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Rethinking the $X^- + CH_3Y$ [$X = OH, SH, CN, NH_2, PH_2$; $Y = F, Cl, Br, I$] S_N2 reactions†

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Moving beyond the textbook mechanisms of bimolecular nucleophilic substitution (S_N2) reactions, we characterize several novel stationary points and pathways for the reactions of X^- [$X = OH, SH, CN, NH_2, PH_2$] nucleophiles with CH_3Y [$Y = F, Cl, Br, I$] molecules using the high-level explicitly-correlated CCSD(T)-F12b method with the aug-cc-pVnZ(-PP) [$n = D, T, Q$] basis sets. Besides the not-always-existing traditional pre- and post-reaction ion-dipole complexes, $X^- \cdots H_3CY$ and $XCH_3 \cdots Y^-$, and the Walden-inversion transition state, $[X-CH_3-Y]^-$, we find hydrogen-bonded $X^- \cdots HCH_2Y$ ($X = OH, CN, NH_2$; $Y \neq F$) and front-side $H_3CY \cdots X^-$ ($Y \neq F$) complexes in the entrance and hydrogen-bonded $XH_2CH \cdots Y^-$ ($X = SH, CN, PH_2$) and $H_3CX \cdots Y^-$ ($X = OH, SH, NH_2$) complexes in the exit channels depending on the nucleophile and leaving group as indicated in parentheses. Retention pathways via either a high-energy front-side attack barrier, $XYCH_3^-$, or a novel double-inversion transition state, $XH \cdots CH_2Y^-$, having lower energy for $X = OH, CN, NH_2$ and becoming submerged (barrier-less) for $X = OH$ and $Y = I$ as well as $X = NH_2$ and $Y = Cl, Br, and I$, are also investigated.

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1. Introduction

Since the discovery of an optical inversion in a chemical reaction by Paul Walden in 1896,¹ bimolecular nucleophilic substitution (S_N2) has become a widely known reaction class in organic chemistry. The atomic-level mechanisms of S_N2 reactions were already described in the 1930s by Ingold and co-workers.² The traditional S_N2 Walden-inversion pathway goes through a double-well potential featuring ion-dipole complexes in the entrance- and exit-channel wells separated by a central transition state (first-order saddle point). In a typical S_N2 reaction $X^- + CH_3Y$, the nucleophile (X^-) attacks the back side (methyl side) of the CH_3Y molecule and while a new X-C bond forms and the C-Y bond breaks an umbrella motion of the H atoms inverts the configuration around the carbon center. The above-described Walden-inversion mechanism of S_N2 reactions has become textbook material and is probably the best-known stereo-specific reaction pathway in chemistry. However, in 2016 Xie and Hase³ published a perspective article “rethinking the S_N2 reaction”, because “the gas-phase dynamics of a paradigm organic reaction are more complex than expected”. This statement on the complexity of S_N2 reactions was based on

recent experimental and theoretical findings revealing several novel and unexpected reaction mechanisms for these paradigm systems.^{4–9} For example, S_N2 reactions can proceed with direct rebound, stripping, and front-side attack mechanisms as well as *via* indirect ion-dipole, hydrogen-bond, and front-side complex forming, roundabout,⁴ and double-inversion⁷ pathways.³ Among the above mechanisms front-side attack is a retention pathway, which proceeds *via* a high-energy $XYCH_3^-$ -like transition state with X-C-Y angle of around 80°. ¹⁰ This front-side attack retention pathway has been known from the early 1930s;² however, a quantitative description of the front-side attack dynamics was just recently achieved in our group utilizing newly developed analytical *ab initio* potential energy surfaces.^{7,11,12} Furthermore, our reaction dynamics simulations on these analytical potentials revealed a new retention mechanism called double inversion,⁷ where a proton-abstraction induced inversion (first inversion) is followed by a Walden inversion (second inversion) resulting in retention of the initial configuration. The non-traditional front-side complex ($H_3CY \cdots X^-$) formation was also quantitatively characterized by our trajectory simulations¹³ motivated by the joint work with the experimental group of Wester and co-workers.⁸ Another non-traditional pre-reaction complex stabilized by a hydrogen-bond between X^- and the methyl group of CH_3Y was also found first by Hase and co-workers¹⁴ and later in our theoretical studies.^{7,11,12,15}

In the present work we focus on “rethinking” the gas-phase $X^- + CH_3Y$ [$X = OH, SH, CN, NH_2, PH_2$; $Y = F, Cl, Br, I$] S_N2 reactions using high-level *ab initio* methods. Among the 20 possible fundamental S_N2 reactions with the above-defined 5 different nucleophiles (X^-) and 4 leaving groups (Y), there are

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only a few which were studied previously in the gas^{16–24} and/or condensed^{25–29} phases, and almost none of them in view of the recent non-traditional mechanisms. Focusing on the gas-phase studies, in the case of Y = F Gonzales *et al.*^{16,17} characterized 3 stationary points, *i.e.*, pre- and post-reaction complexes and a Walden-inversion transition state, for each reaction; however, front-side complex formation, a front-side attack transition state, and double inversion were not investigated, partially due to the fact that some of these were not known at that time. For OH[−] + CH₃F Hase and co-workers^{18,19} described the same 3 stationary points as Gonzales *et al.*^{16,17} and reported interesting direct dynamics results showing that trajectories usually avoid the deep post-reaction minimum.¹⁸ Considering ligands other than Y = F, Tachikawa and co-workers²⁰ investigated again 3 stationary points for the OH[−] + CH₃Cl reaction and recently Wester and co-workers²¹ reported crossed-beam experiments for the CN[−] + CH₃I system and characterized 3 stationary points for each of the C–C and C–N bond forming S_N2 reactions. In the case of X = OH and SH, the X[−] + CH₃Y [Y = F, Cl, Br] reactions were investigated by Longo and co-workers²² reporting again 3 stationary points for each system. Perhaps the most thoroughly studied reaction is OH[−] + CH₃I, for which H-bonded and front-side complex formation were studied in the Hase group²⁴ and experiments were performed in the groups of Viggiano²³ and Wester.²⁴ In 2018 we reported a high-level *ab initio* study on the OH[−] + CH₃Y [Y = F, Cl, Br, I] S_N2 reactions applying core- and post-CCSD(T) correlation corrections, which are usually neglected in the literature, and revealing many stationary points involving H-bonded and front-side complexes as well as front-side attack and double-inversion transition states.³⁰ In the present work we extend our previous studies^{9,30} considering SH[−], CN[−], NH₂[−], and PH₂[−] nucleophiles besides OH[−], which is described again for completeness and comparison. For the first time for X = SH, CN, NH₂, and PH₂ we use the high-level modern explicitly-correlated CCSD(T)-F12b method³¹ to obtain benchmark structures and relative energies for the stationary points. However, instead of presenting technical details of a high-level electronic structure study, the present work aims to provide new qualitative insights into the reaction pathways of 20 different S_N2 reactions, showing that these systems “are more complex than expected”,³ supporting the views of the above-mentioned “rethinking” perspective article.³

