Surprising new dynamics phenomena in Diels–Alder reaction of C_{60} uncovered with AI

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Abstract

Our recently developed physics-informed active learning allowed us to perform extensive AI-accelerated quasi-classical molecular dynamics investigation of the time-resolved mechanism of two Diels–Alder reactions. This investigation revealed that despite the high similarity between static transition state geometries in reactions with ethene and fullerene C_{60} as dienophiles, the dynamics around the transitions are remarkably different. In a substantial fraction (10%) of reactive trajectories, the larger C_{60} non-covalently attracts the 2,3-dimethyl-1,3-butadiene long before the barrier so that the diene undergoes the series of complex motions including roaming, somersaults, twisting, and twisting somersaults around the fullerene until it aligns itself to pass over the barrier. These complicated processes could be easily missed in typically performed quantum chemical simulations with shorter and fewer trajectories. After passing the barrier, the bonds take longer to form than in the case of the ethene reaction: the consequence of the markedly different topology of the PES region between reactants and products. These effects are not captured by static intrinsic reaction coordinate (IRC) calculations that do not reveal any difference in the barrier widths.

Diels–Alder reaction is paradigmatic and was extensively studied experimentally and theoretically. The textbook example is the reaction of ethene as a dienophile with 1,3-butadiene which was observed experimentally.[1, 2] The small system size allowed for detailed static quantum chemical (QC)[3-5] and quasi-classical molecular dynamics (MD)[3] simulations of this reaction that revealed the symmetric transition state (TS) structure and the preference for a concerted mechanism (Figure 1).

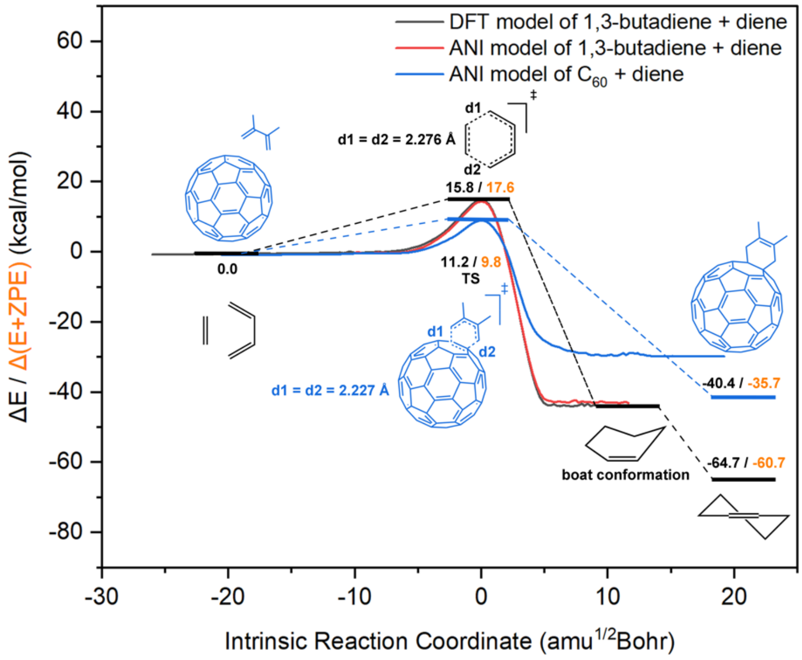

Figure 1. Energy diagram and IRC analysis of Diels-Alder reactions of 1,3-butadiene with ethene (black and red) and 2,3-dimethyl-1,3-butadiene with fullerene C_{60} (blue) at UB3LYP-D4/6-31G* and ANI surrogate model. ANI was used only for IRC (red and blue). IRC calculations with UB3LYP-D4/6-31G* for C_{60} + 2,3-dimethyl-1,3-butadiene are too slow and not shown here as the ANI is likely to reproduce it well (compare the IRC for ethene + 1,3-butadiene with UB3LYP-D4/6-31G* and ANI).

