Base-induced elimination (E2) and bimolecular nucleophilic substitution (SN2) reactions are of significant importance in physical organic chemistry. The textbook example of the retardation of SN2 reactivity by bulky alkyl substitution is widely accepted based on the static analysis of molecular structure and steric environment. However, the direct dynamical evidence of the steric hindrance of SN2 from experiment or theory remains rare. Here, we report an unprecedented full-dimensional (39-dimensional) machine learning-based potential energy surface for the 15-atom $F^- + (CH_3)_3CI$ reaction, facilitating the reliable and efficient reaction dynamics simulations that can reproduce well the experimental outcomes and examine associated atomic-molecular level mechanisms. Moreover, we found surprisingly high “intrinsic” reactivity of SN2 when the E2 pathway is completely blocked, indicating the reaction that intends to proceed via E2 transits to SN2 instead, due to a shared pre-reaction minimum. This finding indicates that the competing factor of E2 but not the steric hindrance determines the small reactivity of SN2 for the $F^- + (CH_3)_3Cl$ reaction. Our study provides new insight into the dynamical origin that determines the intrinsic reactivity in gas-phase organic chemistry.
Recently, crossed beam scattering experiments under single-collision conditions were developed in Wester’s group to directly image the differential cross sections (DCSs) for a series of reactions between anions and methyl-substituted alkyl halides of the X + RY type. These experiments, combined with dynamics theory, provided direct evidence for a variety of reaction mechanisms at the atomic-molecular level, and also the competing S_n2 and E2 reaction pathways. Particularly, it was observed that the S_n2 reactivity decreases for F - reactions with increasing methyl-substituted alkyl halides, which are F + CH_3I, F + C_2H_5I, F + CH_3Br, and F + C_3H_7I. In particular, for F + C_4H_9I, the measured DCSs imply the exclusive contribution from E2, while the S_n2 pathway nearly vanishes.

The measured S_n2 inhibition can be rationalized intuitively with the steric environment: the totally substituted (CH_3)_3CI is so crowded that the reaction cannot occur because the nucleophile is unable to approach the shielded central carbon atom to do a back-side attack. These experimental findings were attributed simply to the steric hindrance at the α-carbon, which is a textbook example of the retarded S_n2 reactivity by bulky alkyl substitution. Nevertheless, the assumed steric effects cannot be directly observed merely by the experiment, and an accurate characterization from the full-dimensional dynamics simulations which can reproduce experimental results and examine the steric effects is highly desirable. A total of ~220,000 CAM-XYG3/AVTZ(-PP) energy points were included in the fitting data set. The overall root mean square error (RMSE) of the fitted PES is only 8.3 meV, representing the high accuracy of the current fitting and 15-atom multi-channel PES as well as the strong capability of the FI-NN approach. In addition, we employed the space partitioning and energy splitting methods to overcome the huge challenge to construct a 39-dimensional multi-channel reaction with long-range interaction in the asymptotes. All details of the fitting approach and properties of the PES are given in the Supplementary Information. The distribution of fitting errors and optimized geometries are shown in Supplementary Figs. 1, 2, respectively.

The F + (CH_3)_3CI reaction involves the two following important product channels:

\[
\text{F}^- + (\text{CH}_3)_3\text{Cl} \rightarrow (\text{CH}_3)_2\text{CCH}_2 + \text{HF} + \text{I}^- \quad (\text{E}_2)
\]

\[
\text{F}^- + (\text{CH}_3)_3\text{Cl} \rightarrow (\text{CH}_3)_2\text{C} = \text{CH}_2 + \text{HF} + \text{I}^- \quad (\text{S}_\text{n}2)
\]

As depicted in Fig. 1, we can find that both E2 and back-side attack S_n2 reactions are barrierless and highly exothermic, associated with pre-reaction wells on the reactant side and post-reaction wells on the product side. There is a high barrier (TS0) pathway, which