II. Computational details

The energies, geometries, and harmonic vibrational frequencies of the stationary points are computed using second-order Møller–Plesset perturbation theory³² (MP2) with the correlation-consistent aug-cc-pVDZ basis set³³ and the explicitly correlated coupled cluster singles, doubles, and perturbative triples CCSD(T)-F12b method³¹ with the aug-cc-pVDZ and the aug-cc-pVTZ basis sets.³³ To obtain the benchmark classical relative energies at the CCSD(T)-F12b/aug-cc-pVTZ geometries single-point computations are performed using the CCSD(T)-F12b method with the quadruple- ζ aug-cc-pVQZ basis set.³³ For bromine

and iodine relativistic small-core effective core potentials³⁴ and the corresponding pseudo-potential basis sets³⁴ are employed.

The benchmark adiabatic relative energies are determined as:

$$\Delta E[\text{CCSD(T)-F12b/aug-cc-pVQZ}] + \Delta \text{ZPE}[\text{CCSD(T)-F12b/aug-cc-pVTZ}] \quad (1)$$

where ΔE is the benchmark classical relative energy and ΔZPE is the harmonic zero-point energy correction. Note that if the CCSD(T)-F12b/aug-cc-pVTZ or the CCSD(T)-F12b/aug-cc-pVDZ geometry optimizations do not converge the CCSD(T)-F12b/aug-cc-pVDZ or the MP2/aug-cc-pVDZ structures are utilized, respectively.

All the structural parameters, harmonic frequencies, absolute energies, and relative energies can be found in the ESI.† For the best stationary-point geometries Cartesian coordinates are also given in the ESI.† in a software-friendly format. We note that in the case of some minima small artificial imaginary frequencies (<100i cm^{−1}) are found most likely due to the uncertainty of the numerical gradient and/or Hessian computations. For the present *ab initio* study the Molpro program package³⁵ is used.

III. Results and discussion

OH[−] + CH₃Y [Y = F, Cl, Br, I]

The OH[−] + CH₃Y [Y = F, Cl, Br, I] S_N2 reactions are exothermic and may proceed *via* back-side attack inversion, front-side attack retention, or double-inversion retention pathways as shown in Fig. 1. Back-side attack is a collective name for several direct and indirect inversion mechanisms such as rebound, stripping, ion-dipole complex formation, hydrogen-bond complex formation, front-side complex formation, and roundabout. The traditional picture says that back-side attack Walden inversion proceeds *via* a pre-reaction ion-dipole complex (PreMIN), a Walden-inversion transition state (WaldenTS), and a post-reaction ion-dipole complex HOCH₃⋯Y[−]. However, instead of the traditional HOCH₃⋯Y[−] complex, Y[−] connects to the OH group with a single hydrogen bond forming a PostHMIN complex for all the four leaving groups, as shown in Fig. 1. Thus, Walden inversion of OH[−] + CH₃F proceeds as PreMIN → WaldenTS → PostHMIN. (Note that besides PostHMIN a hydrogen-bonded F[−]⋯HCH₂OH complex also exists, which is not shown in Fig. 1, but presented in the ESI.†) This is not the end of the nontraditional mechanisms, because for Y = Cl, Br, and I a hydrogen-bonded pre-reaction complex (HMIN), where OH[−] connects to one of the H atoms of the methyl group, and a transition state (HTS) connecting HMIN and PreMIN come into play, where HMIN is below PreMIN by about 2 kcal mol^{−1}. In the case of Y = Cl and Br, OH[−] + CH₃Y Walden inversion occurs *via* HMIN → HTS → PreMIN → WaldenTS → PostHMIN. However, for Y = I the traditional PreMIN and WaldenTS do not exist and the OH[−] + CH₃I inversion proceeds as HMIN → HTS → PostHMIN. Furthermore, for Y = Cl, Br, and I a front-side complex (FSMIN), where OH[−] connects to Y, can also be found, which in the case of Y = I is actually a significantly deeper minimum than HMIN, suggesting a steering effect into a nonreactive orientation,



