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Understanding the Physics and Chemistry of Reaction Mechanisms from Atomic Contributions: A Reaction Force Perspective

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S *Supporting Information*

ABSTRACT: Studying chemical reactions involves the knowledge of the reaction mechanism. Despite activation barriers describing the kinetics or reaction energies reflecting thermodynamic aspects, identifying the underlying physics and chemistry along the reaction path contributes essentially to the overall understanding of reaction mechanisms, especially for catalysis. In the past years the reaction force has evolved as a valuable tool to discern between structural changes and electrons' rearrangement in chemical reactions. It provides a framework to analyze chemical reactions and additionally a rational partition of activation and reaction energies. Here, we propose to separate these energies further in atomic contributions, which will shed new insights in the underlying reaction mechanism. As first case studies we analyze two intramolecular proton transfer reactions. Despite the atom based separation of activation barriers and reaction energies, we also assign the participation of each atom in structural changes or electrons' rearrangement along the intrinsic reaction coordinate. These participations allow us to identify the role of each atom in the two reactions and therfore the underlying chemistry. The knowledge of the reaction chemistry immediately leads us to suggest replacements with other atom types that would facilitate certain processes in the reaction. The characterization of the contribution of each atom to the reaction energetics, additionally, identifies the reactive center of a molecular system that unites the main atoms contributing to the potential energy change along the reaction path.
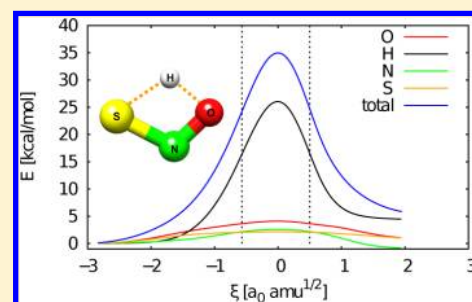
INTRODUCTION

To rationalize chemical reactions, detailed knowledge of the involved physical and chemical processes is needed. Although most current research is focused on the accurate prediction of energy barriers and reaction energies, an atomistic picture of their origin and the underlying reaction mechanism would be desirable, especially for catalysis. In the past years the reaction force was introduced and its versatility to study reaction mechanisms in various reactions and environments has been established.[1,2] Its power to separate structural and electronic contributions of activation barrier and reaction energies served to characterize catalytic effects in various chemical reactions.[3,4]

However, it would be desirable to additionally determine the contributions of specific atoms or fragments to these quantities, thereby establishing the reactive core of the reaction and, at the same time, targeting the possible influence of the environment. On the basis of a recent study of Haas et al.,[5] we propose a methodology where the electronic and structural contributions of energy barriers are assigned to specific atoms along the intrinsic reaction coordinate.

The new methodology was applied to two well studied intramolecular proton transfer reactions by us: the reaction of ONSH to HONS[6,7] (Figure 1a) and the reaction of the neutral to the zwitterionic form of tryptophan, which we characterized recently.[8]

