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Introduction

When people thought the earth was flat, they were wrong. When people thought the earth was spherical, they were wrong. But if you think that thinking the earth is spherical is just as wrong as thinking the earth is flat, then your view is wronger than both of them put together. I. Asimov

1.1 Stereoelectronic effects – orbital interactions in control of structure and reactivity

It is easy to believe that the Earth is flat when driving through the Great Plains. Furthermore, the “flat Earth” approximation works quite well in many other aspects of everyday life. Because the small deviation from planarity – only 8 inches per mile – does not make a difference for everyday activities, we can order a cup of coffee or play a game of golf without worrying about the fine details of planetary shapes. However, once one prepares to launch a satellite instead of a golf ball or to navigate “around the globe”, the planet’s curvature becomes crucial. But *is* Earth a globe? A closer look from space finds that Earth is not a sphere but an “oblate spheroid” that bulges at the equator. Another revision! When should refinements stop and why should a chemist care?

The story of the flat Earth, borrowed from Isaac Asimov,¹ reflects the common evolution of scientific models. Sometimes, models are discarded completely (e.g. phlogiston) but, more often, they are refined and taken to the next level of applicability (such as Newton’s theory of gravity paving the way for Einstein’s theory of relativity). How does it apply to organic chemistry? How adequate are the undergraduate organic foundations for the broad understanding of structure and reactivity? Do we really need to go deeper?

The importance of continuous improvement of models is illustrated by the following “diagnostic quiz” given to first-year graduate students at the Florida State University. Take a minute and test yourself.

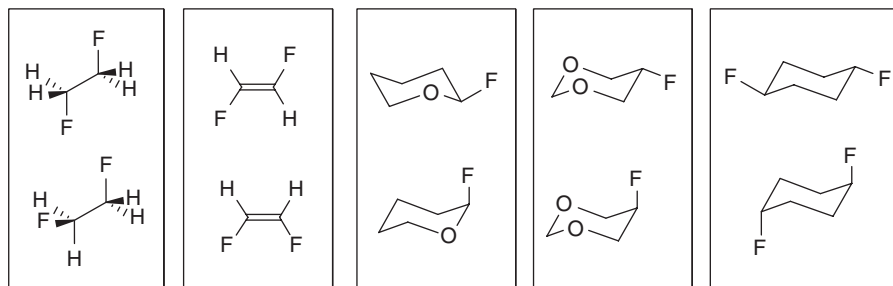


Figure 1.1 Circle the more stable structure in each of the above pairs.

The answers may or may not be surprising, depending on how far the reader is separated from the undergraduate organic class. For each pair in Figure 1.1, the *bottom structure is more stable* than the top structure. In particular, the *gauche* conformation of 1,2-difluoroethane is more stable than the *anti* conformations; *cis*-difluoroethene is more stable than the *trans*-isomer; the equatorial conformers of the two fluoro-substituted oxacyclohexanes are less stable than their axial counterparts; and the *diaxial* 1,4-difluorocyclohexane is ~ 1 kcal/mol *more* stable than the diequatorial conformer. The answer in each case is opposite to expectations based on the steric repulsion – the “flat Earth” models that have served reasonably well as a foundation of undergraduate organic chemistry.

It is not surprising that it is a rare undergraduate student who gives correct answers to all of the above problems. Almost invariably, the correct answers come as a surprise, even to a student with a good mastery of undergraduate organic chemistry. Clearly, a new set of concepts is needed to refine the initial model of organic structure and reactivity. This book aims to introduce these concepts in a way that will provide a logical ascension from a simplified discussion of an undergraduate textbook to a level appropriate for a practicing organic chemist.

Undergraduate organic chemistry lays the foundation of chemical knowledge – a reasonable approximation and a useful and often sufficient way to describe molecules as Lewis structures augmented, as needed, by resonance. However, once one realizes that organic molecules are quantum objects delocalized in space, far from the flat two-dimensional drawings on a sheet of paper or a blackboard, it may not be a complete surprise that this simple concept has its limitations.