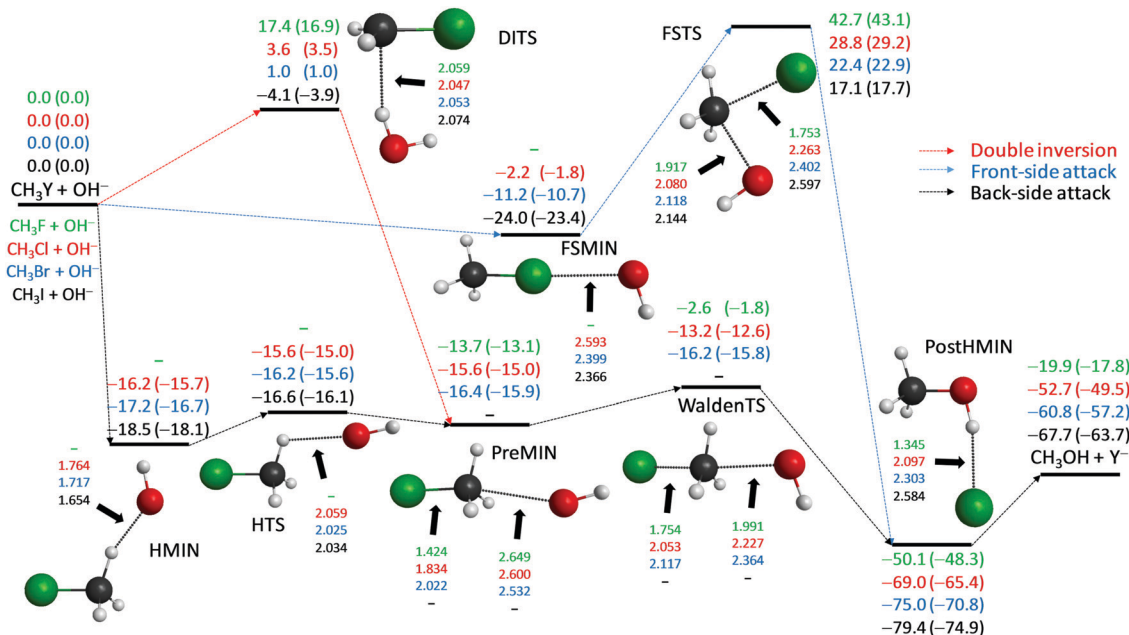


Fig. 1 Schematic potential energy surfaces of the $\text{OH}^- + \text{CH}_3\text{Y}$ [$\text{Y} = \text{F, Cl, Br, I}$] $\text{S}_{\text{N}}2$ reactions showing the classical (adiabatic) CCSD(T)-F12b/aug-cc-pVQZ (+ ΔZPE [CCSD(T)-F12b/aug-cc-pVTZ]) relative energies, in kcal mol⁻¹, and the most important CCSD(T)-F12b/aug-cc-pVTZ structural parameters, in Å, of the stationary points along the different reaction pathways. For core and post-CCSD(T) correlation corrected energies and their comparison with experimental reaction enthalpies see ref. 30.

thereby making the $\text{OH}^- + \text{CH}_3\text{I}$ reaction indirect as previous experiments^{5,8} and our dynamics simulations¹³ suggested for $\text{F}^- + \text{CH}_3\text{I}$. Unlike back-side attack inversion which has submerged stationary points, front-side attack retention proceeds *via* a high-energy transition state (FSTS) with adiabatic barrier heights of 43.1 (F), 29.2 (Cl), 22.9 (Br), and 17.7 (I) kcal mol⁻¹, whereas the corresponding double-inversion transition state (DITS) barrier heights are only 16.9 (F), 3.5 (Cl), 1.0 (Br), and -3.9 (I) kcal mol⁻¹. Thus, double inversion opens a barrier-less retention pathway for the $\text{OH}^- + \text{CH}_3\text{I}$ $\text{S}_{\text{N}}2$ reaction.

$\text{SH}^- + \text{CH}_3\text{Y}$ [$\text{Y} = \text{F, Cl, Br, I}$]

If we replace the OH^- nucleophile with SH^- , the $\text{S}_{\text{N}}2$ reactions become less exothermic and, moreover, endothermic for $\text{Y} = \text{F}$, as shown in Fig. 2. Unlike OH^- , SH^- does not form a hydrogen-bonded pre-reaction complex, except for $\text{Y} = \text{I}$ as shown in the ESI,[†] and the back-side attack inversion pathway proceeds as PreMIN \rightarrow WaldenTS \rightarrow PostHMIN. The WaldenTSs are below the reactants by 1.4, 6.0, and 8.5 kcal mol⁻¹, for $\text{Y} = \text{Cl, Br, and I}$, respectively, whereas the $\text{SH}^- + \text{CH}_3\text{F}$ $\text{S}_{\text{N}}2$ reaction has a positive adiabatic barrier height of 13.7 kcal mol⁻¹. Similar to the reactions of OH^- , the global minimum of the potential energy surfaces of the $\text{SH}^- + \text{CH}_3\text{Y}$ systems is PostHMIN, but in the present case $\text{Y}^- \cdots \text{HC}$ bonded (PostHMIN2) and traditional ion-dipole post-reaction (WaldenPostMIN) complexes are also found with similar energies within 1 kcal mol⁻¹ and above POSTHMIN by a few kcal mol⁻¹, except for $\text{Y} = \text{F}$, where PostHMIN2 is just slightly bonded and WaldenPostMIN does not exist, as shown in Fig. 2. The dissociation energies of the PostHMIN complexes are around 10 kcal mol⁻¹ for $\text{Y} = \text{Cl, Br}$,

and I, whereas much larger, about 38 kcal mol⁻¹, for $\text{Y} = \text{F}$. In the case of $\text{X} = \text{OH}$, the $\text{Y} = \text{Cl, Br, and I}$ PostHMIN complexes are more stable by a few kcal mol⁻¹, however, the $\text{Y} = \text{F}$ complex has a dissociation energy of only about 30 kcal mol⁻¹. These energy trends are in accord with the $\text{Y}^- \cdots \text{HX}$ distances, as these are slightly longer for $\text{X} = \text{SH}$ than OH if $\text{Y} = \text{Cl, Br, and I}$, whereas the $\text{F}^- \cdots \text{HS}$ distance (0.985 Å) is significantly shorter than the $\text{F}^- \cdots \text{HO}$ distance (1.345 Å) as shown in Fig. 1 and 2. Similar to the $\text{OH}^- + \text{CH}_3\text{Y}$ [$\text{Y} = \text{Cl, Br, I}$] reactions, FSMIN complexes are also found for $\text{X} = \text{SH}$ systems, but with longer $\text{Y}^- \cdots \text{X}^-$ distances and consequently with less stability. Here the $\text{H}_3\text{Cl} \cdots \text{SH}^-$ complex is just similarly stable to PreMIN, whereas FSMIN is a significantly deeper minimum than PREMIN in the case of the OH^- complex. We find qualitatively similar DITS and FSTS structures for the reactions of OH^- and SH^- , with significantly higher barrier heights for SH^- . Furthermore, unlike in the case of the OH^- systems, the DITSs of the SH^- nucleophile are always above the corresponding FSTSs.

