

Organizing Organic Reactions: The Importance of Antibonding Orbitals

David E. Lewis

Department of Chemistry, University of Wisconsin–Eau Claire, Eau Claire, WI 54702-4004; lewisd@uwec.edu

Ultimately, all organic reactions can be reduced to a question of the formation and cleavage of chemical bonds, and how one rationalizes these bonding changes is determined by the way one views bonding in organic compounds. For most organic chemists, the Lewis theory of bonding provides the simplest framework for discussing the structure and reactivity of organic compounds. One of the major successes of the Lewis theory of bonding was the way in which it provided a clear qualitative picture of the bonding in chemical compounds, so that the bonding changes occurring during chemical reactions could be rationalized. However, one of the weaknesses of Lewis theory is that it concentrates the student's attention only on the *bonding* interactions within a molecule. After students have been exposed to molecular orbital theory, this tends to result in their concentrating only on the *bonding* molecular orbitals of the molecule. The result, in both cases, is that structure dominates the discussion. To most students, antibonding orbitals are an abstraction at best and a distraction at worst.

In 1965, Woodward and Hoffmann's landmark paper on the conservation of orbital symmetry appeared in *Angewandte Chemie (I)*. Three decades later, frontier orbitals have still to find their way into routine use in the teaching of beginning courses in organic chemistry. In part, this may stem from a perception that the concepts required are too abstract, or from a perception that frontier orbitals can only be applied to reactions in the context of orbital correlation diagrams. This view is reinforced by most modern textbooks in organic chemistry, which relegate frontier orbitals to discussions of pericyclic reactions and to special topics chapters late in the course (i.e., to a point in the course when the student is ready for "difficult" material). This paper will attempt to show that frontier orbital concepts can not only be used in a meaningful way throughout the beginning organic chemistry course, but that they provide both a unifying and a simplifying framework from which organic reaction chemistry can be taught at the introductory level.

LCAO Theory and Molecular Orbitals

The successes of Lewis theory in providing a unifying framework for discussions of organic structure and reactivity are obvious. In order for frontier orbital theory to be equally useful in the classroom, it must be capable of doing at least what Lewis theory was able to accomplish, and we are probably justified in expecting more. Any discussion of frontier orbitals in organic reactions must begin with a description of what is meant by a molecular orbital. By far the most common theory used in beginning organic chemistry to describe molecular orbitals is the LCAO theory, which describes the formation of a molecular orbital as a process of overlap of atomic orbitals. The σ orbitals produced by this theory are generally localized and the π orbitals may be either localized or delocalized.

It is one of the consequences of the mathematics involved in the LCAO overlap process that the total number of orbitals remains constant—during the formation of a set of molecular orbitals from a set of atomic orbitals on two or more atoms, the number of molecular orbitals produced must be exactly equal to the number of atomic orbitals used. This corresponds to a type of "law of conservation of orbitals": orbitals can be altered, but neither created nor destroyed. Moreover, in its most widely used form, the overlap process is restricted to producing molecular orbitals that are mathematically orthogonal, thus placing a further restraint on the permitted modes of overlap.

Pictorially, one can represent the LCAO overlap process as the in-phase overlap of two atomic orbitals, which produces the bonding molecular orbital, and the out-of-phase overlap, which produces the antibonding orbital. It is axiomatic that for every bonding molecular orbital generated by LCAO overlap of a set of atomic orbitals, a corresponding antibonding orbital is generated. In practice, however, we tend to use the term "bond" to describe the filled bonding orbital alone and ignore the presence of the associated antibonding orbital. Nevertheless, it is important to remember that one logical consequence of this axiom is that every covalent bond generated by LCAO overlap of atomic orbitals is related to a *pair* of molecular orbitals, one low-energy occupied orbital (the bonding orbital) and one higher-energy unoccupied orbital (the antibonding orbital).

This leads to a second generalization about covalent bonds generated by the LCAO approach. In the strictest sense bonding is now defined as any situation where the bonding orbital contains more electrons than the antibonding orbital, and the order of the bond is related directly to the difference. Thus, when we use the term bond in the LCAO sense, we should make it clear to our students that we are referring to a situation involving two orbitals, one (the bonding orbital) that is filled and one (the antibonding orbital) that is empty. When both orbitals associated with the bond are equally occupied, the bond breaks.

