2D-Map of Intermolecular Interactions in Organic Chemistry Reveals Underrepresented Area of Research

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ABSTRACT. The molecular orbital (MO) theory is an indispensable model to describe the interaction between two molecular species, particularly during chemical bond formation. Here we show that by plotting the energy difference (E_{DA}) of the HOMO of an electron donor and the LUMO of an acceptor against their overlap integral (S_{DA}), many similar types of bimolecular interactions tend to be clustered near one another on the 2D map. Interestingly, in one of the six arbitrarily divided sections designated as "B2", the interacting molecular pairs appear to present a type of interaction as a "hybrid" between chemical reaction and radical pair formation, a lesser explored area of research. We propose that such interactions could be crucial for the development of materials with unique optical, magnetic, and catalytic properties from purely organic molecules.

KEYWORDS. bimolecular interaction • radical pair• electron transfer • overlap integral • energy gap

When two organic molecules are in proximity with one another, many types of bimolecular interactions (BMI) could happen, including 1) chemical reactions with new bond formation and old bond cleavage, 2) spontaneous single-electron transfer resulting a pair of radicals,[1, 2] and 3) non-bonding interactions such as hydrogen and halogen bonds,[3, 4] π-π stacking[5, 6] or simply Van der Waals forces. However, definitions for such interactions are largely loose or intuitive with many overlapping characteristics. Molecular orbital (MO) theory is a rather powerful and versatile tool for solving problems in organic chemistry, particularly in predicting the reactivity and location of chemical bond formation between two given molecules.[7, 8] In the MO theory, often a pair of electrons from an occupied molecular orbital (usually the highest, or HOMO) of an electron donor molecule move toward an unoccupied molecular orbital (usually the lowest, or LUMO) to form a chemical bond. Whether or not a chemical bond can eventually form depends on 1) the spatial overlap and symmetry, and 2) the energy difference, between the two MOs. The two factors can be qualitatively described by the overlap integral $S_{DA} = < \phi_D | \phi_A >$ and the HOMO-LUMO energy difference $E_{DA} = E_D - E_A$, where E_{D} (an eigenvalue of $\hat{F}\phi_D = E_D\phi_D$) is the orbital energy associated with the donor's HOMO and E_{A} is that of the acceptor's LUMO, involved in the bonding process, respectively. For calculation purposes, it has to be noted that S_{DA} and E_{DA} can vary substantially based on the orbital (e.g., HOMO vs. HOMO-1), reacting configuration and functional selection.[9]

For the other types of BMIs, however, the MO method is not commonly used. Instead, many excellent theories (e.g., electrostatic, dipole, Marcus model,[10, 11] etc.) have been developed to account for the observed phenomena such as cation-π, hydrogen bonding, and charge-transfer complexes. Here in this communication, we explore the possibility of using only two parameters, S_{DA} and E_{DA} from the MO theory to give a very crude but coherent description of all types of

BMIs. For calculations of selected interacting pairs, the optimized geometry is obtained using Gaussian 16 software pack[12] at B3LYP with empirical dispersion and 6-311+G(d, p) level; for consistency, the energy levels of HOMO and LUMO are calculated at the same level, where the overlap integral between the two MOs is calculated using the Multiwfn software[13]. In our method, S_{AB} is specifically referred to as the overlap integral for the transition state for chemical reactions (since there exists many possible local minima for pre-reaction complexes) and electron transfer processes (for reactions without a transition state in cation-anion reactions, we simply tear the product molecule into two separate components); for non-bonding interactions, S_{AB} is calculated from energy-optimized (lowest energy) molecular configurations for the pair of molecules. Again, we do not attempt to build a scientifically scrupulous theory in this communication, but rather provide an alternative way to think about interactions. In addition, the results are obtained with hypothetic interactions in vacuum, which could be far different when the molecules are in solvents.