$\text{CN}^- + \text{CH}_3\text{Y}$ [$\text{Y} = \text{F, Cl, Br, I}$]

The CN^- nucleophile can form either a C-C or a C-N bond in the $\text{S}_{\text{N}}2$ reactions with the CH_3Y molecules. In the present work we study the energetically favored, more exothermic C-C bond formation channel leading to $\text{Y}^- + \text{CH}_3\text{CN}$ products. The $\text{CN}^- + \text{CH}_3\text{Y}$ reactions are more and less exothermic than the corresponding SH^- and OH^- reactions, respectively. Since the CN ligand does not have a hydrogen atom, PostHMIN-type post-reaction complexes do not exist. Here the global minimum is either a traditional ion-dipole WaldenPostMIN (C_{3v} symmetry) or a hydrogen-bonded PostHMIN2 (C_s symmetry) complex,



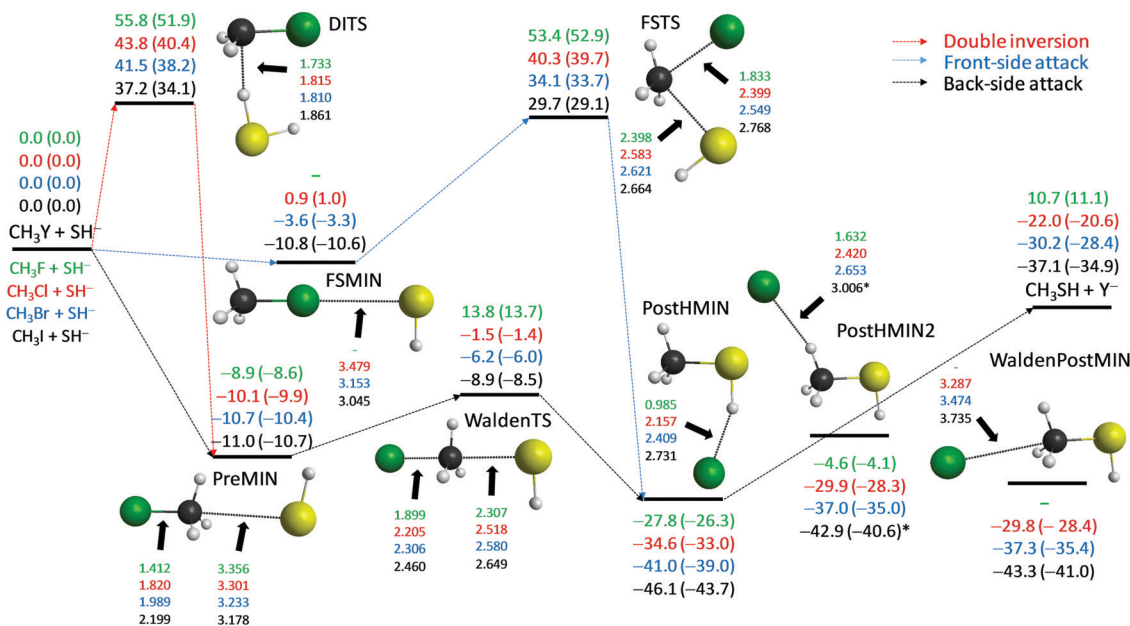


Fig. 2 Schematic potential energy surfaces of the $\text{SH}^- + \text{CH}_3\text{Y}$ [Y = F, Cl, Br, I] $\text{S}_{\text{N}}2$ reactions showing the classical (adiabatic) CCSD(T)-F12b/aug-cc-pVQZ (+ ΔZPE [CCSD(T)-F12b/aug-cc-pVTZ]) relative energies, in kcal mol^{-1} , and the most important CCSD(T)-F12b/aug-cc-pVTZ structural parameters, in Å, of the stationary points along the different reaction pathways. Results indexed by * correspond to CCSD(T)-F12b/aug-cc-pVDZ structures.

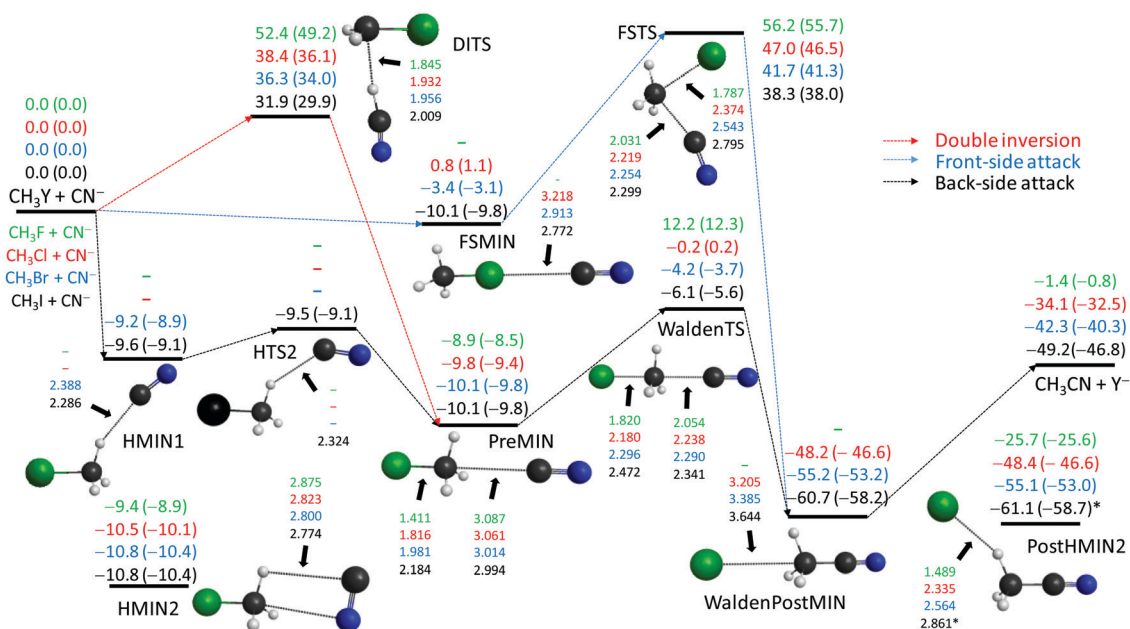


Fig. 3 Schematic potential energy surfaces of the $\text{CN}^- + \text{CH}_3\text{Y}$ [Y = F, Cl, Br, I] $\text{S}_{\text{N}}2$ reactions showing the classical (adiabatic) CCSD(T)-F12b/aug-cc-pVQZ (+ ΔZPE [CCSD(T)-F12b/aug-cc-pVTZ]) relative energies, in kcal mol^{-1} , and the most important CCSD(T)-F12b/aug-cc-pVTZ structural parameters, in Å, of the stationary points along the different reaction pathways. Results indexed by * correspond to MP2/aug-cc-pVDZ structures.