Two Important Principles: Aufbau and Exclusion

There are two extremely important principles that limit the number of ways in which the electron reorganization during a reaction can take place: the Pauli exclusion principle and Pauli's aufbau principle. In order to comply with the exclusion principle, any organic reaction involving the transfer of an electron pair from one reactant to the other can be initiated only by the transfer of a pair of electrons from a filled orbital on one reactant to an empty orbital on the other. One may not transfer electrons from one filled orbital to another. In other words, the unoccupied molecular orbitals of the participating molecules are just as important in the process of initiating reactions as their occupied counterparts. The pre-

requisite that one unoccupied orbital participate in the initiation of these types of reactions is absolute, but it is also a fact which instructors seldom emphasize in their classes. This point was made explicitly for photochemical reactions and cycloadditions by Orchin and Jaffé in their 1967 book (2), but not even these authors extended their discussion to other organic reactions. In fact, the lesson appears to have fallen by the wayside, to the point that it is quite common to see the overlap of two filled molecular orbitals represented in undergraduate organic chemistry textbooks, especially when multi-bond reactions (e.g., the E2 reaction) are being discussed.

Of Horses and Orbitals: HOMO and LUMO, the Frontier Orbitals

The process of electron reorganization in a chemical reaction can be represented by a simple model based on the process of transferring liquids from one cup to another. Assume that one has four identical cups, two red ones filled with water and two blue ones filled with milk, representing the reactant configuration. After the reaction is complete, the red cups contain the milk and the blue cups contain the water. If the problem is how to accomplish the transfer without spilling any liquid, most students immediately see that one needs one empty cup to do so. The same situation applies to molecular orbitals: in order to reorganize the electrons between two reacting molecules, one needs an empty orbital to permit the initial transfer of electrons from one reactant to the other.

After we have decided that the transfer of electron pairs from one reactant to another requires the overlap of a filled orbital on one reactant with an empty orbital on the other, two questions arise: "Which filled orbital and which empty orbital?" and "Does it matter?" One response, albeit a little flip, is to use the analogy of betting on a horse race. Consider that you have money to wager, and ask the same two questions modified this way: "Which horse in which race?" and "Does it matter?" Clearly small differences can be critical—in horses, and in molecules.

The aufbau principle guarantees that every filled molecular orbital of a molecule is lower in energy than any empty molecular orbital of the same molecule. Since the initial stages of a reaction involve the transfer of electrons from a filled orbital to an empty orbital, the process for most reactions is inherently endothermic (the exception is radical recombination). The activation energy of the process is related, albeit not simply so, to the efficiency of orbital overlap between the filled and empty orbitals. This, in turn, is related to the energy gap between the participating orbitals; reactions proceed most readily if the two orbitals are closely matched in energy. The two orbitals best matched in energy will be the highest-energy occupied molecular orbital, or HOMO, on one reactant, and the lowest-energy unoccupied molecular orbital, or LUMO, on the other.

"How does a reaction occur?" Superficially this is a simple question, but it is more complex than it might at first seem. And, given the central position of reactivity in organic chemistry, it is an important one. In the broadest terms, one can define a reaction as a process that takes one stable molecular configuration (or set of nuclei and occupied and unoccupied orbitals) to another stable molecular configuration via unstable configurations.

There are two pivotal processes in a reaction: the initial orbital overlap that starts the system moving away from the reactant along the reaction coordinate, and the overall electron reorganization which takes place. Of these two, the overall electron reorganization is spontaneous once initiated; the system will continue to reorganize until a new stable molecular configuration (that of the product or a stable intermediate) is attained or until the system reverts to its original stable configuration. In this, the electron reorganization in a reaction resembles the domino effect. To make all the dominoes fall, only the first one need be pushed over. It is this simple fact that makes frontier orbital theory so powerful a tool for teaching introductory organic chemistry, because one does not need to describe the entire change in molecular configuration; one need only specify the initial HOMO–LUMO overlap. The advantages are even more apparent if one considers the level of sophistication required to specify only the frontier orbitals that initiate the reaction and the level required to develop a full-fledged orbital correlation diagram for the reaction. In the first case, the student need only identify the two frontier orbitals; in the latter, the fates of all orbitals must be considered.

