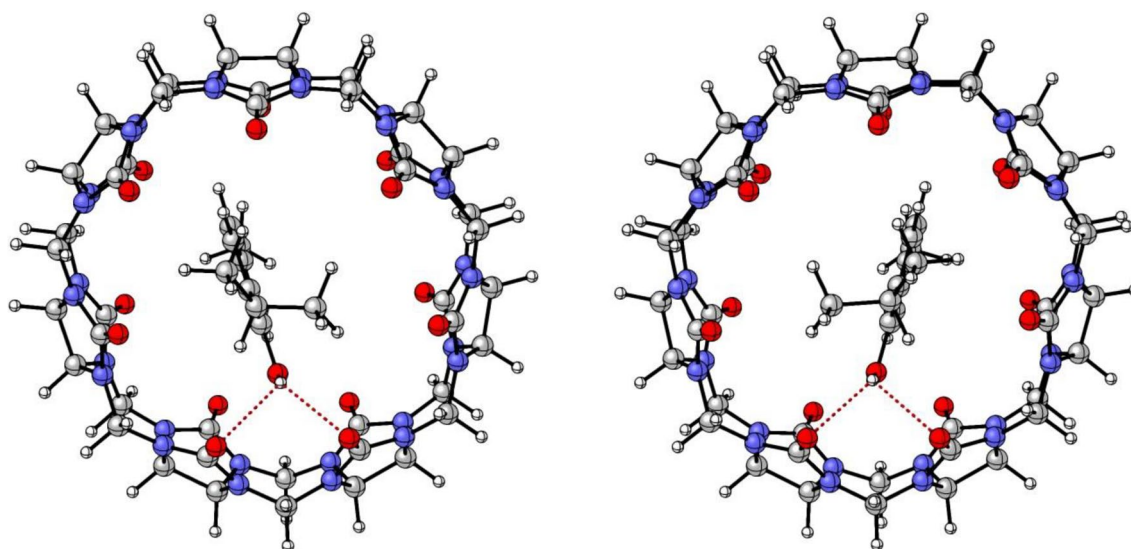


Fig. 9 Putative global minima of the inclusion process for thymol@cucurbit[7]uril identified by Kick-MEP and molecular docking

The stacked bar plot in Fig. 8 compares the number of times the global minimum is identified for the thymol@cucurbit[7]uril complex using molecular docking and Kick-MEP guided selection. Molecular docking has been chosen for comparison as it is a state-of-the-art method for exploring the PES of such complexes. From both the molecular docking and the Kick-MEP processes, we selected the 16 best structures according to their energy or energy descriptor and optimized them at the GFN2-xTB level. As shown in Fig. 8, among the 16 initial Kick-MEP structures, 11 (69%) converge to the GM after optimization, compared to 3 from docking (19%). This indicates that Kick-MEP is highly effective in identifying the lowest energy structure in this type of system, *highlighting* its potential for broader application. The putative global minima identified consists of two chiral, non-superimposable mirror-image structures with the same energy, as shown in Fig. 9. Figure S6 shows that optimizing the structures selected by Kick-MEP at the PBE0/SDDALL or PBE0-D3/SDDALL levels provides results similar to those at the GFN2-xTB level. However, it is important to note that PBE0-D3/SDDALL more frequently converges to the pGM.

$\langle JV \rangle_{AB}$ as a good descriptor of interaction energy

Figure 10 shows the effectiveness of using the descriptor $\langle JV \rangle_{AB}$ in the initial screening of structures. This graph depicts the energy (at the PBE0-D3/Def2-TZVP level) of 100 structures selected by the descriptor, compared to 100 randomly selected structures from a population of 100,000 generated by the Kick process. As shown, the structures chosen by the descriptor are clearly lower in energy. Moreover, since $\langle JV \rangle_{AB}$ is proposed as a simple and easy-to-compute