whose energies agree within 1 kcal mol^{-1} as shown in Fig. 3. Note that for Y = F, only PostHMIN2 is found. Traditional PreMINs and WaldenTSs are found for all the four leaving groups and unlike in the case of OH^- and SH^- , these stationary points have C_{3v} symmetry with collinear Y-C-C-N arrangements. WaldenTSs are clearly submerged for Y = Br and I with classical (adiabatic) energies of -4.2 (-3.7) and -6.1 (-5.6) kcal mol^{-1} ,

respectively, relative to the reactants. For Y = Cl the barrier height is close to zero, *i.e.* -0.2 (0.2) kcal mol^{-1} , whereas for Y = F Walden inversion has a positive barrier of 12.2 (12.3) kcal mol^{-1} , similar to the $\text{SH}^- + \text{CH}_3\text{F}$ reaction. Besides the ion-dipole PreMIN complexes, we find hydrogen-bonded complexes (HMIN1) for Y = Br and I and a transition state connecting HMIN1 and PreMIN for Y = I as seen in Fig. 3. Unlike in the OH^- case, here HMIN1 is



slightly above PreMIN. Furthermore, for all the four $\text{CN}^- + \text{CH}_3\text{Y}$ systems we find pre-reaction complexes (HMIN2), where the C and N atoms of CN^- are connected to the H and C atoms of CH_3Y , respectively, as seen in Fig. 3. These HMIN2 complexes are slightly more stable than the PREMINS; thus, HMIN2 configurations are the deepest regions of the entrance channels. Similar to the OH^- and SH^- reactions, front-side FSMIN complexes are found for $\text{Y} = \text{Cl}$, Br , and I , but unlike in the former cases, the $\text{H}_3\text{CY} \cdots \text{CN}^-$ complexes have C_{3v} symmetry. In the $\text{Y} = \text{I}$ case the depth of FSMIN is similar, $10 \pm 1 \text{ kcal mol}^{-1}$, to the other minima in the entrance channel, whereas for $\text{Y} = \text{Br}$ the classical (adiabatic) FSMIN depth is only 3.4 (3.1) kcal mol^{-1} . For $\text{Y} = \text{Cl}$ FSMIN is unbonded, with an energy slightly above the reactant asymptote. The retention pathways have large barriers between 30 and 60 kcal mol^{-1} depending on the leaving group. Similar to the $\text{OH}^- + \text{CH}_3\text{Y}$ systems, DITSS are always below the corresponding FSTSS, but whereas the $\text{OH}^- + \text{CH}_3\text{I}$ reaction has a negative double-inversion barrier, the classical (adiabatic) barrier height of the $\text{CN}^- + \text{CH}_3\text{I}$ reaction is 31.9 (29.9) kcal mol^{-1} .

$\text{NH}_2^- + \text{CH}_3\text{Y}$ [$\text{Y} = \text{F}, \text{Cl}, \text{Br}, \text{I}$]

The $\text{S}_{\text{N}}2$ reactions of NH_2^- with CH_3Y are the most exothermic among the systems studied in this work; the enthalpies of the $\text{NH}_2^- + \text{CH}_3\text{Y}$ reactions are more negative by 15–20 kcal mol^{-1} than those of the corresponding, also highly exothermic $\text{OH}^- + \text{CH}_3\text{Y}$ processes. Similar to the reactions of OH^- , the global minima of the $\text{NH}_2^- + \text{CH}_3\text{Y}$ potential energy surfaces correspond to PostHMIN complexes, where Y^- is connected to the NH_2 group of CH_3NH_2 with a single hydrogen bond as seen in Fig. 4. The D_e (D_0) dissociation energies of the $\text{CH}_3\text{NH}_2 \cdots \text{Y}^-$ complexes are 18.2 (17.9), 10.0 (9.5), 8.7 (8.3), and 7.3 (7.0) kcal mol^{-1}

for $\text{Y} = \text{F}, \text{Cl}, \text{Br}$, and I , respectively, whereas the corresponding D_e (D_0) values of $\text{CH}_3\text{OH} \cdots \text{Y}^-$ are 30.2 (30.5), 16.3 (15.9), 14.2 (13.6), and 11.7 (11.2) kcal mol^{-1} , in order. The lower stability of the $\text{CH}_3\text{NH}_2 \cdots \text{Y}^-$ complexes is in accord with the longer $\text{NH} \cdots \text{Y}^-$ bond lengths of 1.579 (F), 2.330 (Cl), 2.539 (Br), and 2.826 (I) Å with respect to the corresponding 1.345 (F), 2.097 (Cl), 2.303 (Br), and 2.584 (I) Å values of the OH systems. The back-side attack $\text{NH}_2^- + \text{CH}_3\text{F}$ $\text{S}_{\text{N}}2$ reaction proceeds *via* the PreMIN \rightarrow WaldenTS \rightarrow PostHMIN inversion pathway featuring a slightly submerged transition state with a classical (adiabatic) energy of -3.0 (-1.9) kcal mol^{-1} relative to the reactants. For $\text{Y} = \text{Cl}$ a hydrogen-bonded pre-reaction complex (HMIN) is also found with similar energy, around $-14 \text{ kcal mol}^{-1}$, to that of PreMIN and WaldenTS is at -12.8 (-12.1) kcal mol^{-1} . In the case of $\text{Y} = \text{Br}$ we could not find a WaldenTS, and HMIN is deeper than PreMIN by about 1 kcal mol^{-1} . For $\text{Y} = \text{I}$ neither a traditional PreMIN nor WaldenTS is found, but HMIN and a pre-reaction transition state (PreTS) exist as seen in Fig. 4. The submerged PreTS with a classical (adiabatic) energy of -15.6 (-15.2) kcal mol^{-1} relative to the reactants differs from WaldenTS in the orientation of the NH_2 unit and the relative stretching of the C–Y distance, because C–F and C–Cl WaldenTS distances are stretched by 0.324 and 0.220 Å relative to the corresponding bond lengths of the CH_3Y molecule, whereas the C–I PreTS distance is just longer by 0.107 Å than the same bond in CH_3I . Therefore, PreTS may be viewed as an early WaldenTS. As always front-side complexes are found for $\text{Y} = \text{Cl}, \text{Br}$, and I with D_e (D_0) dissociation energies of 1.7 (1.1), 12.5 (11.5), and 25.8 (24.4) kcal mol^{-1} , respectively. Thus, the stability of the front-side complex is negligible for $\text{Y} = \text{F}$, comparable to that of HMIN in the case of $\text{Y} = \text{Br}$, and