Frontier Orbital Energies and Activation Energy of Reactions

The presence of heteroatoms complicates the picture somewhat because of the different energies of the orbitals involved. Polar covalent bonds are somewhat more problematic. The molecular orbitals of a covalent bond between different atoms are obtained by incomplete mixing of the atomic orbitals, so that the molecular orbitals more closely resemble the atomic orbitals from which they are derived than is the case with a bond between like atoms. The greater the energy difference between the starting atomic orbitals, the less the degree of mixing. However, translating this situation into a "rule of thumb" is not simple. For polar covalent bonds between carbon and more electronegative elements, one may state that both frontier orbitals associated with polar covalent bonds are lower in energy than those of a similar carbon–carbon bond. Lone pairs on heteroatoms permit an easier generalization: the more electronegative the heteroatom, the lower the energy of its lone pairs (provided that both are in the same row of the periodic table) (3).

Another useful generalization can be framed for species that carry formal charges: as the formal charge on a species becomes more positive, the energies of its frontier molecular orbitals decrease. This is nicely illustrated by the HOMO and LUMO of the series H_3O^+ , H_2O , and OH^- . In all three species, the atoms involved are oxygen and hydrogen; only the formal charge on the oxygen atom changes. The hydronium ion, whose oxygen carries a formal positive charge, has the lowest HOMO and LUMO energies; its low LUMO energy makes it a strong acid but its low HOMO energy effectively prevents it from functioning as a base under normal circumstances, despite the presence of a lone pair on oxygen. Hydroxide anion, whose oxygen carries a formal negative charge, has the highest HOMO and LUMO energies; its high HOMO energy makes it a strong base but its high LUMO energy effectively prevents it from functioning as an acid under normal circumstances, despite the presence of the potentially

Table 1. Possible HOMO–LUMO Combinations

HOMO	LUMO	Result
an occupied n orbital	an empty a orbital	bond formation only
an occupied n orbital	a σ^* orbital	bond formation and bond rupture
an occupied n orbital	a π^* orbital	bond formation and bond rupture
a π orbital	an empty a orbital	bond formation and bond rupture
a π orbital	a σ^* orbital	bond formation and bond rupture
a π orbital	a π^* orbital	bond formation and bond rupture
a σ orbital	an empty a orbital	bond formation and bond rupture
a σ orbital	a σ^* orbital	bond formation and bond rupture
a σ orbital	a π^* orbital	bond formation and bond rupture

acidic O–H bond. Water, whose oxygen is formally neutral, represents the intermediate case in which the HOMO and LUMO energies are accessible, but only just: it is a weak acid and a weak base.

The point was made above that the activation energy of a reaction is closely related to the efficiency of the overlap between the interacting frontier orbitals. This, in turn, depends on the energy gap between the HOMO and the LUMO and on the mode of overlap of the orbitals. Like the overlap of atomic orbitals to form molecular orbitals, the overlap of frontier orbitals can occur with σ (coaxial) and π (coplanar) geometry. Coaxial overlap of atomic orbitals generally results in the lower-energy bonding orbital (the more stable bond), and coaxial overlap of the frontier orbitals generally results in the lower-energy pathway from reactants to products. Likewise, in multiple-lobe orbitals where the lobes are different sizes, the most efficient overlap occurs when the larger lobes of the two orbitals interact.