Fig. 1 | Schematic PES of the F^- + (CH_3)_3CI reaction. Green curve: back-side attack S_n2; Purple: front-side attack S_n2; Black: anti-E2; Red: syn-E2. The relative energies obtained from CAM-XYG3/AVTZ(-PP) and CCSD(T)/AVTZ(-PP) (in brackets) methods are all in eV.
corresponds to the front-side attack SN2, with a slightly shallower pre-reaction minimum (CP0) than CP1. The E2 reaction undergoes either a lower energy pathway of anti-E2 or a higher one of syn-E2, indicating the anti-E2 pathway is more kinetically favorable. We note that the SN2 reaction shares an ion-dipole bound pre-reaction complex (CP1) with the anti-E2 pathway, which lies −1.11 eV below the reactant asymptote. The submerged barrier for SN2 is 0.24 eV higher than that for anti-E2, but the exothermic energy for SN2 is much larger than that for E2.

To further demonstrate the accurate behavior of full-dimensional PES, we show two contour plots of back-side attack SN2 and anti-E2 pathways in Fig. 2. The contours of front-side attack SN2 and syn-E2 pathways with higher energy profiles are depicted in Supplementary Figs 3, 4, respectively. These contours are plotted using the full-dimensional optimization on the global full-dimensional PES. As seen, these contours are quite smooth, and the position and energies of reactants, pre-reaction minimums, transition states, post-reaction minimums, and products, are all well described. To the best of our knowledge, this is also the first time these contours can be made for such large reactive systems. These contours further reflect the high accuracy of the current fitting and reliability of 15-atom multi-channel PES, as well as the strong capability of the FI-NN approach. We can go much further than predicting reaction pathways based on stationary points with an accurate, full-dimensional, analytical PES, and produce observable outcomes and ultimately provide deep insight into the dynamical mechanisms of competing SN2 and E2 pathways and associated steric effects for this ion-molecule reaction.

**Reaction dynamics simulations**

Standard QCT calculations were carried out at the collision energies (Ec) ranging from 0.2 to 1.9 eV based on the full-dimensional PES. A total of 4.2 million trajectories were run for (CH3)3CI initially in the ground rovibrational state for each collision energy. It is worth mentioning that we developed the computational approach to get analytical gradients from the FI-NN PES, which raises the computational speed by about ten times as compared to the numerical gradients, and facilitates the calculations of a large number of trajectories for good statistics. Detailed information on QCT calculations are given in the Supplementary Information.

We found the collision of F– with (CH3)3Cl leads to nearly the E2 product channel, while the cross section of SN2 is roughly 50 times smaller than that of E2 at all the collision energies, indicating the SN2 reactivity can be negligible in resulting in F– product ions. In addition, the limited SN2 reactivity results from exclusively the back-side attack mechanism, and no front-side attack mechanism was seen, presumably due to the much higher barrier. Thus, “SN2” below refers to back-side attack SN2 for simplicity. This finding is consistent with the recent experiment, which indicates the exclusive E2 reaction.30
Product angular and translational energy distributions
A comparison of detailed dynamics from theory (PES and dynamics) and experiment can test the reliability of the former. Figure 3 shows the computed center-of-mass (CM) angular and translational energy distributions for I 2 product ions, together with the experimental results30 at three collision energies. We found a very good agreement between theory and experiment.

At the lowest collision energy of 0.4 eV, both theoretical and experimental angular distributions are almost forward-backward symmetric, with slightly more intensity in the forward direction from theory. This is associated with the dominant indirect E2 mechanism at low collision energies, due to the pre-reaction minimum. The intensity in the forward direction from the QCT calculations results from the contributions from a small fraction (~11%) of the direct E2 mechanism. With the increasing collision energy, the computed angular distributions exhibit more intensity in the forward and sideways directions, consistent with the experimental results showing more signals in the forward scattering. We found the direct mechanism of E2 increases when the collision energy increases in the QCT simulations, as shown in Supplementary Fig. 5 for the cross sections of direct and indirect pathways, and this trend was also predicted by the experiment30. Due to the lower minimum energy path of anti-E2, the reaction via the anti-E2 pathway dominates over syn-E2 (Supplementary Fig. 6). Animations of typical indirect and direct trajectories via anti-E2 and syn-E2 are given in the supplementary Movies 1–4.