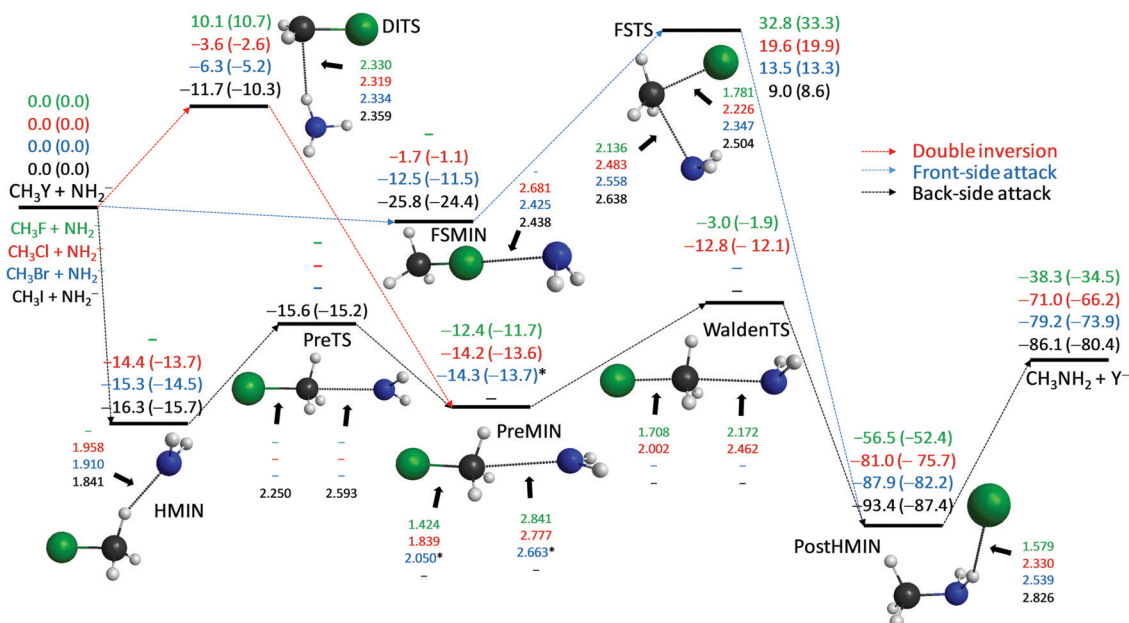


Fig. 4 Schematic potential energy surfaces of the $\text{NH}_2^- + \text{CH}_3\text{Y}$ [$\text{Y} = \text{F}, \text{Cl}, \text{Br}, \text{I}$] $\text{S}_{\text{N}}2$ reactions showing the classical (adiabatic) CCSD(T)-F12b/aug-cc-pVQZ (+ ΔZ PE[CCSD(T)-F12b/aug-cc-pVTZ]) relative energies, in kcal mol^{-1} , and the most important CCSD(T)-F12b/aug-cc-pVTZ structural parameters, in Å, of the stationary points along the different reaction pathways. Results indexed by * correspond to MP2/aug-cc-pVDZ structures. "Experimental" 0 K reaction enthalpies, with $\pm 0.1 \text{ kcal mol}^{-1}$ uncertainties, are -34.7 , -66.1 , -73.7 , and $-79.9 \text{ kcal mol}^{-1}$ for $\text{Y} = \text{F}, \text{Cl}, \text{Br}$, and I , respectively.³⁶



significantly stronger than that of HMIN for $Y = I$. Note that $H_3CI \cdots NH_2^-$ is the most strongly bonded front-side complex investigated in the present study. The retention pathways of the title reactions are the most favored in the case of the NH_2^- nucleophile. All the DITS and FSTS barrier heights are below the corresponding, also favorable, OH^- barriers by about 10 kcal mol^{-1} . Furthermore, all the DITS barriers are below the corresponding FSTS ones by about 20 kcal mol^{-1} ; thus, double inversion opens a significantly lower energy retention pathway compared to the more traditional front-side attack. Moreover, for $Y = Cl, Br,$ and I double inversion has negative classical (adiabatic) barrier heights of -3.6 (-2.6), -6.3 (-5.2), and -11.7 (-10.3) kcal mol^{-1} , respectively, opening retention pathways which may become competitive with inversion especially for the iodine leaving group.

$PH_2^- + CH_3Y$ [$Y = F, Cl, Br, I$]

The $PH_2^- + CH_3Y$ reactions are less exothermic than the analogous $NH_2^- + CH_3Y$ systems due to the weaker C-P bonds compared to the binding energy of a C-N bond. For the reactions of PH_2^- we find a PostHMIN complex only for $Y = F$; however, its structure differs from the geometry of the PostHMIN complexes of the other nucleophiles. Here, the P...H distance is significantly stretched, whereas the F-H distance is close to the bond length in the HF molecule; thus, this PostHMIN is better viewed as a post-reaction proton-abstraction (proton transfer from the PH_2 group to F^-) complex. For all the four leaving groups we find hydrogen-bonded complexes in the exit channel (PostHMIN2), where Y^- connects to one of the H atoms of the methyl group as seen in Fig. 5. Note that the proton-abstraction-like PostHMIN, found for $Y = F$, is a deeper minimum