Classifying Organic Reactions by the Participating Frontier Orbitals

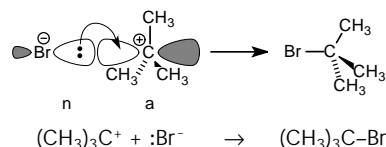
The classification of reactions according to reactant type is a time-honored tradition of organic chemists, with the result that the functional group organization remains the standard textbook approach to teaching organic chemistry. However, one can also categorize reactions according to the frontier orbitals involved. Only three types of orbital are commonly encountered as the HOMO of an organic molecule or ion: a filled σ orbital, a filled π orbital, and a filled nonbonding (n) orbital. Likewise, there are only three commonly encountered types of LUMO: an empty σ^* orbital, an empty π^* orbital, and an empty nonbonding (atomic, a) orbital. Thus, there are nine and only nine possible HOMO–LUMO combinations; they are tabulated in Table 1. Every known intermolecular polar organic reaction in which a new bond is formed fits one of these nine HOMO–LUMO combinations.

The transfer of a pair of electrons from the HOMO to the LUMO is, by definition, a reaction between a Lewis acid and a Lewis base. The compound that reacts via its HOMO is functioning as an electron-pair donor, that is, a Lewis base or a nucleophile. A nucleophile, or Lewis base, participates in reactions via its HOMO. The compound that reacts via its LUMO is functioning as an electron-pair acceptor, that is, a Lewis acid or an electrophile. An electrophile, or Lewis acid, participates in reactions via the LUMO.

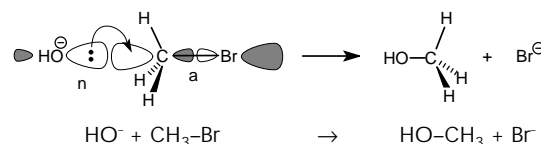
With the exception of the hydrogen cation, H^+ , which has no electrons at all and therefore cannot have a HOMO, all molecules and ions possess both a HOMO and a LUMO. Therefore there are always, in principle, two possible HOMO–LUMO combinations for reactions in which H^+ is not a participant. Fortunately, one of these combinations is usually obviously right and the other is usually obviously wrong. The nine possible HOMO–LUMO combinations in Table 1 are all represented by real reactions in organic chemistry, although the first six entries represent much more common reaction types.

Reactions Where the Electron Donor Is a Lone Pair

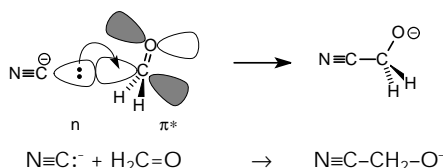
1. $n + a$. This combination of frontier orbitals leads to the classical formation of a Lewis acid–Lewis base complex between ammonia and boron trifluoride, as well as the second step of the S_N1 reaction. Conceptually, it is the simplest of the frontier orbital interactions for most students to grasp because of the absence of concomitant bond rupture.



2. $n + \sigma^*$. This combination of frontier orbitals is the overlap that gives rise to the S_N2 reaction between simple heteroatom nucleophiles and alkyl halides. One of the biggest problems in teaching multi-bond reactions lies in rationalizing reaction stereochemistry—why does the S_N2 reaction proceed with inversion? The derivation of reaction stereochemistry from the orbitals involved is one of the most useful aspects of the frontier orbital approach to teaching organic reactions. In the S_N2 reaction, for example, the students can deduce “back-side attack” directly from the coaxial overlap of the n and σ^* orbitals; the orientation of the orbitals involved requires this reaction geometry. This allows the instructor to then introduce inversion of configuration without many of the “hand-waving” explanations that this often entails.

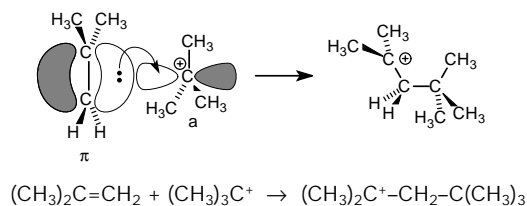


3. $n + \pi^*$. This combination of frontier orbitals is the overlap involved in the addition of nucleophiles such as amines, oxanions, and cyanide ion to the carbonyl group of an aldehyde or ketone, and for conjugate additions of nucleophiles to conjugated carbonyl compounds. Although it is not strictly correct to do so owing to the covalent nature of the metal–carbon or metal–hydrogen bonds, this set of frontier orbitals can also be used for discussions of Grignard additions to carbonyl compounds and for complex metal hydride reductions. At a more advanced level, the frontier orbital overlap involved in this type of reaction can be used to rationalize observations and theories such as the Bürgi–Dunitz trajectories (4–6) and Baldwin's rules for ring closure at unsaturated centers (7).