METHODOLOGY: ATOMIC CONTRIBUTIONS

To calculate atomic contributions, first the reaction path and the structures on this path have to be obtained. Once the transition state was optimized for the respective reaction, the reaction path was derived by the IRC procedure as implemented in the Gaussian 03 package.[9] This procedure uses the algorithm of Gonzalez and Schlegel[10,11] in mass-weighted internal coordinates where the intrinsic reaction coordinate,[12] ξ, is constructed by following the instantaneous acceleration vector represented by the imaginary frequency starting at the transition state. In general, the next structure on the reaction path is obtained by a projection of the acceleration vector of the current structure by half the step size employed. From this pivot point a constrained optimization on a hypersphere is performed to identify the next point (structure) on the path such that the acceleration vector of the next point (structure) is parallel to the vector between the pivot point and this new point on the reaction path. The obtained path represents an arc of a circle between the two points of the reaction path representing the current and the new structure. To minimize the error in the projection of the tangent and curvature vectors, a small step size of 0.01 a_0 amu$^{1/2}$ was
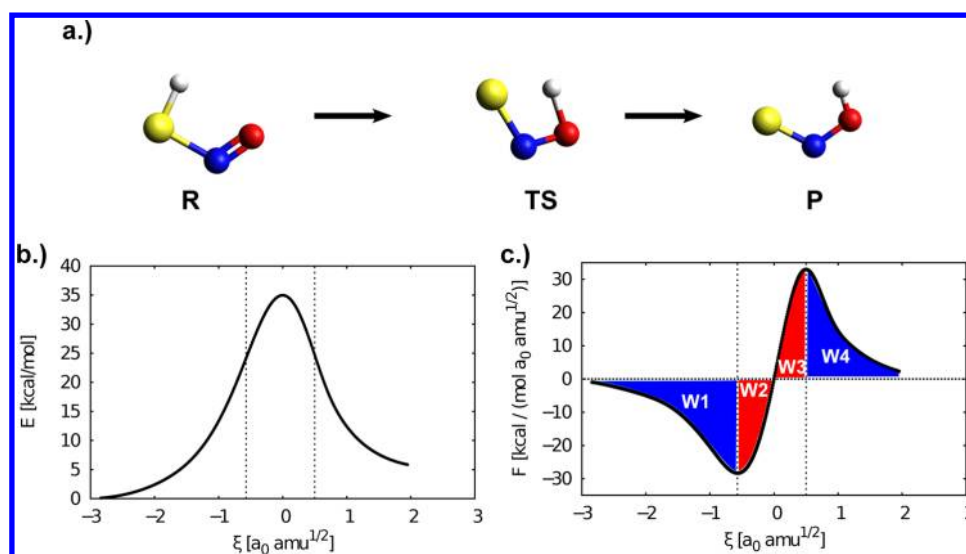
Figure 1. (a) Reactant, transition state, and product obtained at the CCSD/aug-ccpcdz level of theory in the proton transfer reaction from ONSH to HONS. (b) Potential energy and reaction force profile along the intrinsic reaction coordinate for the same reaction. The dotted lines represent the minimum and maximum of the force, which divides the reaction in three regions. The derived reaction works W_{1-4} are represented as the area below the reaction force.

employed. Recently, a more advanced method for finding reaction paths based on holonomic constraints and kinetic energy potentials[13] was reported, which does not make use of force projections and should be, in principle, more accurate.

Once the reaction path and the structures resembling the path are obtained, the gradient $g_{i,\alpha,[x,y,z]}$ of atom i in the structure characterized by the value of α, which corresponds to a structure of the intrinsic reaction coordinate ξ, is calculated along the three Cartesian coordinates.[5] The work required to move an atom from the position in the current structure to its position in the next structure on the path is calculated against the gradient along the three Cartesian coordinates and summed up along the reaction path starting at the reactant ($\xi = 0$):

$$W_{i,\xi} = \sum_{\alpha=0}^{\xi} \sum_{k}^{x,y,z} g_{i,\alpha,k} d_{i,a,k}$$

(1)

$W_{i,\xi}$ represents the contribution of atom i until the point ξ on the intrinsic reaction coordinate, $g_{i,\alpha,k}$ the gradient of atom i along the Cartesian coordinate k for structure characterized by α and $d_{i,\alpha,k}$ the displacement required to move atom i along the coordinate k from the actual structure α to the next structure on the reaction path $\alpha+1$.

In the limit of infinitesimal displacements the sum over all atomic contributions resembles the potential energy obtained from the IRC procedure described above.

■ COMPUTATIONAL METHODS

All calculations were performed with the Gaussian 03 package.[9] Reactant, transition state, and products were optimized with various methods depending on the system size (see Supporting Information) and verified by harmonic vibrational analysis. Starting at the transition state the proton transfer reaction in ONSH was followed along the intrinsic reaction coordinate ξ using mass-weighted internal coordinates (step size = 0.01 a_0 amu$^{1/2}$) with the CCSD method and the aug-cc-pvdz basis set as implemented in the Gaussian 03 package. For the more atoms involving water assisted reaction in tryptophan the

implemented B3LYP functional with the 6-31G(d,p) basis set was employed.