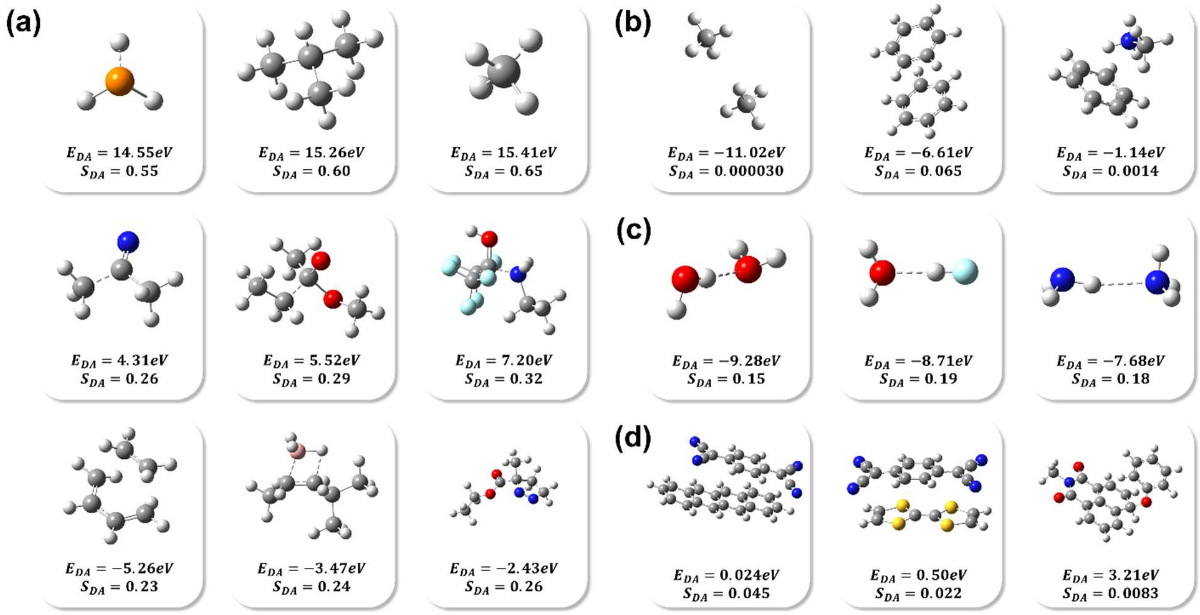

Figure 1. Optimized molecular configurations in the following bimolecular interactions: **(a)** PH_2^- anion and proton, tert-butyl anion and proton, methyl anion and proton, acetyl cation and methyl anion, ethyl acetate and ethyl anion, ethylamine and acetone hexafluoride, ethylene and cis-butadiene, (Z)-4-methylpent-2-ene and borane, ethyl methacrylate and diazomethane; **(b)** methane and methane, benzene and benzene, benzene and methylammonium cation; **(c)** water and water, water and hydrogen fluoride, ammonia and ammonia; **(d)** tetracene and p-benzenedimalononitrile, tetrathiafulvalene and p-benzenedimalononitrile, N-methyl-1,8-naphthalimide and phenol anion.

As can be seen from Figure 1a, the majority of S_{DA} values for the transition state of a chemical reaction fall within the range of 0.65 – 0.20, which is not surprising since a chemical bond does require substantial initial energy gain from in-phase overlap to offset the energy cost on nuclear rearrangements. The energy difference E_{DA} in these limited examples of chemical reactions in vacuum falls between -5.26 eV (for slow reactions such as non-substituted Diels-Alder reactions) and +15.26 eV for reactions that are violent or essentially explosive (e.g., tBu^- and H^+). Figure 1b shows examples of typically very weak non-bonding interactions such as CH_4…CH_4 (-11.02 ev), and strong ones like $CH_3NH_3^+$…C_6H_6 (-1.14 eV). However, compared to interactions leading to chemical reactions, non-bonding pairs exhibit S_{DA} values close to zero (e.g., 0.065 for C_6H_6…C_6H_6). The reason for a small S_{DA} is most likely a combination of longer distance (due to stronger Coulombic repulsion) and/or bad symmetry between frontier orbitals. It is interesting to notice that the S_{DA} is larger for two benzene molecules vs. two methane ones due to stronger C_6H_6…C_6H_6 attraction, which is quite consistent with the reality that the benzene is more easily to form a condensed phase while methane is not. However, the S_{DA} value for the two benzene molecules is still significantly smaller than that of the chemical reaction because of out of phase cancellation despite a relatively close distance. The "in-between cases" for situations shown in Figure 1a and 1b ($E_{DA} < 0$ and $S_{DA} = 0.10\text{-}0.20$) are presented in Figure 1c, where S_{DA} is smaller compared to that of the bimolecular chemical reactions from Figure 1a but larger than that of non-bonding pairs in Figure 1b. Interestingly, we found that such interactions are exclusively hydrogen bonding in nature. Figure 1d shows an interesting class of interactions with positive E_{DA} and near zero S_{DA} values. These pairs appear to form what are known as "charge transfer complexes (CTCs)", with a single electron spontaneously transferred from a donor to an acceptor and a pair of radicals generated.[14] A positive E_{DA} suggests that thermal electron transfer is favorable; again, since there tends to be more nodes in the frontier MOs in large π-conjugated molecules, it is unfavorable to form chemical bonds because the overall overlap is unlikely to due to many out-of-phase interactions.