The agreement between theory and experiment for the translational energy distributions of I 2 is impressive (Fig. 3d–f). Overall, the three translational energy distributions show nearly invariant with respect to the collision energies, which all peaks at around 0.3 eV and vanishes at around 1.0 eV. The product translational energy release is independent of the reactant collision energy, supporting that the SN2 reaction via the E2 pathway but nothing is changed for SN2, by adding a repulsive potential barrier. The minimum energy paths were determined by the quadratic steepest descent method44. The two minimum energy paths are connected to E2 with a shared pre-reaction minimum, followed by a slightly higher submerged barrier than that for anti-E2, but a more deep well of post-reaction minimum and lower product energies. Therefore, the near vanish of S02 is unexpected, and the assumption of complete steric hindrance of the S02 reactivity remains in doubt.

**Intrinsic** reactivity of S02
It is important to find out the “intrinsic” reactivity of S02 regardless of the competing E2, which can be accomplished based on the current PES. We propose a numerically simple but efficient way to block the E2 pathway but nothing is changed for S02, by adding a repulsive potential between F− and β-H in the vicinity of the E2 transition state of the global PES. The form of the repulsive potential is expressed as follows.

\[
\Delta V = \frac{1}{10 \times (1 + \exp(10 \times (R - 1.3)))}
\]

Here, \(R_{11}\) is the distance between F− and β-H. Figure 4 shows the minimum energy paths of the S02 reaction obtained from the original FF-NN PES and the modified PES, which shows excellent agreement between them. The minimum energy paths were determined by the quadratic steepest descent method44. The two minimum energy paths were also verified by the direct CAM-XY3/AVTZ(PP) calculations. We have also shown the contour plot of the S02 reaction on the modified PES in Supplementary Fig. 8, which is exactly the same as the contour plot on the original full-dimensional PES (Fig. 2a). In addition, we have randomly selected two S02 trajectories and calculated the potential energies of configurations along the two trajectories. As shown in

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**Fig. 3 | Theory and experiment.** Comparisons of normalized angular distributions (a–c) and translational energy distributions (d–f) of product I 2 in the center of the mass frame at the collision energy of 0.4, 1.1, and 1.9 eV between the experimental measurement and QCT calculations.
SN2 reactivity is roughly 50 times smaller than the E2 reactivity on the failure. The cross sections of F\textsuperscript{−}-(CH\textsubscript{3})\textsubscript{3}Cl with that of F\textsuperscript{−}+(CH\textsubscript{3})\textsubscript{3}Cl. For instance, the barriers are much higher, the pre-reaction and post-reaction wells are shallower, and the products are not that exothermic for the Cl\textsuperscript{−}+ (CH\textsubscript{3})\textsubscript{3}Cl reaction, we investigated one more reaction, Cl\textsuperscript{−}+(CH\textsubscript{3})\textsubscript{3}Cl, to make our claim stronger.

Supplementary Fig. 9, the energies from the original FI-NN and modified PESs are basically the same, and they are all well reproduced by CAM-XYG3/AVTZ(-PP) calculations. The E2 scattering events were no longer found in QCT calculations on the modified PES, indicating the E2 channel is completely blocked. As a result, the impose of Eq. (2) on the FI-NN PES leads to a modified PES, which does not change the full-dimensional PES of SN\textsubscript{2} or the behavior of all 39 degrees of freedom of SN\textsubscript{2}, but completely blocks the E2 pathway.

Cross sections of SN\textsubscript{2} and E2

The computed integral cross sections for the E2 and SN\textsubscript{2} pathways on the FI-NN PES as well as on the modified PES are shown in Fig. 5. The SN\textsubscript{2} reactivity is roughly 50 times smaller than the E2 reactivity on the FI-NN PES, but the situation changes dramatically on the modified PES. It is surprising that the SN\textsubscript{2} reactivity rises to almost the same magnitude as the original E2 reaction, after the E2 channel was completely blocked on the modified PES, which reflects that those trajectories that intended to proceed via the E2 pathway now go to the SN\textsubscript{2} pathway instead, due to a shared pre-reaction minimum. This fact is in contradiction with the assumption that the steric hindrance suppresses the SN\textsubscript{2} reactivity since the steric effect on α-C associated with SN\textsubscript{2} remains unchanged after modifying the PES. Further analysis shows the SN\textsubscript{2} reaction proceeds via the direct or indirect backside attack mechanism. The direct mechanism rises with the increase of collision energy. It is evident that the rather small reactivity of SN\textsubscript{2} for the title reaction is due to the inevitable competition with the highly reactive E2 pathway, but not the steric hindrance. Animations of typical indirect and direct SN\textsubscript{2} trajectories are given in Supplementary Movies 5, 6.