However, many chemically interesting Diels–Alder reactions involve much bigger molecules,[6-8] which may have very different behavior compared to small systems. For example, this reaction type provides a powerful route for the functionalization of fullerenes[6-8] and was used to form an adduct of fullerene C_{60} with 2,3-dimethyl-1,3-butadiene which is the main subject of this study (Figure **1**). The typical fullerene size alone constitutes a challenge for QC simulations and the above system comprising fullerene and diene has 76 atoms. This imposes a big limitation on performing extensive analysis of the time-resolved mechanism of the reaction with quasi-classical MD. The MD simulations of the similarly-sized but smaller system with 57 atoms were reported to take almost 2–6 days for a single trajectory on 16 CPUs.[9] To make matters worse, such investigations require[10] many hundreds of trajectories to obtain precise results and detect rare events. Due to the cost limitations, the propagation time is also limited and the dynamics is often propagated just long enough to see the bond formation and breaking events as defined by some cutoffs. Any interesting events occurring after this would be missed. Hence, the MD simulations of the Diels–Alder reactions with bigger molecules are very costly, require high-performance computing (HPC) facilities, and are prohibitively expensive in many cases.

Luckily, advances in artificial intelligence (AI) allow us to bring the simulation cost down and enable investigations of big systems and longer time scale.[11-13] AI has been instrumental in understanding and discovering interesting mechanistic details in chemical reactions such as roaming.[14-17] The bottleneck of such AI studies is the construction of robust machine learning potentials and many solutions based on active learning (AL) were suggested to overcome it.[18-25] One of these solutions is our recent efficient physics-informed AL protocol which was able to reproduce the earlier quasi-classical MD investigation[3] of the ethene and 1,3-butadiene at UB3LYP/6-31G* in a fraction of computational cost without requiring any HPC.[26]

Here, this AL protocol enabled us to investigate the time-resolved mechanism of the Diels–Alder reaction between fullerene C_{60} and 2,3-dimethyl-1,3-butadiene on a much larger scale than similar state-of-the-art QC investigations (see *Computational details*).[3] We propagated one thousand forward and backward quasi-classical trajectories to obtain statistically precise results and extended the propagation time to 1500 fs: this is 10 times longer than in the previous study[3] on the reaction of much smaller ethene and 1,3-butadiene. More trajectories and longer simulations have allowed us to uncover phenomena previously unknown for this reaction, which smaller-scale simulations would have missed.

Our quasi-classical MD simulations showed that the large size of the C_{60} and 2,3-dimethyl-1,3-butadiene reactants leads to a dynamics behavior in rare trajectories qualitatively different from the cycloaddition reaction of ethene and 1,3-butadiene (Figure 2). Unlike the reaction between ethene and 1,3-butadiene where two reactants move closer to each other and form bonds directly without roaming, the bulkier 2,3-dimethyl-1,3-butadiene undergoes a prolonged phase of alignment around the C_{60} buckyball in 10% of the reactive trajectories (Figure **3**). During the alignment phase, the diene displays complex ‘acrobatic’ movements such as somersault (4.6%), twisting (3.9%), twisting somersault (1.4%), and other roaming (0.4%) (Figure 2, videos of selected trajectories are available on https://figshare.com/[upon publication]). We assume that the alignment phase happens if the distances between two bonding carbon atoms and C_{60} are shorter than 5.0 Å after 1.5 ps; otherwise, the trajectories are deemed to correspond to a direct reaction.