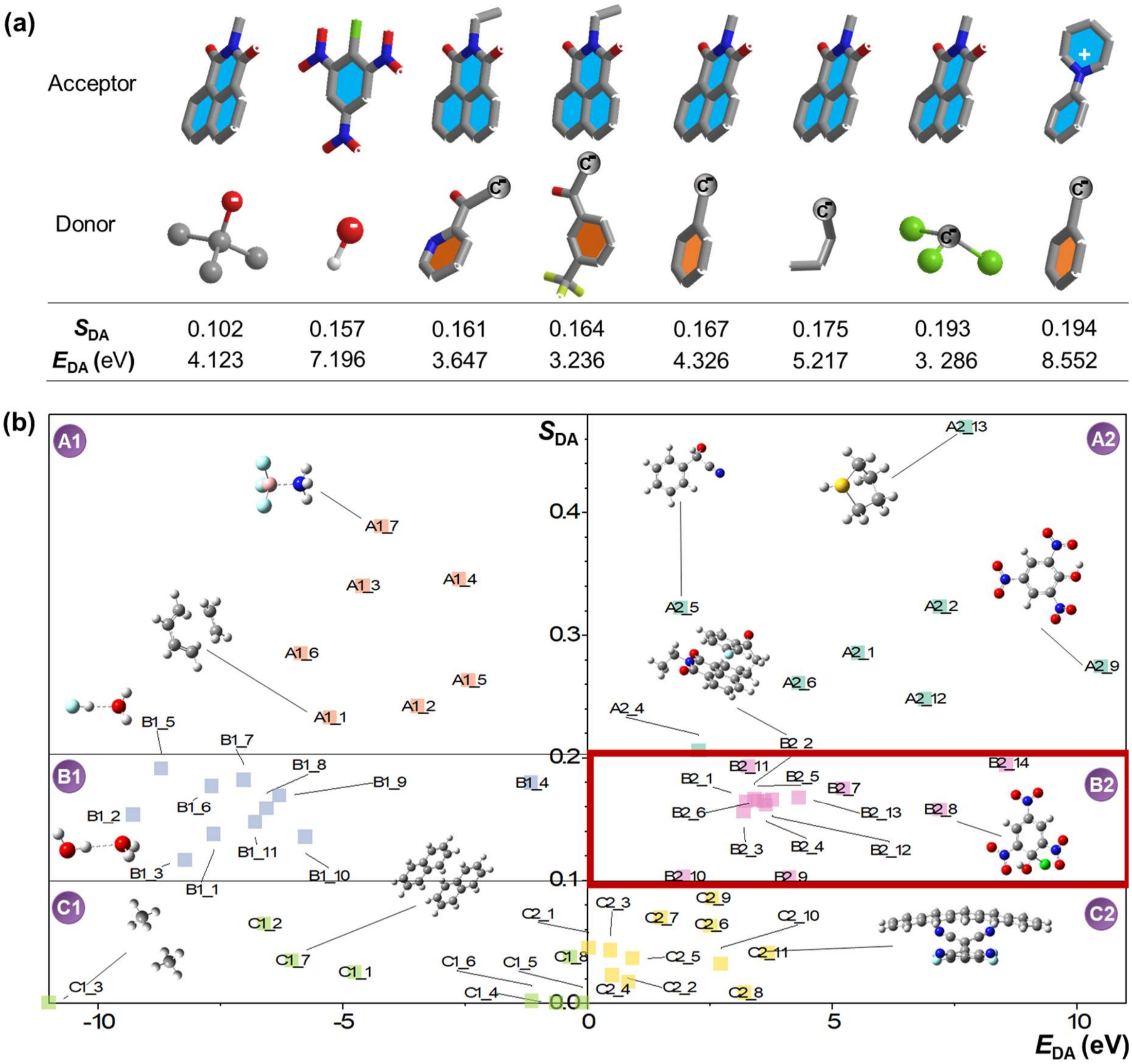

Figure 2. **(a)** Representative donor/acceptor pairs in the B2 region and their calculated overlap integral (S_{DA}) and energy gap (E_{DA}) values (in the order of increased S_{DA} value; hydrogen atoms are omitted for clarity except for hydroxyl ion). **(b)** Two-dimensional diagram showing where the calculated bimolecular interactions reside in arbitrarily divided regions: A1: "mild" chemical reactions; B1: hydrogen bonding; C1: non-bonding interactions; A2: "extreme" chemical reactions; B2: a hybrid interaction in between chemical reactions and single electron transfer; C2: spontaneous single electron transfer. The chemical structures and calculated details for all the molecules are provided in the Supporting Information.

As the trend becomes clear with more calculated pairs, we can plot a two-dimensional map, shown in Figure 2, using E_{DA} as the X axis and S_{DA} as the Y axis. If we arbitrarily divide the map into six sections (which are labelled A1, A2, B1, B2, C1 and C2, respectively), they could then represent six different types of BMIs. Logically, A1 and A2 are “mild” and “easy” or “violent” chemical reactions, respectively; interactions in C1 and C2 should correspond to non-bonding interactions and single-electron transfer, respectively. As a transition region from A1 to C1, B1 should in principle be filled with cases of “special bonding”, primarily hydrogen bonds. A borderline situation between a piperidine donor and a C_{60} acceptor (E_{DA} = -2.029 eV; S_{DA} = 0.104, Figure S1) indicates that such an interaction might be much stronger than van der Waals force but weaker than a conventional chemical bond. Indeed, the pair is recently examined by Hobza et al.