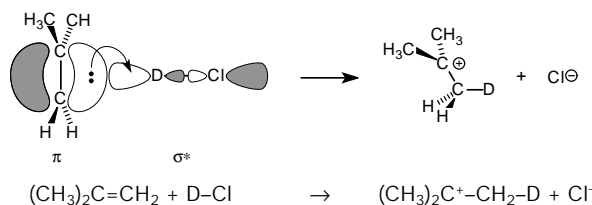


Reactions Where the Electron Donor Is a π Bond

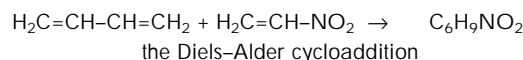
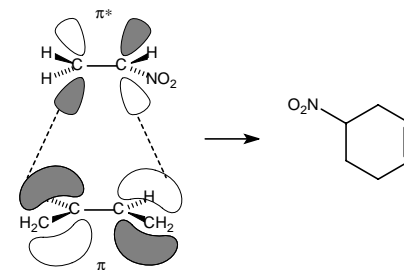
4. $\pi + a$. This combination of frontier orbitals corresponds to the initial overlap of orbitals during the addition of a carbocation to an alkene. Unlike the $n + a$ overlap, which results only in bond formation, $\pi + a$ overlap leads to the rupture of the π bond as well as formation of the new σ bond.



5. $\pi + \sigma^*$. This combination of frontier orbitals is one of the most frequently encountered in organic chemistry. It corresponds to the orbital overlap that initiates the transfer of a proton from a protic acid to an alkene, as in the first step of electrophilic addition of a hydrogen halide to an alkene, or the orbital overlap that initiates the formation of a cyclic bromonium ion by the reaction between bromine and an alkene.



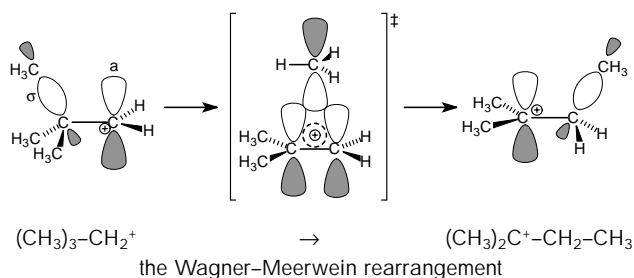
6. $\pi + \pi^*$. This frontier orbital overlap initiates the Diels–Alder cycloaddition reaction. This reaction is generally initiated by the overlap between the diene HOMO and the dienophile LUMO, although the alternative combination (diene LUMO and dienophile HOMO) gives the same result.



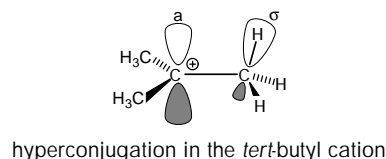
The same $\pi + \pi^*$ overlap initiates several other reactions, including the Prins (8) and Mukaiyama (9) reactions; it also initiates the aldol addition of enolate anions to carbonyl compounds (although the π orbital involved as the HOMO is actually a nonbonding orbital).

Reactions Where the Electron Donor Is a σ Bond

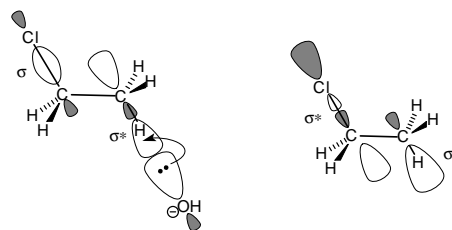
7. $\sigma + a$. The σ -type overlap of these two frontier orbitals does not occur very often in organic reactions, but π -type overlap of a filled σ orbital involving one atom (the HOMO) and an empty atomic orbital (the LUMO) on the adjacent atom is important in two places in organic chemistry: the Wagner–Meerwein rearrangement and hyperconjugation. In the Wagner–Meerwein rearrangement of carbocations (10), the HOMO is the C–C σ orbital and the LUMO is the empty p orbital on the adjacent carbon atom.