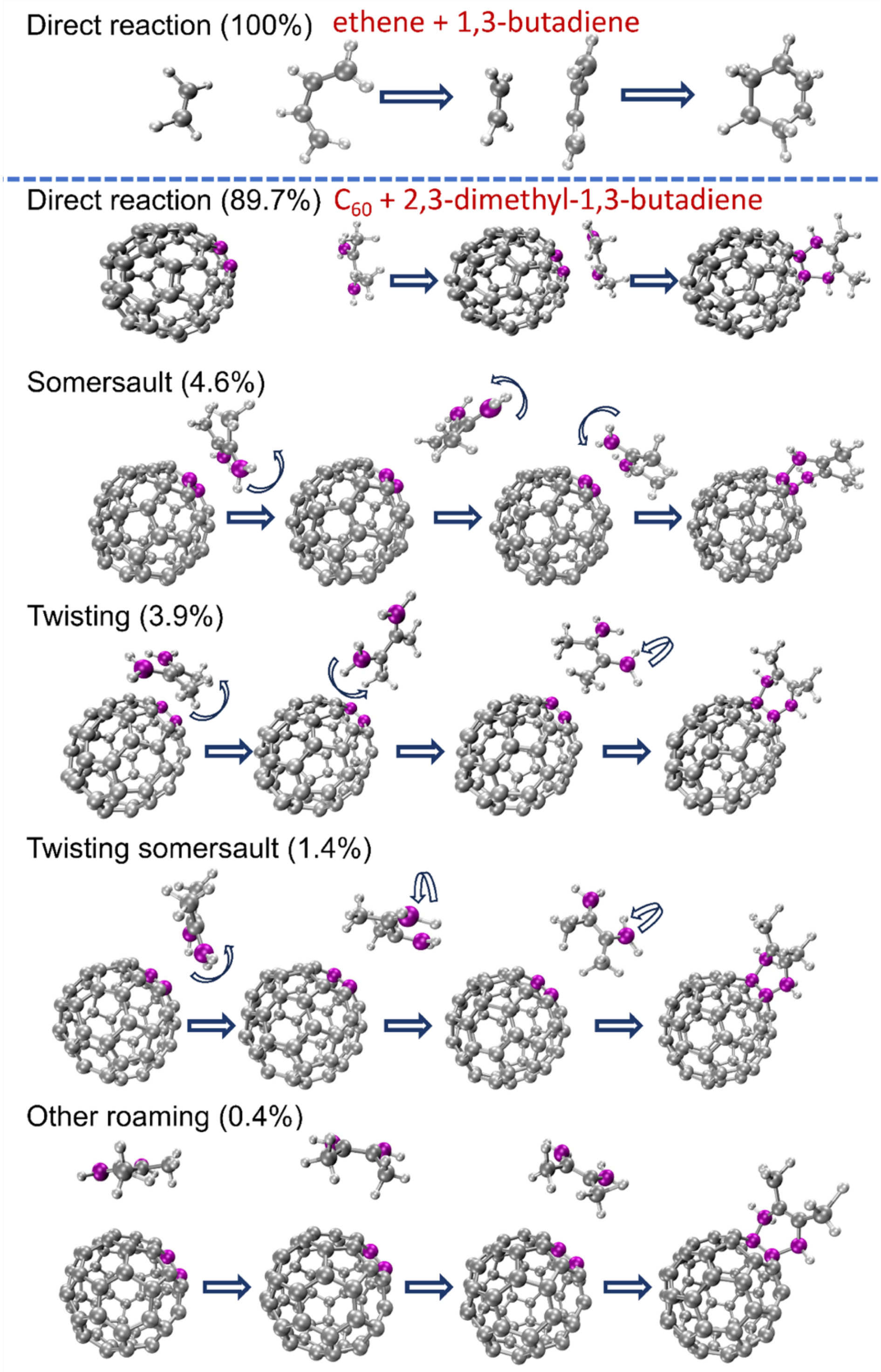

Figure 2. Snapshots of reactive trajectories of two Diels–Alder reactions. The carbon atoms of two forming C–C bonds in the reaction between 2,3-dimethyl-1,3-butadiene and fullerene are highlighted in purple. Numbers in the parenthesis are percentages of different reaction pathways to the total number of reactive trajectories. The somersault means that the diene molecule rotates around the axis along the double bond, while the twisting means the diene molecule rotates around the axis perpendicular to the molecule plane.