[17] and is concluded to be a dative bond. At this point, it is not difficult to notice that B2 is not populated with any commonly seen interactions. However, as a transition region from A2 to C2, B2 should mainly contain interactions exhibiting characters with both chemical bonding and electron transfer. It is well-known that a radical pair (RP) is created post single-electron transfer.[1, 2, 15] However, it must also be considered that cases in B2 should also exhibit bonding character, i.e., localized electron pair. If we designate the RP state as Ψ_{RP} and chemical bonding state as Ψ_{CB}, the “hybrid” B2 state should be described as $\Psi_{\mathrm{Hybrid}} = (a<\Psi_{\mathrm{RP}}| + b<\Psi_{\mathrm{CB}}|)/N$, where a and b are weight factors, and N is the normalization factor. Therefore, B2 depicts a peculiar state that is more localized than conventional RPs but more delocalized than conventional chemical bonding; the superimposed state can yield either outcome during measurement (e.g., with only a percentage of population exhibiting single electron signals while the rest stays dormant). Does such a state exist? A positive E_{DA} value means that the state should at least consist a very strong donor or acceptor; a small but unneglectable S_{DA} indicates that the wave functions of the donor and the acceptor cannot contain too few or too many nodes at the same time, i.e., one of them should be simple like that of an inner shell atomic orbital and the other one complicated, such as that of a π^* or an atomic orbital with a high principle quantum number.