NBO analysis were performed with the NBO program 3.1 as implemented in the Gaussian 03 package.[14]

■ RESULTS AND DISCUSSION

ONSH → HONS: Energy Barriers and Reaction Works. Figure 1a shows the structure of the reactant (ONSH), the transition state and the product (HONS) for the intramolecular proton transfer reaction obtained at the CCSD/aug-ccpvdz level of theory together with the potential energy and the reaction force along the intrinsic reaction coordinate ξ. The reaction force, defined as the negative derivative of the potential energy along the path, divides the reaction coordinate into three regions through its minimum ($\xi_{min} = -0.6\ a_0$ amu$^{1/2}$) and maximum ($\xi_{max} = 0.6\ a_0$ amu$^{1/2}$): the reactant, the transition state, and the product region (Figure 1b). The analysis of several reactions assigned the first, the reactant region ($0 \le \xi \le \xi_{min}$), to mostly structural changes that are needed to transform the reactant into a reactive species. The reactive species at the reaction force minimum identifies the onset of electronic activity characterized by the rearrangement of the electrons in the second region, the transition state region ($\xi_{min} \le \xi \le \xi_{max}$), which includes the transition state (where the reaction force is zero) and reaches until the reaction force maximum. After the reaction force maximum the system relaxes through structural changes in the product region.

From these regions, a structural contribution W_1 of 24.2 kcal/mol to the activation barrier ($\Delta E^{\ddagger} = 35.0$ kcal/mol) is derived, which corresponds to the potential energy required to reach the reaction force minimum (ξ_{min}) from the reactant (Figure 1c). The electronic contribution W_2 of 10.8 kcal/mol corresponds to the potential energy difference between the transition state and the reaction force minimum. Accordingly, the relaxation from the transition state toward the product involves first an electronic contribution W_3 of −10.3 kcal/mol, which covers the completion of the rearrangement of the electron density (within the Born−Oppenheimer approximation) and is characterized by the potential energy difference

between the reaction force maximum (ξ_{max}) and the transition state. Finally, further relaxation of the system is achieved through structural changes represented by W_4, which amounts to −19.2 kcal/mol (potential energy difference between the product and ξ_{max}). Summing up all contributions W_{1-4} yields the reaction energy of 5.5 kcal/mol. These values are in agreement with earlier studies by us[2,6,7] improving their quality through new high-level ab initio calculations (comparison of different basis sets and post Hartree−Fock methods are available in the Supporting Information).

ONSH → HONS: Atomic Contributions. The energy barrier, the reaction energy and the contributions W_{1-4} can now be separated further in atomic contributions, obtained as cumulative works along the intrinsic reaction coordinate (for details see the Methodology section). The contribution of each atom in the reaction of ONSH to HONS is shown in Figure 2, where the total potential energy is recovered as the sum of its atomic contributions.
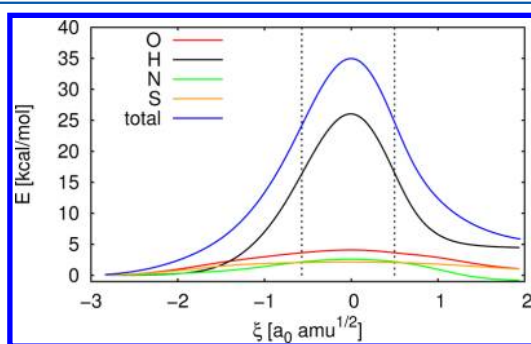

Figure 2. Atomic contributions to the total potential energy for the intramolecular proton transfer reaction of ONSH to HONS.

For the whole reaction under study the largest contribution comes from the hydrogen atom followed by the oxygen atom. The atomic contributions show also a dependence on the regions defined by the reaction force: In the first region all atoms contribute to the total potential energy reflecting structural changes needed to bring the reactant into a reactive conformation, which is in agreement with our recent studies.[2,6] In the second region the heavy atoms do not contribute considerably to the total potential energy and the hydrogen atom concentrates all energy needed to reach the transition state. This concentration on the hydrogen atom reflects the rearrangements of the electrons that govern this region and may be understood as a proton coupled electron transfer mechanism.[15] Indeed, in a recent study, we showed that in a diabatic representation of the reaction this region localizes most of the electronic coupling between the two diabatic surfaces.[2] It also confirms the result of the reaction force constant becoming negative.[6] After the reaction force maximum the whole system relaxes through structural rearrangements reflected in the atomic contributions of the hydrogen atom and the heavy atoms.