than PostHMIN2, but the enthalpy of the $HF + CH_3PH^-$ channel ($-8.4 \text{ kcal mol}^{-1}$) is less exothermic than that corresponding to the $F^- + CH_3PH_2$ S_N2 products ($-10.3 \text{ kcal mol}^{-1}$). A traditional ion-dipole complex (WaldenPostMIN) is only found for $Y = Br$, but with slightly less stability than the corresponding PostHMIN2. In the entrance channel hydrogen-bonded complexes are not found unlike for the analogous NH_2^- reactions. For $Y = F, Cl,$ and Br traditional ion-dipole complexes (PreMIN) and WaldenTSs are found as shown in Fig. 5. Note that in the $Y = F$ case the Walden-inversion pathway has a positive classical (adiabatic) barrier of 9.7 (9.8) kcal mol^{-1} , whereas WaldenTSs are submerged for $Y = Cl$ and Br . For $Y = Cl, Br,$ and I we find PreTSs similar to the $Y = I$ case of the NH_2^- reactions. For $Y = I$ PreTS is the only entrance-channel stationary point with a reactive orientation. Front-side complexes (FSMIN) are found for $Y = Cl, Br,$ and I , but in the case of $Y = Cl$ the stationary point has a slightly positive energy relative to the reactants. The $H_3CI \cdots PH_2^-$ complex has D_e (D_0) values of 13.8 (13.5) kcal mol^{-1} ; thus, this configuration is the global minimum of the entrance channel similarly to the OH^- and $NH_2^- + CH_3I$ reactions. The retention pathways of the $PH_2^- + CH_3Y$ reactions proceed *via* high barriers and, unlike in the OH^- and NH_2^- reactions, DITSs are slightly above the FSTSs similarly to the SH^- systems.

IV. Summary and conclusions

Motivated by a recent perspective article entitled "Rethinking the S_N2 reaction"³ and our previous findings about a novel double-inversion⁷ pathway and front-side complex formation,¹³ we have investigated the stationary points and possible reaction mechanisms of 20 different gas-phase S_N2 reactions involving

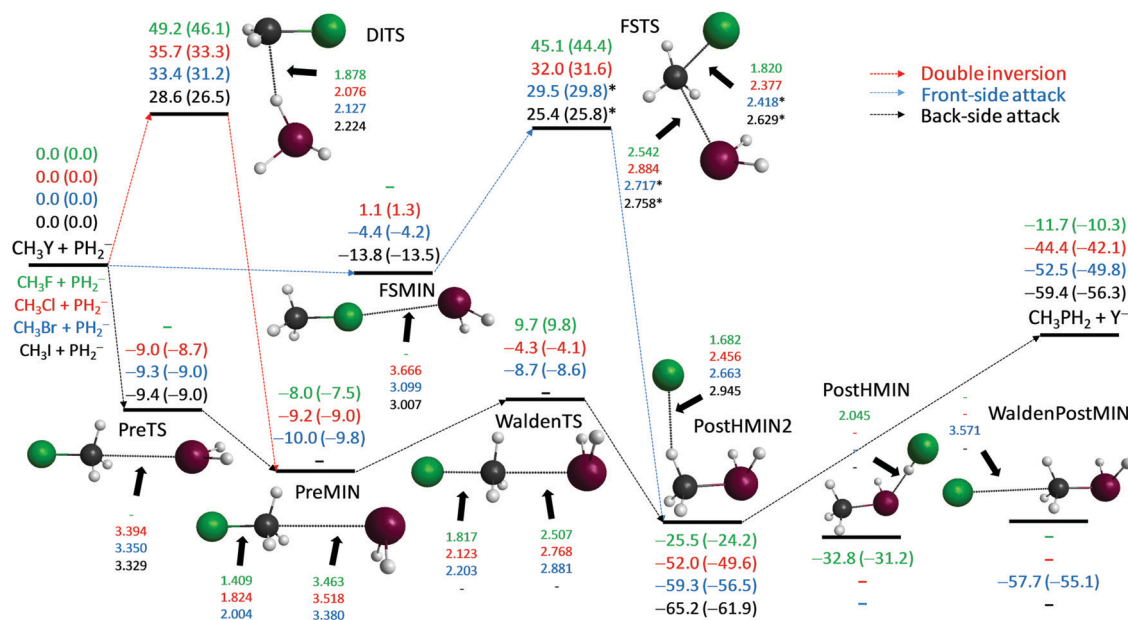


Fig. 5 Schematic potential energy surfaces of the $PH_2^- + CH_3Y$ [$Y = F, Cl, Br, I$] S_N2 reactions showing the classical (adiabatic) CCSD(T)-F12b/aug-cc-pVQZ (+ ΔZPE [CCSD(T)-F12b/aug-cc-pVTZ]) relative energies, in kcal mol^{-1} , and the most important CCSD(T)-F12b/aug-cc-pVTZ structural parameters, in \AA , of the stationary points along the different reaction pathways. Results indexed by * correspond to MP2/aug-cc-pVDZ structures.



OH^- , SH^- , CN^- , NH_2^- , and PH_2^- nucleophiles and methyl-halide molecules (CH_3Y , $\text{Y} = \text{F}, \text{Cl}, \text{Br}, \text{I}$). Previous work usually reported three stationary points, *i.e.*, pre- and post-reaction complexes and a central transition state, for some of these $\text{S}_{\text{N}}2$ systems. In the present comprehensive high-level explicitly-correlated *ab initio* study we reveal that these reactions are much more complex and many stationary points play a role in the dynamics. In the entrance channel, besides the traditional ion-dipole complex and Walden-inversion transition state, hydrogen-bonded and front-side complexes are found. Pre-reaction hydrogen-bond formation usually occurs between OH^- , CN^- , and NH_2^- nucleophiles and CH_3Y , where $\text{Y} = \text{Cl}, \text{Br}$, and I , and the hydrogen-bonded complex is more stable than the traditional ion-dipole complex for OH^- and NH_2^- . Front-side complexes, where the nucleophile connects to the leaving group, are found in all cases except $\text{Y} = \text{F}$. For $\text{X} = \text{OH}$, NH_2 , and PH_2 , the $\text{H}_3\text{C}\text{I} \cdots \text{X}^-$ complex is the deepest region in the entrance channel suggesting indirect dynamics, because the deep front-side minimum may steer the reactants into a non-reactive orientation. In the exit channel a hydrogen-bonded $\text{H}_3\text{CX} \cdots \text{Y}^-$ complex may be formed for $\text{X} = \text{OH}$, SH , and NH_2 , which is the global minimum of the potential energy surface. In the case of $\text{X} = \text{CN}$ and PH_2 , the Y^- rather forms a hydrogen bond with one of the H atoms of the methyl group or in some cases a traditional ion-dipole complex is also found. Besides the Walden-inversion mechanisms, we report, in most cases for the first time, front-side attack and double-inversion retention pathways for the title reactions. Front-side attack always has a positive, usually large, barrier, whereas the double-inversion barrier heights are below the front-side attack ones in the case of the OH^- , CN^- , and NH_2^- nucleophiles. Moreover, for the $\text{OH}^- + \text{CH}_3\text{I}$ and the $\text{NH}_2^- + \text{CH}_3\text{Y}$ [$\text{Y} = \text{Cl}, \text{Br}, \text{I}$] reactions the double-inversion transition state is submerged, thereby opening a barrier-less retention pathway for these $\text{S}_{\text{N}}2$ reactions. We hope that the present study motivates future experimental and theoretical investigations on the dynamics of the title reactions and shapes the way how we think about $\text{S}_{\text{N}}2$ reactions.