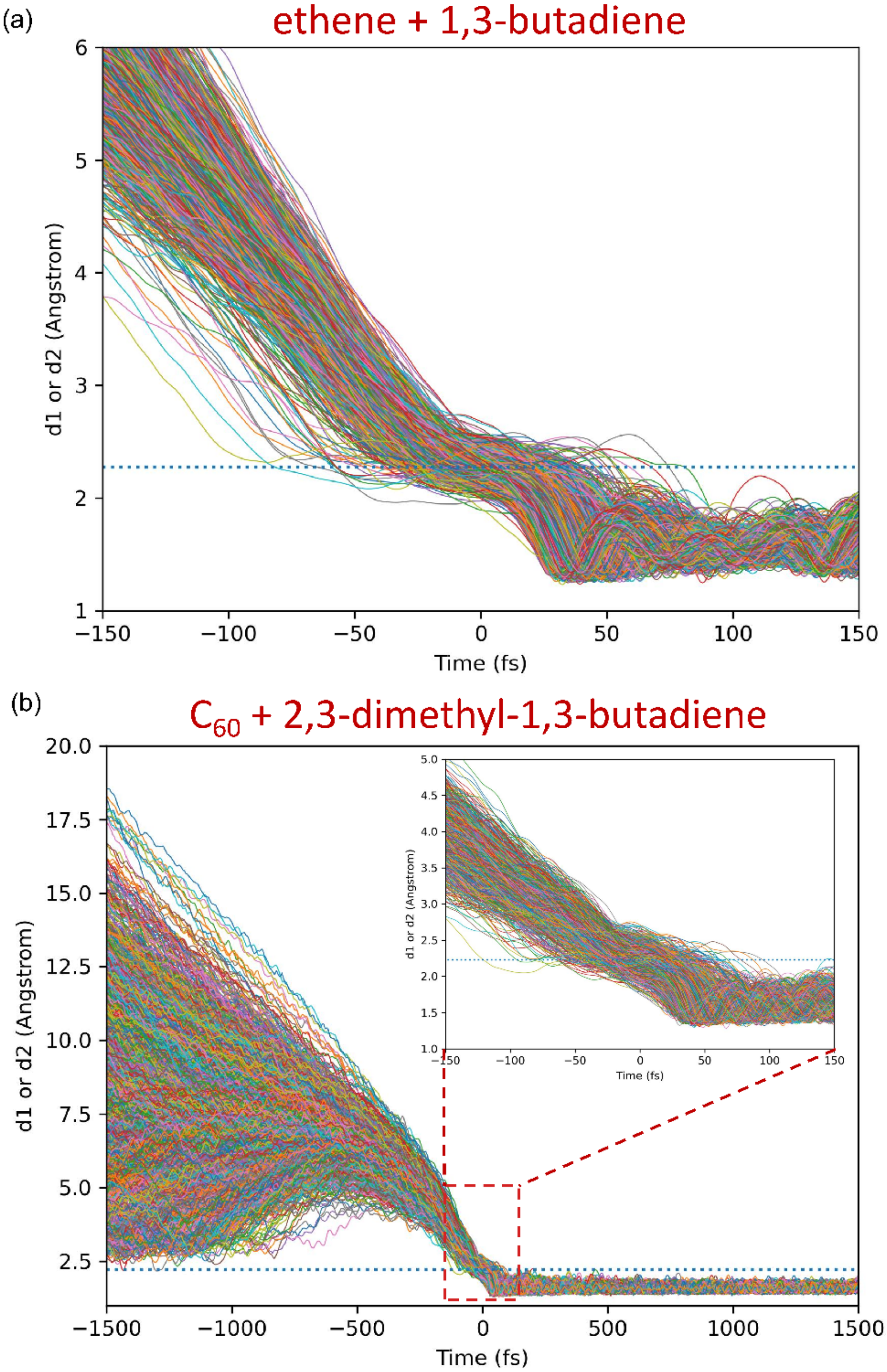

Figure 3. The C–C distance for atom pairs forming bonds as a function of time in the reactive quasi-classical MD trajectories for the Diels–Alder reaction a) between 1,3-butadiene and ethene and b) between 2,3-dimethyl-1,3-butadiene and fullerene. The blue dot lines show the distances in the TSs.

All of the calculations were performed with the UB3LYP[27]-D4[28]/6-31G*[29, 30] level because B3LYP/6-31G* was shown to be a suitable and affordable method for reaction description as it provides similar results to the higher-level QC calculations.[31, 32] D4 dispersion corrections were included in the calculations as their effect is non-negligible, particularly for a large system, according to the static calculations, see Table S2 in Supporting Information (SI). In our AL procedure, we used the ANI-type model[33] as a surrogate for UB3LYP-D4/6-31G*. Predictions of ANI models in a fraction of trajectories exceeded thresholds defined by our uncertainty quantification[26] procedure; these uncertain trajectories were removed so that only confident results were analyzed.

Remarkably, dynamics simulations unveiled the substantial differences between the two reactions investigated here, which the static calculations are incapable of capturing. The static calculations show that the bonds being formed are remarkably similar in TSs of both reactions: 2.23 Å in C_{60}+2,3-dimethyl-1,3-butadiene and 2.27 Å in ethene+1,3-butadiene, despite their very different sizes (Figure **1**). Also, static intrinsic reaction coordinate[34] (IRC) calculations do not show any big difference in the barrier width (Figure 1).