It is also important to compare the “intrinsic” SN\textsubscript{2} reactivity of F\textsuperscript{−}+(CH\textsubscript{3})\textsubscript{3}Cl with that of F\textsuperscript{−}+CH\textsubscript{3}I. Supplementary Fig. 10 shows the cross sections of F\textsuperscript{−}+(CH\textsubscript{3})\textsubscript{3}Cl on the modified PES and those of F\textsuperscript{−}+CH\textsubscript{3}I on the PES developed by ref. 5 as well as on another PES developed by us. The cross sections of F\textsuperscript{−}+CH\textsubscript{3}I on two different PESs are consistent, indicating both the two PESs are sufficiently accurate. It is interesting that the “intrinsic” SN\textsubscript{2} reactivity of (CH\textsubscript{3})\textsubscript{3}Cl is even larger than that of CH\textsubscript{3}I, probably due to the more exothermic energy of (CH\textsubscript{3})\textsubscript{3}Cl. These results unambiguously show the SN\textsubscript{2} reactivity doesn’t decrease as the substrate becomes bulkier, which is also evidence of steric hindrance failure.

PES and dynamics for Cl\textsuperscript{−}+(CH\textsubscript{3})\textsubscript{3}Cl

In addition to the title F\textsuperscript{−}+(CH\textsubscript{3})\textsubscript{3}Cl reaction, we investigated one more reaction, Cl\textsuperscript{−}+(CH\textsubscript{3})\textsubscript{3}Cl, to make our claim stronger.

Supplementary Fig. 11 shows the schematic of the PES, with important stationary-point geometries and energies illustrated. We can see a different minimum energy path of Cl\textsuperscript{−}+(CH\textsubscript{3})\textsubscript{3}Cl as compared with that of F\textsuperscript{−}+(CH\textsubscript{3})\textsubscript{3}Cl. For instance, the barriers are much higher, the pre-reaction and post-reaction wells are shallower, and the products are not that exothermic for the Cl\textsuperscript{−}+ (CH\textsubscript{3})\textsubscript{3}Cl reactant initially in the ground rovibrational state. A total of roughly 1.3 million trajectories were run. The computed integral cross sections for the E2 and SN\textsubscript{2} pathways on the new PES as well as on the modified PES are shown in Supplementary Fig. 12. The SN\textsubscript{2} cross section on the new PES is only four times smaller than that of E2, indicating the reactivities of the two pathways are in the same order of magnitude. This is understandable because the SN\textsubscript{2} pathway has a higher barrier, although it is more exothermic. After the E2 pathway was completely blocked on the modified PES, the SN\textsubscript{2} reactivity rises remarkably by about a factor of 2, which is about one-half of the E2 reactivity. Hence the "intrinsic" SN\textsubscript{2} reactivity is closely related to the competition of E2 for Cl\textsuperscript{−}+(CH\textsubscript{3})\textsubscript{3}Cl, but not the steric hindrance, as we concluded for F\textsuperscript{−}+(CH\textsubscript{3})\textsubscript{3}Cl.

Discussion

Regarding the high reactivity of the E2 pathway, there are 9 hydrogen atoms in three methyl groups (here the bulk for the title reaction), either of which can react with the attacking F. If the bulk consists of non-reactive groups, just as we want to demonstrate a similar way in this work by blocking the E2 pathway but maintaining the existence of bulk, the incoming F can attack the α-carbon easily, and the SN\textsubscript{2} reactivity can reach very high. As a result, the nearly vanish of the SN\textsubscript{2} reactivity is not due to the steric congestion of the bulk, but the high reactivity of the bulk, which consumes all incoming F. In other words,
if the E2 reactivity was not that high to consume all incoming F−, one would observe the SN2 reactivity comparable to E2.