Besides the atom based separation of the total energy the activation barrier, the reaction energy and the reaction works W_{1-4} can be subdivided in contributions arising from specific atoms. The obtained values are presented in Table 1 (small differences in the sum over all atoms to the values reported before are originated from small integration errors). As expected, the hydrogen atom presents the largest atomic contributions to all energies. Starting from the reactant, W_1

Table 1. Atomic Contribution to the Reaction Energy, Activation Energy, and Reaction Works in kcal/mol

	ΔE^0	$\Delta E^{\ddagger}$	W_1	W_2	W_3	W_4
oxygen	1.0	4.1	3.6	0.5	−0.5	−2.6
hydrogen	4.5	26.0	16.4	9.7	−9.5	−12.0
nitrogen	−0.8	2.6	2.2	0.4	−0.4	−3.0
sulfur	1.0	2.2	2.1	0.1	−0.1	−1.0
Σ_i^{atoms}	5.7	34.9	24.3	10.7	−10.5	−18.6

representing structural contribution to the activation barrier is dominated by the oxygen and the hydrogen atom. This reflects the first part of the reaction where the angle between the three heavy atoms decreases bringing the hydrogen atom in a closer position to the oxygen. For the electronic part of the activation barrier W_2 the atomic contribution of the heavy atoms is very small and the hydrogen atom concentrates the energy, as noted above. The same holds for W_3 where the system relaxes through the rearrangement of the electrons. After the maximum in the reaction force initiating the structural relaxation, the main atomic contributions come from the nitrogen and oxygen atom despite the hydrogen atom. This points to a relaxation of the nitrogen and oxygen atom around the sulfur atom, which being heavier does not contribute to the structural relaxation.

Interestingly, the nitrogen atom presents a negative reaction energy contribution in contrast to all the other atoms, suggesting that it rather prefers its configuration in the product state. To discern the origin of this preference, we carried out a detailed natural bond order study of the reactant and the product (see Supporting Information). This analysis revealed that the product presents a larger degree of electron delocalization over the heavy atoms as evidenced from the Wiberg bond indices. In addition, the nitrogen atom shows a larger contribution to the sp^2 natural molecular orbitals involving the sulfur and the oxygen atom in the product state than in the reactant. The π-double bonds, in contrast, show no significant difference between reactant and product. The larger localization of the σ bonding orbitals on the nitrogen atom in the product is in line with its negative natural charge ($q_{N,p}$ = −0.106), which in the reactant is positive ($q_{N,r}$ = 0.131). This increased localization on the nitrogen atom together with the larger electron delocalization over the heavy atoms explain the observed negative atomic contribution of the nitrogen atom to the reaction energy: it rather prefers to be in the bonding configuration of the product than in the one of the reactant.

This difference in the bonding pattern between reactant and product can also be understood from the electronegativity difference between the involved atoms: In the reactant the nitrogen atom is the less electronegative atom in the double bond with the oxygen atom, this being reversed in the double bond to the sulfur atom of the product. If one would replace the nitrogen atom with a less electronegative atom (less than the sulfur atom), the electronegativity difference between the atoms involved in the double bonds of reactant and product would be the same and one would expect a smaller value in the overall reaction energy. Indeed, in our first study of this reaction we replaced nitrogen by a CH group and obtained almost an isoenergetic reaction.[7]

Finally, also the activation barrier can be separated in atomic contributions: the hydrogen atom is the main contributor followed by the oxygen atom and smaller contributions of the nitrogen and sulfur atom. This confirms that two key processes are required to reach the transition state: to bring the oxygen

and the hydrogen atom together in a reactive conformation and the subsequent reorganization of the electrons.