Likewise, π -type orbital overlap of an empty p orbital with an adjacent filled σ orbital may be invoked to rationalize the delocalization of the charge density of a carbocation over the adjacent alkyl groups by hyperconjugation (11, 12).

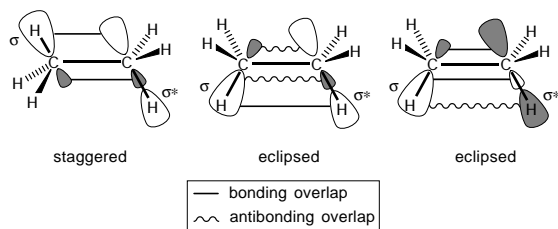


8. $\sigma + \sigma^*$. The σ -type overlap of these two frontier orbitals is not common in organic chemistry, but π overlap is. Neither the σ - nor the π -type overlap occurs commonly as the primary overlap in organic reactions, but π -type overlap is an important part of the orbital overlap in the E2 reaction, where the σ and σ^* orbitals on adjacent atoms must be coplanar in order for the elimination to be concerted.



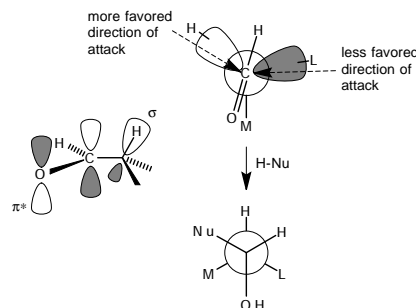
the E2 elimination reaction

The same overlap almost certainly plays an important part in the conformational preference of ethane for the staggered conformation. If steric factors alone were responsible for this preference, the barrier to rotation in neopentane would be much higher than 4.8 kcal mol⁻¹, given the value of 3.0 kcal mol⁻¹ for ethane (13–15). As is apparent from the diagram below, in the staggered conformation the π overlap between adjacent bonding and antibonding orbitals is maximized, and the overlap is of bonding type in both lobes of each orbital. However, in the eclipsed conformation, it is impossible for both lobes of the σ orbital to simultaneously participate in bonding overlap: the π overlap of one lobe of the σ orbital with the adjacent σ^* orbital is nonbonding. Both possible phase sets of the σ and σ^* orbitals on the adjacent carbon atoms are shown below to illustrate this point.



9. $\sigma + \pi^*$. This overlap is formally responsible for the Grignard addition to carbonyl groups, but little is gained pedagogically by using this representation instead of the conceptually simpler $n + \pi^*$ approach illustrated above. Where this type of overlap is important, however, is in discussions of hyperconjugation where the C–H σ orbital overlaps the π^* orbital of the adjacent alkene, arene, or carbonyl group. The stabilization of a conformation in which this overlap occurs may be used, for example, to rationalize the Cram rule for addition of nucleophiles to chiral aldehydes (16, 17). As illustrated below, the conformation involving this overlap requires that either the large or the small alkyl substituent at the α carbon eclipse the carbonyl oxygen; one would predict on simple steric grounds that the smaller of the two groups will eclipse the carbonyl oxygen. In this conformation, the nucleophile must approach the carbonyl carbon along a trajectory eclipsing either the C–H bond or the C–C bond of the larger alkyl group. The product predicted by this model is, in fact, the Cram isomer, and it is worthwhile noting that

the conformation used to generate the prediction is related to that originally proposed by Cram, in which the aldehyde hydrogen eclipses the largest α -alkyl substituent, by a simple rotation through 60°.



Conclusion

In conclusion, the point should be made that frontier orbital concepts—in simplified form—provide a powerful tool for discussing organic reactivity that goes beyond the conventional discussions based on mechanism. By recognizing the central importance of the antibonding orbitals, one can use the root reactivity of the molecule as a basis for discussing organic reactions and reactivity. The preceding examples have been chosen to demonstrate this by illustrating just how wide a variety of organic chemical concepts, including conformations and reactions, can be accommodated by this model.

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