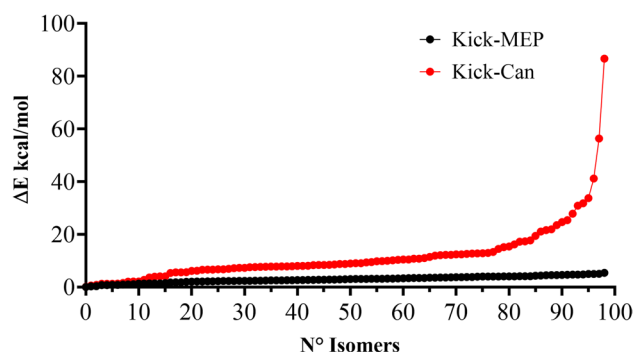


Fig. 10 Comparative plot of single-point energy of Kick-MEP vs. Kick-Canonical structures for the water trimer, $(\text{H}_2\text{O})_3$. From an initial population of 100,000 structures, the best 100 (Kick-MEP) or 100 at random (Kick-Canonical) were selected

descriptor without high computational resource demands, it is important to compare it with a more accurate energy calculation, like DFT (at the PBE0-D3/Def2-TZVP level). Figure 11 shows this comparison for the water trimer, demonstrating an acceptable correlation, considering that $\langle JV \rangle_{AB}$ only accounts for electrostatic interactions based on isolated fragments. Note that for Fig. 11, structures have been chosen that cover the entire spectrum of descriptor values, from the minimum to the maximum, to facilitate comparison.

Comparison of Kick-MEP and Kick-Canonical performance on $\text{Li}_{12}\text{Si}_{10}$ and $\text{OSC}(\text{H}_2\text{O})_n$ clusters

As shown in Tables S1 and S2, Kick-MEP demonstrates superior performance compared to the Kick-Canonical method. One hundred candidate structures were compared and selected based on Kick-Canonical and Kick-MEP approaches. For the $\text{Li}_{12}\text{Si}_{10}$ isomers (Table S1), Kick-MEP reduces optimization time and identifies more structures closer to the GM, with four structures compared to two identified by the Kick-Canonical method. In the case

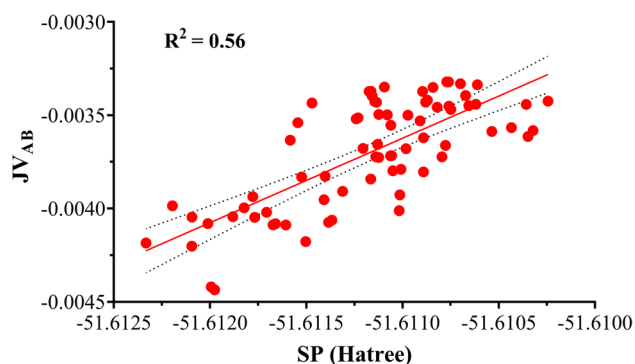


Fig. 11 Correlation between the $\langle JV \rangle_{AB}$ and the single-point energy, at PBE0-D3/Def2-TZVP level, of the water trimer $(\text{H}_2\text{O})_3$

of $\text{OSC}(\text{H}_2\text{O})_n$ clusters, the optimization times are comparable, but overall, Kick-MEP identifies a greater number of structures with energies close to the GM. These results support the effectiveness of Kick-MEP in guiding the exploration of the PES. All calculations were performed on a computational cluster with nodes utilizing 28 CPUs (Intel® Xeon® CPU E5-2660 v4 @ 2.00G Hz) and 128 GB of RAM.

Conclusions

The electrostatic descriptor $\langle JV \rangle_{AB}$, derived from the Coulombic integral between the extreme electrostatic potential values of *A* and *B* molecular fragments, has proven to be an effective predictor of interaction energies. The Kick-MEP methodology is both effective and computationally efficient for exploring potential energy surfaces in molecular systems characterized by significant non-covalent interactions. By combining the stochastic Kick algorithm with a descriptor based on the extreme values of the molecular electrostatic potential, Kick-MEP enables the rapid identification of low-energy molecular configurations from a large set of candidate structures.

The method has been evaluated in various systems, including water clusters, carbonyl sulfide-water complexes, lithium-silicon clusters, and the inclusion of thymol in cucurbit[7]uril. In these case studies, Kick-MEP consistently and reliably identified the lowest energy (global minimum) structures with minimal computational expense. Although the lowest energy isomers are also identified by the Kick-canonical method, Kick-MEP achieves this with greater computational efficiency. Furthermore, in the thymol@cucurbit[7]uril system, Kick-MEP outperformed the commonly used molecular docking method by more frequently identifying the putative global minimum. This highlights its potential for broader applications in molecular recognition processes governed by non-covalent interactions.

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Author contributions CC, OY, and WT designed the work and concepts, analyzed the data, drafted the manuscript, and finalized it. OY and WG-A programed the Kick-MEP algorithm. WG-A, LR, and DI conducted the global minima search, structural data analysis, and energy refinements; they also performed the comparative analysis between approaches and constructed the Figures. All authors participated in discussions and approved the final manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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