Reaction Mechanisms

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Electron Flow in Reaction Mechanisms—Revealed from First Principles**

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Abstract: *The "curly arrow" of Robinson and Ingold is the primary tool for describing and rationalizing reaction mechanisms. Despite this approach's ubiquity and stellar success, its physical basis has never been clarified and a direct connection to quantum chemistry has never been found. Here we report that the bond rearrangements expressed by curly arrows can be directly observed in ab initio computations, as transformations of intrinsic bond orbitals (IBOs) along the reaction coordinate. Our results clarify that curly arrows are rooted in physical reality—a notion which has been challenged before—and show how quantum chemistry can directly establish reaction mechanisms in intuitive terms and unprecedented detail.*

A major goal of chemistry is to establish reaction mechanisms. In this endeavor the most powerful empirical tool is the "curly arrow" of Robinson and Ingold,[1,2] which has emerged as the language of choice for describing and rationalizing bond rearrangements during a reaction. However, despite the curly arrows' ubiquity and indisputable value, their connection to physical reality remains vague at best. Indeed, we found only three articles[3–5] examining their physical basis at all, of which one concludes it does not exist,[3] and two are limited to semiempirical studies of hyperconjugation.[3,4] In practice, computational chemists often just determine the "mechanic" aspects of reaction mechanisms through first principles, that is, they determine the relevant intermediates and transition states of a reaction by using various geometry optimization techniques.[6] This is sufficient to describe what physically happens in a reaction, but says little about the how or why in terms of bonding concepts; if an "electronic mechanism" in terms of curly arrows is then inferred, this is done solely by geometric changes along the reaction paths connecting those states, with no regard to their actual wave functions. Current textbooks on computational chemistry[7,8] regard curly arrows as theoretically problematic; they prefer to interpret reactions in terms of frontier orbital theory,[9] which, however, offers no local perspective of bond transformations. While elegant mechanistic theories of the potential energy surface[10] and the electron localization function or electron density topology[11] exist, they also provide no direct connection to the familiar orbital picture. Consequently, curly arrow mechanisms cannot be tested for "correctness". In practice, they are accepted if they intuitively "make sense" and are reasonably consistent with quantitative facts. This is particularly troublesome in transition-metal-catalyzed reactions; here even the catalysts themselves often feature a perplexing electronic structure, thus making an intuitive assignment of reaction mechanisms difficult.

Encouraged by an earlier result in Fe-NO catalysis,[12] we here report that these problems can be overcome by intrinsic bond orbitals (IBOs),[13] a physically well-defined, essentially non-empirical form of localized molecular orbitals (MOs) designed for chemical interpretation. We show that once the intermediates and transition states of a reaction are determined (i.e. the "mechanic" reaction mechanism), the (continuous) rearrangement of IBOs along the reaction paths connecting those states can be identified with the electron flow expressed by curly arrows. This identification allows the electronic reaction mechanisms to be deduced in terms of intuitive bond transformations directly from first principles. Apart from its potential impact on computational chemistry, the current study provides strong evidence for the physical reality of the empirical electron flow concept.

Let Φ denote a self-consistent field (SCF) wave function obtained by density functional theory. Such wave functions are typically computed in terms of delocalized (occupied) MOs φ_i. The core idea of the IBO method is to exactly re-express Φ through local MOs φ'_i, which correspond to chemical bonds and lone pairs of electrons. This is possible because Φ is a Slater determinant and thus invariant to unitary transformations amongst its MOs. Already in 1989, Pipek and Mezey[14] proposed exploiting this freedom by recombining the occupied MOs such that they are spread over as few atoms as possible. The local MOs $\varphi'_i(\vec{x}) = \sum_k \varphi_k(\vec{x}) U_{ki}$ are thus defined by maximizing the localization functional (1)[14] (occ = occupied) with respect to the unitary matrix U_{ki},

$$L = \sum_{i}^{\text{occ}} \sum_{A}^{\text{atoms}} q_A(i')^2 \Rightarrow \max \qquad (1)$$

where $q_A(i')$ denotes the partial charge $q_A(i')$ of orbital φ'_i on atom A. As illustrated in Figure 1, this functional prefers sets of local MOs over equivalent sets of nonlocal MOs, and by maximizing it we recover the bonds and lone pairs in H_2O—without any reference to a Lewis structure. Unlike the earlier

