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Response to the Comment on “The Interplay between Steric and Electronic Effects in S_N2 Reactions”

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Abstract: Only by allowing full geometry optimization for all energy points along the reaction coordinates does it become possible to perform a meaningful analysis of the variation of the various energy terms during a chemical reaction. Great care should also be taken in the definitions of the energy terms, and only Pauli repulsion should be included in the steric interaction term.

Keywords: energy decomposition analysis · molecular modeling · nucleophilic substitution · reaction mechanisms · steric hindrance

We reply to the preceding Correspondence article in this issue by Zeist and Bickelhaupt,[1] in which the authors challenge the interpretation of the energy decomposition analysis (EDA)[2] that was applied by us in a recent study of the reaction course of S_N2 reactions.[3] Unlike previous work, in which the S_N2 reaction often is analyzed in terms of interactions between an attacking nucleophile and a substrate, we also considered the effect of the leaving group on the energy terms of the EDA along the reaction path. We think this is a particularly reasonable approach for an identity reaction such as $X^- + R_3C{-}X$, where in the transition structure $[X{\cdots}R_3C{\cdots}X]^-$ the nucleophile and the leaving group are equivalent, and also since this is a heterolytic process. We found that the steric repulsion between the nucleophile and the substrate is overcompensated by the loss of steric repulsion between the substrate and the leaving group. This conclusion was reached by calculating the interactions between $[X{\cdots}X]^{2-}$ and CR_3^+ along the least energy reaction path and by applying the EDA to the calculated energies.

Zeist and Bickelhaupt used the same approach and obtained numerical results for the systems $F^- + R_3C{-}F$ (R = H, Me), which are essentially identical to our data. The curves of the EDA values that are shown in Figure 1b in their Correspondence[1] support the conclusion that the steric repulsion, which is identified with the ΔE_{Pauli} term of the EDA, decreases along the reaction path and that the ΔE_{Pauli} value for the transition structure is smaller than for the reactants. The small hump in the curve for $F^- + Me_3C{-}F$, which was already observed by us in our previous study,[3] is interesting but not relevant for the present topic. Zeist and Bickelhaupt then introduce a new scenario where they consider a *hypothetical* system in which they suppress the geometric relaxation of the substrate when the nucleophile approaches. Not surprisingly, they observe a steep rise of the Pauli repulsion yielding a curve that exhibits an increase of the ΔE_{Pauli} term along the reaction course (Figure 1c in the Correspondence by Zeist and Bickelhaupt). The authors thus conclude that “increased steric congestion around the five-coordinate central atom causes the barrier in the S_N2 reaction”.

We do not consider this statement of Zeist and Bickelhaupt to be valid. The use of a *hypothetical* system where the geometry of the substrate is frozen implies by necessity that the Pauli repulsion term increases as the nucleophile approaches. This procedure is also questionable from a formal point of view since only electronic and not nuclear degrees of freedom are optimized. The behavior of this artificially constrained system is exactly opposite of what was found in the system for which the positions of the nuclei are allowed to adjust. In addition, the conclusion of Zeist and Bickelhaupt is based on a different interpretation of the EDA because energy terms in the EDA, which are not associated with steric repulsion, are arbitrarily added to the ΔE_{Pauli} term. The statement in the second paragraph of the Correspondence by Zeist and Bickelhaupt, which states: “It

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is therefore crucial to be aware that the overall effect of steric hindrance…is contained not only in the steric or Pauli repulsion but also in the changes in other energy terms..” runs counter not only to our conclusion but also to the physical interpretation of the EDA terms that has been advocated in the past.[4] This is unfortunate since the original EDA provides precisely defined mathematical terms that make it possible to identify chemical concepts with numerical data in a consistent manner.[5] The central term of the EDA is the instantaneous interaction energy ΔE_{int} between the fragments *in the geometry of the species that is the subject of the analysis* [Eq. (1)]:

$$\Delta E_{\mathrm{int}} = \Delta E_{\mathrm{elstat}} + \Delta E_{\mathrm{Pauli}} + \Delta E_{\mathrm{orb}} \quad (1)$$

The term $\Delta E_{\mathrm{elstat}}$ gives the electrostatic interaction energy between the fragments, $\Delta E_{\mathrm{Pauli}}$ refers to the steric repulsion between the fragments, and ΔE_{orb} is the orbital interaction term, which can be identified with covalent bonding. In cases where the investigated species is an equilibrium structure the interaction energy ΔE_{int} and the bond dissociation energy D_e are related by the expression given in Equation (2).:

$$-D_e = \Delta E_{\mathrm{prep}} + \Delta E_{\mathrm{int}} \quad (2)$$

The term ΔE_{prep} gives the relaxation of the fragments from the geometry in the molecule to the equilibrium structure. This term is named $\Delta E_{\mathrm{strain}}$ by Zeist and Bickelhaupt. Essential to this discussion, is the fact that the unfavorable ΔE_{prep} term of the R_3C moiety within the tetrahedral R_3CX species is almost fully released in passing from reactants to transition structure, since the R_3C unit within $[X\cdots R_3C\cdots X]^-$ for all practical reasons has the same planar geometry as in the reference state. If ΔE_{prep} (or $\Delta E_{\mathrm{strain}}$) becomes further partitioned into the energy terms given in Equation (1), which is the approach applied by Zeist and Bickelhaupt in the preceding Correspondence, it would mean that the EDA results refer to a geometry that does not represent the actual structure of the investigated species. This position was previously expressed in review articles by Bickelhaupt et al.[6] and by some of us.[7] We prefer to use the *real* system using the optimized geometries rather than a hypothetical system with non-equilibrium structures for the bonding analysis that is inherent to the EDA. There is agreement between the work of Zeist and Bickelhaupt and ours that the *actual* activation barriers for the systems $F^- + R_3C{-}F$ ($R=H$, Me) come from weaker orbital interactions due to the rather long carbon–fluorine distances in the transition states rather than steric repulsion.

Finally, we would like to comment on the statements about steric hindrance by Zeist and Bickelhaupt made in the last paragraph of their Correspondence. They write: “Indeed, steric hindrance is not an observable in the sense of a “Hermitian operator for steric hindrance”. *But steric hindrance is the observable behavior of the eigenvalue of a quantum mechanical operator, namely, the Hamiltonian*.” We find the two statements contradict each other. Strictly speaking, what is observable is the change of the *total* energy of a system that comes from the change in nuclear configuration during the course of a reaction. The identification of an energy change with *steric hindrance* is subject to an interpretation that may be plausible and useful and yet, which is always arbitrary. Nature does not know steric hindrance, only energy changes.

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[5] For a pertinent example see the EDA definitions of hyperconjugation, conjugation, and aromaticity in: a) D. Cappel, S. Tüllmann, A. Krapp, G. Frenking, *Angew. Chem.* **2005**, *117*, 3683; *Angew. Chem. Int. Ed.* **2005**, *44*, 3617; b) I. Fernández, G. Frenking, *Chem. Eur. J.* **2006**, *12*, 3617; c) I. Fernández, G. Frenking, *Faraday Discuss.* **2007**, *135*, 403.

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