In contrast, the quasi-classical MD shows that the bond formation and dissociation in the Diels–Alder reaction of fullerene are slower than in the reaction of ethene after passing the TS (Table 1). After crossing the TSs, the bonds are broken and formed much slower in the C_{60} reaction than in the ethene reaction: 95% of the C–C bonds are formed within 88.0 fs and 69.0 fs, respectively, and 95% of the bonds are dissociated within 372.0 fs and 160.0 fs, respectively (Figure **4**). Similarly, the average time of bond formation is 23% slower and the average bond dissociation time is slower by a fraction of 2.2. In this analysis, we adopted the previous thresholds in distances: 1.6 Å and 5.0 Å for bond forming and dissociation, respectively (both bonds are considered).[3] In addition, the C_{60} and 2,3-dimethyl-1,3-butadiene find themselves 50% (30 fs) longer in the transition zone compared to the smaller system of ethene and 1,3-butadiene (Table 1 defined as the forming C–C bond length range that includes 98% of the initial points obtained by a normal mode sampling, see *Computational details*).

Table 1. Time to traverse the transition zone and time gap of C–C bond formation for Diels–Alder reaction of diene (1,3-butadiene and 2,3-dimethyl-1,3-butadiene) and dienophile (ethene and fullerene C_{60}, respectively) at 298 K. The bond-forming time and -dissociating time are also shown with standard deviations. Medians are given in parentheses. Uncertain trajectories were removed, hence, the total number of trajectories is fewer than 1000.

Reaction	Average time to traverse the transition zone (fs)	Average bond forming time (fs)	Average bond dissociating time (fs)	Number of trajectories: reactive/total
1,3-butadiene + ethene	57.8 (55.0) ± 15.3	35.2 (31.5) ± 17.4	119.7 (117.75) ± 24.5	894/938
2,3-dimethyl-1,3-butadiene + C_{60}	84.7 (81.0) ± 22.4	43.4 (38.0) ± 39.7	268.3 (255.5) ± 97.2	841/917

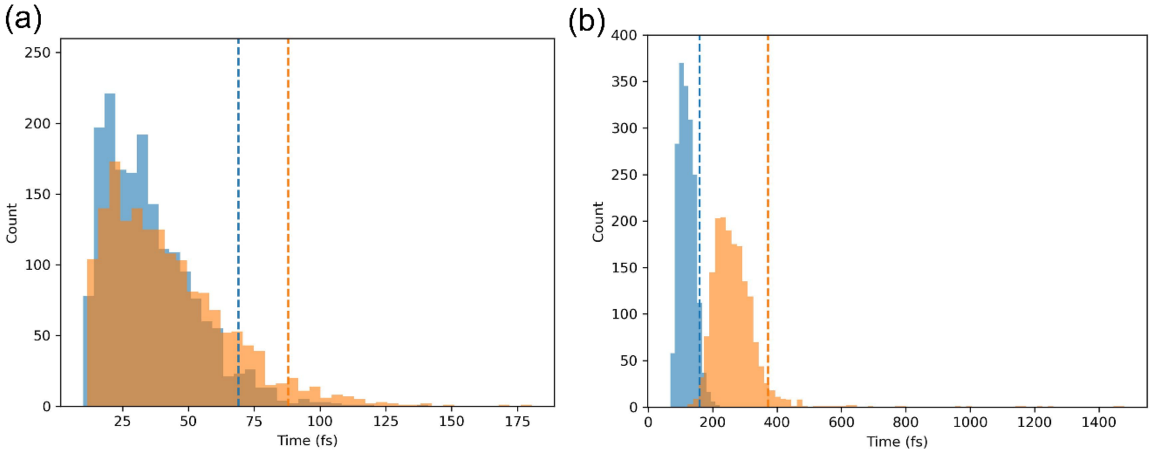

Figure 4. The histogram of the C–C a) bond-forming time and b) bond-dissociation after crossing the transition state of the Diels–Alder reaction between 1,3-butadiene and ethene (blue), and between 2,3-dimethyl-1,3-butadiene and fullerene (orange). The bonds are considered formed if they are shorter than 1.6 Å. The bonds are considered dissociated if they are longer than 5 Å for the first time. The time within which 95% of bonds are formed or dissociated is shown as the dashed line.