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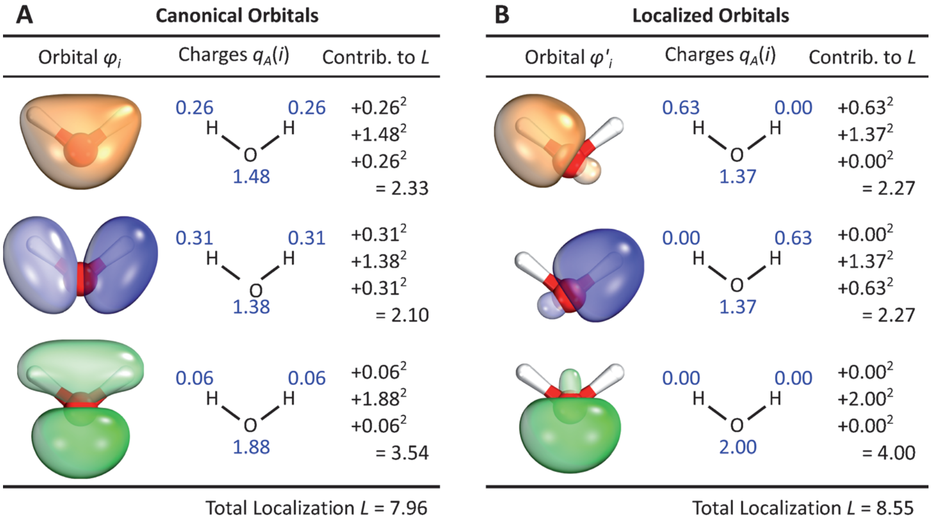

Figure 1. Illustration of the functional L [Eq. (1)]. The description of H_2O in terms of canonical orbitals φ_i (A) and localized orbitals $\varphi'_i = \sum_k \varphi_k U_{ki}$ (B) is physically equivalent. However, L is larger in (B), where orbital charge is spread over fewer atoms. One oxygen lone pair is not shown.

localization by Foster and Boys,[15] the Pipek–Mezey localization distinguishes σ and π orbitals (Figure S3), and unlike Edminston–Ruedenberg localization,[16] it is computationally inexpensive. However, despite its conceptual appeal, the Pipek–Mezey definition suffers from a serious problem: it determines $q_A(i)$ as Mulliken charges, which are highly erratic and explicitly depend on arbitrary calculation parameters—the basis set. This makes Pipek–Mezey orbitals risky in studies of chemical bonding, and may even cause a complete failure of the method (e.g. Figure S3 in the Supporting Information, Figure 2, Ref. [17]). Our IBO method solves this problem by basing Equation (1) on partial charges that are physically well-defined, effectively parameter-free, and consistent with many empirical laws.[13] Subsequently, similar localization methods were put forward by Lehtola and Jónsson[18] and by West et al.[19] (based on work by Ruedenberg et al.[20,21]), and a close relationship between the underlying intrinsic bases[13,19,21] was established by Janowski.[17]