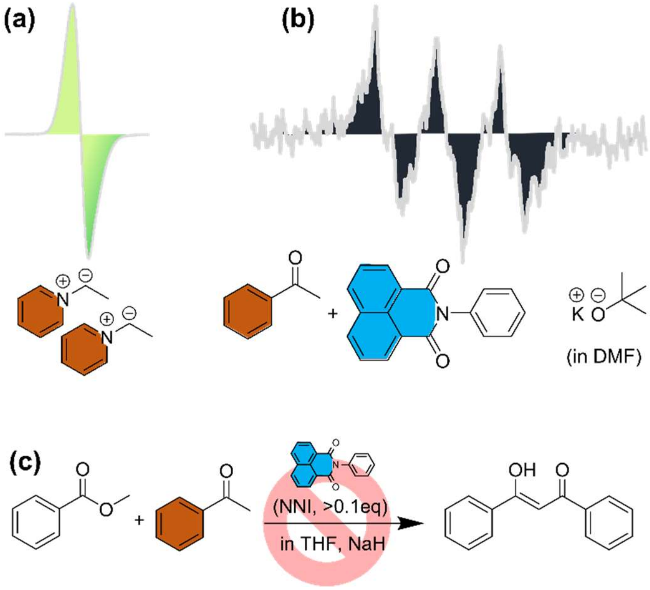

Figure 3. **(a)** Chemical structure of a pyridinium ylide and its EPR spectrum; **(b)** ^{1}H NMR spectrum of acetophenone and an N-substituted naphthalimide mixture in the presence of potassium tert-butoxide; **(c)** Schematic illustration of a failed Claisen condensation when an N-substituted naphthalimide is present.

We recently encountered a handful of molecules that exhibit bizarre physical properties which are hard to justify with traditional viewpoints. For example, we were unable to get any NMR signals for a series of pyridinium ylides,[15] which are conventionally viewed as nucleophiles. Concomitantly, electron paramagnetic resonance (EPR) experiment uncovered their radical character – although the intensity is one order of magnitude weaker compared to that of classical nitroxide or phenol radicals (Figure 3a). Similarly, we also reported the discovery of unusually strong BMI between a carbanion (produced from a carbon acid such as acetophenone and a strong base such as tBuOK) and an N-substituted naphthalimide (Figure 3b), the solutions of which not only exhibit vivid colors ranging from violet to green or indigo depending on the carbanion used, weak EPR spectra were also obtained with undiscernible NMR spectra. The system was first uncovered from failed attempts to conduct Claisen condensation reactions between acetophenone and ethyl acetate under basic condition, provided that N-substituted naphthalimide (Figure 3c, NNI, >0.1 eq.) was present. For the binary system, we here also calculate the two parameters and find they fall right into the B2 region: E_{DA} = 3.664 eV, S_{DA} = 0.165. The common traits for the two systems are apparent: 1) the donor HOMO is higher in energy than the acceptor LUMO; 2) the donor wave function is quite simple and the acceptor complicated, which generates small but not near-zero overlap integral. Another recent example is from Eisenberg et al.,[16] who found that when an ammonium salt is held close to an indole residual within a protein, the pair appeared to show a ground-state radical like state which is not obviously predicted by conventional knowledge. Although cation-π* interaction is not uncommon, it is still puzzling to observed radical-like character between the pair and is hard to justify with conventional knowledge. However, when the present protocol is applied using the protein coordinates, we find substantial in-phase overlap between the C-N σ* and the indole π orbitals, although the E_{DA} value is slightly negative which may well be attributed to difference in solvent environment or computational method. Nonetheless, the small negativity can easily be overcome by thermal or photo-agitation to send the pair from B1 to B2.

In summary, the communication raises the possibility of systematically considering bimolecular interactions using the molecular orbital theory, where two indices, S_{DA} and E_{DA}, related to the frontier orbitals of a donor and acceptor can be used to generate a two-dimensional diagram. The simplistic model puts chemical bonding on par with van der Waals complex, which is an unprecedented way of modeling molecular interactions. Nonetheless, it was found that similar types of BMIs are clustered near each other in this 2D-plot. Interestingly, a lesser studied region appears to be evident on this plot and is proposed as a hybrid BMI case between a conventional chemical bond and charge-transfer complex. The hybrid is predicted to possess both stability and unpaired electron activity. The theory is also used to justify a few perplexing examples from recent studies from us and others.

SUPPORTING INFORMATION DESCRIPTION

Supporting Information is available, including additional calculation details.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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