It is important to stress the fact that the previous analysis provides a complete characterization of the physical and chemical nature of the activation energy: 70% of $\Delta E^{\ddagger}$ in the ONHS ↔ HONS reaction can be physically identified with structural effects and the remaining 30% should be associated to electronic effects, as evidenced by the reaction force; and the chemical nature of the activation energy was put forward through the partition in atomic contributions, which indicated that 74% of it should be associated to the migrating hydrogen atom whereas the other 26% is shared by the heavy atoms.

Water Assisted Proton Transfer Reaction in Tryptophan. To extend the new method to more complex systems with more atoms we also applied the new methodology to the water assisted intramolecular proton transfer reaction in tryptophan, which was studied recently by us in different environments.[8] Here, we will only focus on the reaction in vacuum. Figure 3 shows the transition state obtained at the B3LYP/6-31G(d,p) level together with the employed atom labels for the following presentation of the results.
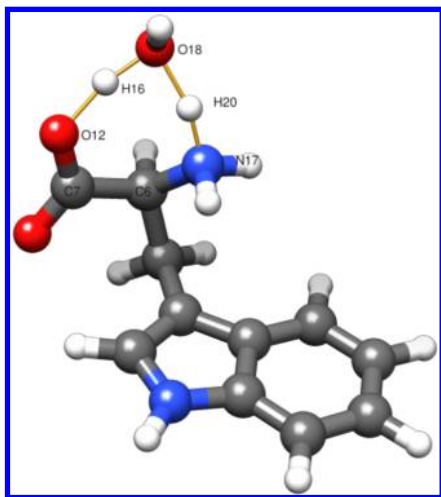

Figure 3. Transition state structure obtained at the B3LYP/6-31G(d,p) level for the intramolecular proton transfer reaction in tryptophan together with the employed atom labels.

The potential energy along the intrinsic reaction coordinate starting from the neutral form of the amino acid is shown in Figure 4 together with the atomic contributions (for clarity only the main atomic contributions are displayed). Atoms in the amino acid side chain (indole group) do not contribute considerably to the energetics of the reaction; the reactive center is concentrated on the seven-membered ring involving the bridging water molecule and the corresponding atoms in the amino acid (for comparison Table 2 shows the sum of all atomic contributions and of the reactive center only). The presence of a reactive center that concentrates all relevant processes confirms a recent comparative study of the intramolecular proton transfer reaction in different amino acids by us where we could show that side chains play only a marginal role.[16]

Table 2 presents the atomic contributions to the reaction energy, the activation barrier, and the reaction works W_{1-4} for the atoms in the reactive center. The reaction energy is governed by the contributions of the two transferred hydrogen atoms followed by the oxygen atom of the bridging water
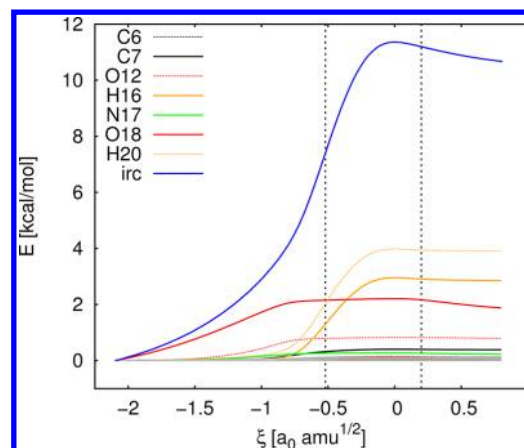

Figure 4. Atomic contributions together with the total potential energy along the intrinsic reaction coordinate for the water assisted intramolecular proton transfer reaction in tryptophan. Dashed line identifies the minimum and maximum of the mean reaction force.