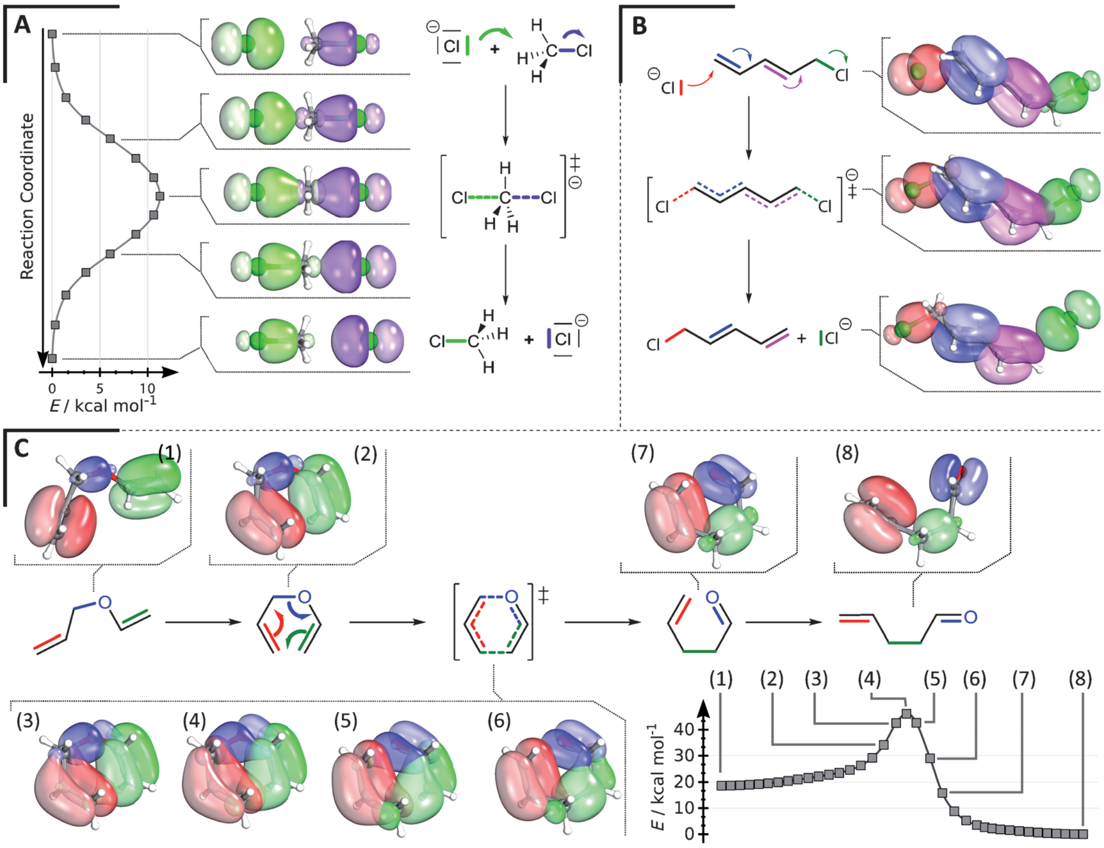

Figure 2. Curly arrows and IBOs in simple reactions. Electron pairs correspond to IBOs of the same color. A) The S_N2 reaction $Cl^- + CH_3Cl \rightarrow ClCH_3 + Cl^-$. Shown are the ab initio reaction path (IRC), IBOs of the two reactive orbitals, and the classical mechanism. B) A S_N2' displacement showing the migration of conjugated π bonds. C) The Claisen rearrangement. In structures (3)–(7), one σ bond turns into a π bond, one π bond into a σ bond, and one π bond moves. Relaxation [(7) and (8)] leads to the product. In all cases, the IBOs continuously transform from the electronic structure of the starting material to that of the product, and follow the classical curly arrow mechanisms.

Defining bond orbitals by minimizing their spread over atoms, as in Equation (1), differs from the state of the art approach to interpretation, the seminal natural bond orbital (NBO) method of Weinhold and co-workers.[22] NBOs are based on a discrete localization criterion, which explicitly searches for Lewis structures most closely matching a given wave function Φ. A direct application of this idea prevents following orbitals along reaction paths,[23] because the Lewis structures of starting materials and products will typically be different. This problem can be alleviated in natural resonance theory (NRT),[24] but the discrete Lewis structures becoming relevant along a reaction path still must be identified and chosen,[23] which is not always easy. Similar ambiguities in the discrete choice and physical meaning of resonance structures occur in valence bond (VB) theory.[25] Atoms in molecules[26] and adaptive natural density partitioning,[27] two other widely used conceptual theories, also employ discrete criteria: the existence of bond paths between atoms, and the center decomposition of the density matrix, respectively. In contrast, the criterion used in IBOs [Equation (1)], is continuous. It recovers intuitive bond orbitals only implicitly, because they are the most compact expression of the wave function according to Equation (1). We thus conjectured that the transformation of IBOs can also be followed along reaction paths, and that this movement of local orbitals—not of pairs of electrons, which are indistinguishable—is the information encoded in the curly arrows of mechanisms. Unlike in NRT or VB theory, where arrows indicate shifts in weight between dominant resonance structures (e.g. Refs. [28,29]),[30] or in previous work by Andrae et al.,[31] where arrows represent electron flux between orbital density surfaces derived by Pipek–Mezey localization, here the curly arrows would represent a change in the bond orbitals themselves along the reaction path. We now demonstrate by example that this is indeed viable.