Hence, our dynamics simulations uncovered an interesting situation when the kinetically faster reaction takes longer to pass through the transition zone (the barrier of C_{60}+2,3-dimethyl-1,3-butadiene reaction is smaller by 7.8 kcal/mol than of ethene+1,3-butadiene, Figure **1**, and, therefore, the former reaction must be faster according to TS theory). Barrier width is the first suspect to check[35] for conceptual rationalization of the paradox but, as mentioned before, the IRC calculations show essentially the same barrier width for both reactions and that's why cannot explain the paradox.

We interpret this paradox by highlighting the importance of taking into account the topology near TS zone and overall barrier shape rather than only the barrier height or width. The fullerene reaction involves passing through a much flatter barrier than the ethene reaction. Because the latter is more exothermic by 24.9 kcal/mol (Figure **1**), it leads to the higher energy barrier measured from the products which translates to the stronger thermodynamic driving force and the higher kinetic energy of atoms moving faster away from the transition state. Another contributor to the paradox is that the transition zone (but not the barrier width as defined by IRC) is broader for the reaction between fullerene and 2,3-dimethyl-1,3-butadiene as the bonds to be formed range from 1.86 to 2.60 Å compared to the range of 2.02 to 2.52 Å in the reaction between ethene and 1,3-butadiene (see also the histogram of the bond lengths in the initial conditions, Figures S1, S2).

To summarize, large systems can display qualitatively different behavior due to their size and extensive dynamics simulations are essential to uncover them as we demonstrate on an example of the Diels–Alder reaction of C_{60} fullerene with 2,3-dimethyl-1,3-butadiene. These simulations are now possible with efficient active learning implementations and should become standard. Our study unveiled the crucial shape of the barrier shape and noncovalent interactions that can lead to prolonged alignment phases including complex dynamics behavior before the reaction happens.

Computational details

The MLatom ecosystem[36, 37] was used in all the simulations. UB3LYP/6-31G* calculations are done via Gaussian 16[38], the D4 dispersion correction via dftd4[28, 39] and calculations with machine learning ANI models via TorchANI[40] interfaces to MLatom. ANI models were trained with the default MLatom settings whose settings are default ones in MLatom. The models are trained on 90% of the labeled data set and validated on the remainder.

Geometry optimization and frequency calculations are done through the interface to Gaussian [41]. The initial conditions were sampled from the harmonic quantum Boltzmann distribution[26, 42] at 298 K using the normal modes analysis of TS. In addition, the TS state of the Diels–Alder reaction of C_{60} with 2,3-dimethyl-1,3-butadiene has several low-frequency modes which can result in very distorted structures in normal mode sampling (as observed before for similar sampling procedures[43, 44]), hence, we set these frequencies as 100 cm^{-1} if they are smaller than this value; this procedure was introduced here but later found useful also in the context of nonadiabatic dynamics submitted earlier than this work[44].

The trajectories were propagated with the time step 0.5 fs in the NVE ensemble as implemented in MLatom[45] with batch parallelization[26]. One thousand trajectories were propagated in each direction (forward and backward, where the difference is only in the initial velocities, which are set in opposite directions). The settings and detailed outcome of active learning are reported in Table S1 of SI.

In this study, we used the development version of MLatom and most of the simulations can be performed with the already-released version, while we are preparing the full release with all the remaining capabilities.

Data availability

Data is available as described in https://figshare.com/[upon publication].

Code availability

Code is available as described in https://figshare.com/[upon publication]. All simulations can be performed with the open-source MLatom (https://github.com/dralgroup/mlatom) and MD with the trained models can be run on XACS cloud computing[46].

Author contributions

P.O.D. conceived the project. Q.Z. performed static calculations and their analysis. Y.H. and Q.Z. carried out the active learning, and performed quasi-classical dynamics. Y.H. made additional implementations for active learning and analysis. All authors analyzed the results of dynamics simulations. P.O.D. and Y.H. wrote the original version of the manuscript with input from Q.Z. All authors revised the manuscript. Y.H. and Q.Z. prepared all the figures.

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