Conflicts of interest

There are no conflicts of interest to declare.

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References

- P. Walden, *Ber. Dtsch. Chem. Ges.*, 1896, **29**, 133.
- W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman and A. D. Scott, *J. Chem. Soc.*, 1937, 1252.
- J. Xie and W. L. Hase, *Science*, 2016, **352**, 32.
- J. Mikosch, S. Trippel, C. Eichhorn, R. Otto, U. Louderaj, J.-X. Zhang, W. L. Hase, M. Weidemüller and R. Wester, *Science*, 2008, **319**, 183.
- J. Mikosch, J. Zhang, S. Trippel, C. Eichhorn, R. Otto, R. Sun, W. A. de Jong, M. Weidemüller, W. L. Hase and R. Wester, *J. Am. Chem. Soc.*, 2013, **135**, 4250.
- J. Xie, R. Otto, J. Mikosch, J. Zhang, R. Wester and W. L. Hase, *Acc. Chem. Res.*, 2014, **47**, 2960.
- I. Szabó and G. Czakó, *Nat. Commun.*, 2015, **6**, 5972.
- M. Stei, E. Carrascosa, M. A. Kainz, A. H. Kelkar, J. Meyer, I. Szabó, G. Czakó and R. Wester, *Nat. Chem.*, 2016, **8**, 151.
- I. Szabó and G. Czakó, *J. Phys. Chem. A*, 2017, **121**, 9005.
- I. Szabó and G. Czakó, *J. Phys. Chem. A*, 2015, **119**, 3134.
- I. Szabó, H. Telekes and G. Czakó, *J. Chem. Phys.*, 2015, **142**, 244301.
- B. Olasz, I. Szabó and G. Czakó, *Chem. Sci.*, 2017, **8**, 3164.
- I. Szabó, B. Olasz and G. Czakó, *J. Phys. Chem. Lett.*, 2017, **8**, 2917.
- J. Zhang, J. Mikosch, S. Trippel, R. Otto, M. Weidemüller, R. Wester and W. L. Hase, *J. Phys. Chem. Lett.*, 2010, **1**, 2747.
- I. Szabó, A. G. Császár and G. Czakó, *Chem. Sci.*, 2013, **4**, 4362.
- J. M. Gonzales, R. S. Cox, S. T. Brown, W. D. Allen and H. F. Schaefer, *J. Phys. Chem. A*, 2001, **105**, 11327.
- J. M. Gonzales, C. Pak, R. S. Cox, W. D. Allen, H. F. Schaefer III, A. G. Császár and G. Tarczay, *Chem. – Eur. J.*, 2003, **9**, 2173.
- L. Sun, K. Song and W. L. Hase, *Science*, 2002, **296**, 875.
- L. Sun, K. Song, W. L. Hase, M. Sena and J. M. Riveros, *Int. J. Mass Spectrom.*, 2003, **227**, 315.
- H. Tachikawa, M. Igarashi and T. Ishibashi, *J. Phys. Chem. A*, 2002, **106**, 10977.
- E. Carrascosa, M. Bawart, M. Stei, F. Linden, F. Carelli, J. Meyer, W. D. Geppert, F. A. Gianturco and R. Wester, *J. Chem. Phys.*, 2015, **143**, 184309.
- Y. G. Proenza, M. A. F. de Souza and R. L. Longo, *Chem. – Eur. J.*, 2016, **22**, 16220.
- J. Xie, S. C. Kohale, W. L. Hase, S. G. Ard, J. J. Melko, N. S. Shuman and A. A. Viggiano, *J. Phys. Chem. A*, 2013, **117**, 14019.
- J. Xie, R. Sun, M. R. Siebert, R. Otto, R. Wester and W. L. Hase, *J. Phys. Chem. A*, 2013, **117**, 7162.
- J. Chen, Y. Xu and D. Wang, *J. Comput. Chem.*, 2014, **35**, 445.
- H. Yin, D. Wang and M. Valiev, *J. Phys. Chem. A*, 2011, **115**, 12047.
- Y. Xu, T. Wang and D. Wang, *J. Chem. Phys.*, 2012, **137**, 184501.
- Y. Xu., J. Zhang and D. Wang, *Phys. Chem. Chem. Phys.*, 2014, **16**, 19993.
- Y. Xu., J. Zhang and D. Wang, *J. Chem. Phys.*, 2015, **142**, 244505.
- D. A. Tasi, Z. Fábrián and G. Czakó, *J. Phys. Chem. A*, 2018, **122**, 5773.



- 31 T. B. Adler, G. Knizia and H.-J. Werner, *J. Chem. Phys.*, 2007, **127**, 221106.
- 32 C. Møller and M. S. Plesset, *Phys. Rev.*, 1934, **46**, 618.
- 33 T. H. Dunning Jr., *J. Chem. Phys.*, 1989, **90**, 1007.
- 34 K. A. Peterson, D. Figgen, E. Goll, H. Stoll and M. Dolg, *J. Chem. Phys.*, 2003, **119**, 11113.
- 35 H.-J. Werner, P. J. Knowles, G. Knizia, F. R. Manby, M. Schütz *et al.*, *Molpro, version 2015.1, a package of ab initio programs*, see <http://www.molpro.net>.
- 36 B. Ruscic and D. H. Bross, Active Thermochemical Tables (ATcT) values based on ver. 1.122d of the Thermochemical-Network (2018); available at ATcT.anl.gov.