Figure 2 A shows the S_N2 reaction $Cl^- + CH_3Cl \rightarrow ClCH_3 + Cl^-$. Along the intrinsic reaction coordinate (IRC),[32] the IBOs transform continuously from the electronic structure of the starting material to that of the product. Two IBOs show a concerted transformation of one Cl^- lone pair (left) into a Cl–C σ bond, while the C–Cl σ bond (right) breaks and transforms into a lone pair. All other IBOs (not shown) represent nonreactive electron pairs and stay on the atoms they start on.[*] This picture from first principles corresponds exactly to the classical reaction mechanism in curly arrow notation, shown on the right. Although this reaction is simple, even here a direct relationship between curly arrows and orbital rearrangements is nontrivial. For example, an analysis of canonical orbitals in the similar $H^- + CH_3Cl$ reaction led Keeler and Wothers[7] to note that "… *As we have seen before, the redistribution of the electrons implied by the curly arrows is not the same as that predicted by the behavior of the orbitals*"—in contrast to the present result.

Although only the two directly reacting orbitals were involved in Figure 2 A, Figure 2 B shows that IBOs also convey indirect effects on other orbitals. A nucleophilic attack on the terminal C atom leads to a concerted migration of the conjugated double bonds along the chain, and a simultaneous destabilization of the C–Cl σ bond—in full agreement with the curly arrow mechanism proposed almost a century ago.[1] As far as we know, such a bond transformation process has never before been visualized on the basis of a first principles calculation.

Figure 2 C shows the continuous transformation of bonds in a Claisen rearrangement. This demonstrates that IBOs can characterize the bonding in nontrivial transition structures, and can follow the conversion between π and σ bonds. This may seem surprising, as Pipek–Mezey localization is generally thought to cleanly separate σ and π orbitals.[14,18] Furthermore, the movement of IBO charges along the IRC clearly establishes this reaction as concerted (see Figure S1 in the Supporting Information). Figure S3 in the Supporting Information reveals that neither canonical nor large-basis Pipek–Mezey orbitals can describe this mechanism, while Boys orbitals exaggerate its complexity.[*]

The true value of IBOs becomes evident when analyzing complex reactions whose electronic changes are not well characterized in terms of intermediates and transition states alone. Although it is commonly assumed that determining these states is sufficient to characterize a reaction, Cremer, Kraka, and co-workers[10] have unambiguously shown that what appears to be a single reaction step in the intermediate/transition-state picture can correspond to multiple elementary chemical transformations (even barrierless reactions can have nontrivial mechanisms[34]!). An excellent example was recently reported by Haven et al.[33] They developed a calcium-catalyzed cyclopropanation, in which four bonds are formed by a reaction path with only one transition state and no intermediates in-between. In Figure 3, we demonstrate how by following IBOs we can derive the detailed mechanism of this process in terms of curly arrows. This includes elucidating both the nature and the sequence (Figure S2) of the chemical transformations. This kind of direct insight into the bond rearrangements would be hard to obtain by other means.

While no kind of orbital can be physically observable, IBOs are an exact and simple representation of a realistic ab initio electronic wave function. Additionally, only a minimal number of IBOs change their nature or connectivity during a reaction. Both facts distinguish IBOs from other orbital choices, and combined they provide a powerful framework for analyzing chemical reactions. They also suggest a strong physical basis of the IBOs themselves, and of curly arrows, which describe IBO rearrangements along the IRC. Furthermore, IBOs and IRCs can be easily calculated in practice, and earlier results in Fe-NO catalysis[12,35] illustrate their potential for complex mechanisms. Thus, the here-discovered link from quantum chemistry to intuitive reaction

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[*] As measured by their partial charge displacement $\|\vec{q}_i(s) - \vec{q}_i(0)\|^2$ along the IRC, where $\vec{q}_i(s)$ is a vector of atomic partial charges at IRC point s; see the Supporting Information. In this reaction, $\delta\vec{q}_i(s) \leq 0.02\,e^-$ for inert orbitals i.