Table 2. Atomic Contributions to the Reaction Energy, Activation Energy, and Reaction Works in kcal/mol for the Water Assisted Intramolecular Proton Transfer Reaction in Tryptophan

	ΔE^0	$\Delta E^{\ddagger}$	W_1	W_2	W_3	W_4
O5	0.10	0.13	0.11	0.03	−0.01	−0.03
C6	0.12	0.14	0.12	0.02	−0.00	−0.01
C7	0.38	0.40	0.32	0.08	−0.01	−0.01
O12	0.79	0.83	0.79	0.03	−0.00	−0.03
H16	2.85	2.96	1.30	1.66	−0.05	−0.06
N17	0.23	0.27	0.26	0.01	−0.01	−0.03
O18	1.88	2.21	2.15	0.06	−0.04	−0.29
H20	3.91	3.98	2.03	1.95	−0.04	−0.03
H26	0.11	0.14	0.11	0.03	−0.01	−0.02
$\Sigma_i^{\text{reactive}}$	10.37	11.06	7.19	3.87	−0.17	−0.51
$\Sigma_i^{\text{all atoms}}$	10.66	11.37	7.46	3.88	−0.17	−0.51
IRC	10.67	11.36	7.40	3.96	−0.16	−0.53

molecule. As for the reaction discussed above, a NBO analysis of the reactant and the product was performed to discern its origin (Wiberg bond indices for the relevant bonds are presented in the Supporting Information). The bond indices reflect a higher degree of electron delocalization throughout the seven-membered ring in the product and smaller bond indices of the new covalent bonds. In addition, the hydrogen atom transferred from the water molecule is covalently bonded to the nitrogen atom in the product and presents a hydrogen bond to the water oxygen atom. This is clearly less favorable than the reactant configuration with an oxygen covalent bond and the hydrogen bond to the nitrogen atom and explains the largest contribution to the reaction energy of this atom. For the other hydrogen atom the bonding partners are in both conformers two oxygen atoms. However, the bond indeces of both bonds are larger in the reactant than in the product, favoring the bonding configuration in the reactant and explaining the positive atomic reaction energy.

The origin of the activation barrier can now deduced from the structural and electronic contribution and their atomic contributions. The latter, W_1, is dominated by the oxygen and hydrogen atom of the water molecule together with the OH group of the carboxyl group, although small contributions from other atoms can be identified. The underlying process is the

reduction of the two hydrogen bond distances between water and amino acid. Once the reactive conformation is reached at the reaction force minimum, the energy for the electronic rearrangement W_2 is centred again only on the hydrogen atoms as for the reaction discussed above. Here as observed in the reaction energy, the transferred hydrogen atom of the water molecule presents the largest contribution. This confirms the larger energy required to rupture the covalent bond to the oxygen atom to form the new weaker one to the nitrogen atom. Once the transition state is reached, the system relaxes to the zwitterionic product almost completely through the atomic contribution of the water oxygen atom, which reflects the displacement of the water molecule away from the amino acid to form the new hydrogen bonds.

CONCLUSIONS

In summary, atomic contributions identified the reactive center and the key role of the water molecule in the energetics of the water assisted proton transfer reaction in tryptophan. In the proton transfer reaction of ONSH they identified physical and chemical processes as structural changes of the heavy atoms and the favored bonding configuration of the nitrogen atom in the product along the reaction path. Therefore, atomic contributions represent a new theoretical-computational tool that identifies the role of each atom in the reaction mechanism and assigns its contribution to structural and electrons' rearrangements taking place along the reaction coordinate.

Additionally, the previous analysis showed that a complete characterization of the physical and chemical nature of the activation energy is possible. The reaction force, on the one hand, indicates the prevalence of structural or electronic effects, thus identifying the physical nature of the activation energy and the chemical partition of the reaction profile, on the other hand, distributes the activation energy in specific atomic contributions, thus shedding light on its chemical nature.

The classification of main atomic contributors to the overall reaction energetics should promote new ways to study catalysis. Despite identifying the role of each atom in catalysis, it may even point out replacements by special atom types facilitating a process and speeding up the overall reaction. In addition, this tool also discerns the reactive center of a reaction, which is crucial for hybrid descriptions of systems as in QM/MM calculations.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Comparison of different ab initio methods for the ONSH reaction and the results of the NBO analysis (table of reaction energies and activation barriers and of atomic contributions; figures showing Wiberg bond indices). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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