To summarize, we have unraveled the dynamical origin of the very small S2r reactivity in the gas-phase F− + C4H9I reaction, by developing an accurate 39-dimensional PES and performing QCT simulations based on this global PES. The experimental angular and translational energy distributions are well reproduced. To the best of our knowledge, this is the first time the dynamics simulations based on a reliable full-dimensional PES can yield accurate dynamics information for a reactive system with up to 15 atoms. As opposed to the textbook example of the steric retardation of S2r reactivity by bulky substitution, it was found that the suppression of S2r for the prototype F− + C4H9I reaction results from the high reactivity of the three methyl groups, i.e., E2 pathway. With the aid of current analytical PES, we verify that in the absence of E2 competition, the “intrinsic” reactivity of S2r can reach that high even though there exists steric congestion. Our work might provide a possible way to raise the S2r reactivity by suppressing the reactivity of the competing pathway rather than changing the steric environment of S2r in physical organic chemistry.

For the F− + (CH3)3Cl gas-phase reaction, the transition states are much lower than reactants, i.e., submerged barrier. The reason why the reactions almost proceed to S2r when E2 is blocked is because the pre-reaction complex well is deep, thus crossing the S2r transition state to form S2r products is much easier than dissociating back to reactants, especially at low collision energies. For the gas-phase Cl− + (CH3)3Cl, the transition state of S2r is about 0.23 eV higher than reactants and the pre-reaction complex well is not as deep, hence some fractions of reaction would dissociate back to reactants and some would proceed to S2r when E2 is blocked. We expect a similar scenario in other gas-phase S2r/E2 competitive reactions, whose transition states are much higher than reactants.

Methods

Potential energy surface

The full-dimensional PES for the F− + C4H9I reaction was developed by the FI-NN fitting approach based on a total of roughly 220,000 CAM-B3LYP/AVTZ(pp) energy points. Because the configuration space of the investigated system is very large, we employed the space partitioning and energy splitting methods to overcome the huge difficulties of fitting all the data points. The overall fitting error is only 8.3 meV, measured in terms of root mean square error, indicating the PES is highly accurate. The theoretical and computational approaches used for Cl− + (CH3)3Cl are basically the same as those for F− + (CH3)3Cl. A full-dimensional PES of Cl− + (CH3)3Cl was developed by FI-NN fitting to about 270,000 data points. The overall fitting error of the fitted Cl− + (CH3)3Cl PES is 18.7 meV. In addition, a new computational approach was developed to produce the analytical gradients of the FI-NN PES, which facilitates efficient and accurate dynamics simulations.

QCT calculations

Standard QCT calculations for the F− + (CH3)3Cl reaction were carried out at collision energies ranging from 0.2 to 1.9 eV on the FI-NN PES, for the (CH3)3Cl reactant initially in the ground rovibrational state. We randomly sampled the normal coordinates and momenta to get the initial coordinates and momenta of (CH3)3Cl. Adjustments were then made to the momenta to force the angular momentum of (CH3)3Cl to zero. All trajectories were run using the Velocity-Verlet integration algorithm with a time step of 0.024 fs for a maximum time of 25 ps. We terminated the trajectory when any two fragments reach a separation of 30 Bohr, ending up with the formation of (CH3)3C=CH2 + HF + I− or (CH3)3CF + I− or returning to the reactants. A total of roughly 4.2 million trajectories were run to obtain the detailed dynamical information of the product Γ at each collision energy.

Data availability

The data presented in the analysis can be reproduced using code which is available from the corresponding author on reasonable request.

Code availability

The code used for the analysis in the current study is available from the corresponding author on reasonable request.

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Author contributions
D.H.Z. and B.F. conceived and supervised the research; X.L., L.L., C.S., and R.C. performed the research; X.L., L.L., B.F., X.X., and D.H.Z. analyzed the data; and B.F. and D.H.Z. wrote the manuscript.

Competing interests
The authors declare no competing interests.

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