[*] If used very carefully, Pipek–Mezey orbitals could in principle give a useful account of chemical transformations. However, we found no prior studies connecting Pipek–Mezey orbitals and curly arrows.

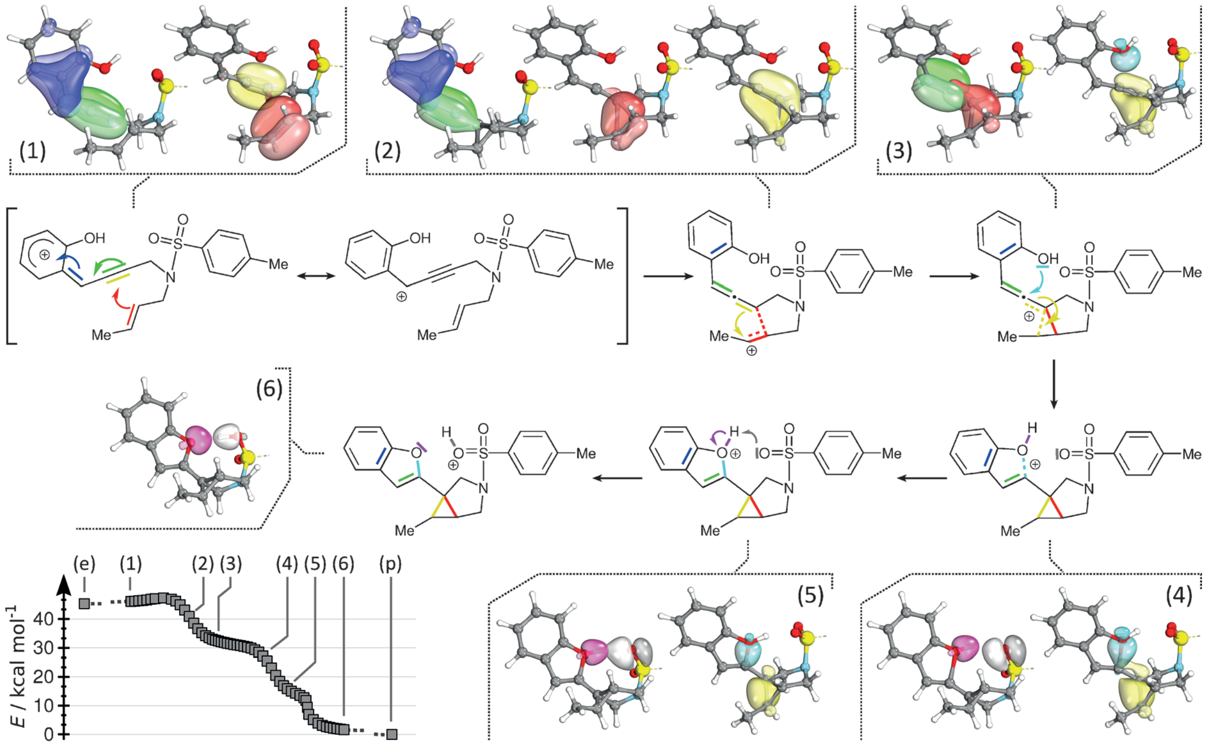

Figure 3. The cyclopropanation of Haven et al. Four bonds are formed in a single downhill reaction path.[33] By following the IBOs we can derive the precise reaction mechanism (middle). Grouped images show IBOs at the same IRC point, multiple images are used to avoid IBOs obstructing each other. The *p*-tolyl fragment is hidden. The derived mechanism is discussed in Figure S3 of the Supporting Information.

mechanisms clears the way to studying mechanisms in a directness and detail not seen before. An IBO program is freely available,[36] and extensions to multireference wave functions and non-adiabatic reactions are underway.

Keywords: ab initio calculations · bond theory · quantum chemistry · reaction mechanisms

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