The way to get to the next step in understanding molecular structure is to move from the flat Lewis structures on a flat sheet of paper to the 3rd dimension. The elements of stereochemistry are introduced, of course, in undergraduate courses. However, this important step is not enough – when one needs to design, understand, and control new reactions, it is crucial to start thinking about organic molecules as intrinsically delocalized and spatially anisotropic quantum objects. This book focuses on the importance of delocalization – the deviation of real molecules, quantum objects par excellence, from idealized Lewis structures.

The laws of chemical attraction in the world of atoms and molecules are defined by quantum mechanics. Constructive interference of electronic wavefunctions is the quantum essence of chemical bonding that “glues” smaller fragments into larger molecular assemblies. As a result, the chemical world at the molecular level is defined by interactions between atomic and molecular orbitals. Because orbitals and molecules are three-dimensional, such interactions depend on the relative atomic arrangements in space. The modulations of electronic interactions by changes in molecular geometry are generally referred to as *stereoelectronic effects*. In organic chemistry, stereoelectronic effects can be defined as *stabilizing electronic interactions maximized by a particular geometric arrangement which can be traced to a favorable orbital overlap*. Stereoelectronic interactions are omnipresent in chemistry, as only a small subgroup of electronic effects, i.e. the long-range² electrostatic effects, can be considered, with a degree of approximation, as not having a substantial stereoelectronic component.

There is one common misunderstanding that needs to be addressed early: “stereoelectronic” is not the same as “steric + electronic”! By definition, stereoelectronic effects are *always* stabilizing, reflecting increased delocalization at favorable conformations. Repulsive steric interactions also depend on the arrangement of orbitals in space but, historically, are not included under the umbrella of stereoelectronic effects.

Stereoelectronic factors control interactions between different atoms or molecules and interactions between different parts of a single molecule. Although our focus will be on the latter, we will also briefly illustrate the fundamentals of intermolecular interactions, because they broaden the conceptual foundation for subsequent discussion and illustrate the key patterns for orbital overlap without intramolecular constraints being imposed on the geometries.

Understanding the role of orbital interactions can be beneficial from the practical perspective. For example, the symmetry of frontier molecular orbitals can explain why thermal [2+2] cycloaddition fails, whereas the analogous reaction of transition metal alkylidenes, compounds that can be described as having a metal–carbon double bond, proceeds efficiently under mild conditions (Figure 1.2). In this case, *an extra orbital node is the difference between a failed reaction and a Nobel Prize!*

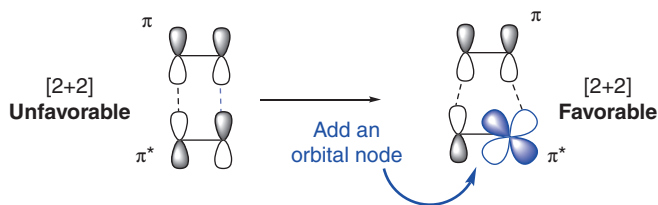


Figure 1.2 The striking effect of orbital symmetry on [2+2] cycloadditions.

1.2 Orbital interactions in theoretical chemistry

The concept of stereoelectronic effects resulted from the cross-pollination of quantum-mechanical ideas (both valence bond, VB and molecular orbital, MO) with the three-dimensional thinking of organic chemists. The involvement of orbitals evolved over the 20th century from the qualitative ideas of Lewis and Pauling through the approximations of Hückel and semi-empirical treatments to the sophisticated accuracy of modern multiconfigurational approaches. However, even the most complex wavefunctions can still be analyzed in terms of individual orbitals using such methods as natural bond orbital (NBO) analysis (introduced in Chapter 4). Such dissection allows one to recover the basic Lewis concepts that seem to be lost in the mathematical jungle and to use them as a foundation for developing the deeper understanding of electronic structure.

In parallel, experimental organic chemistry grew in scope and sophistication. A large body of information was acquired allowing precise measurements of molecular geometries, spectroscopic parameters, and reaction kinetics to provide the necessary basis for the fruitful application of stereoelectronic ideas on a quantitative basis.

The accuracy of computational methods has started to rival experimental measurements, but finding the optimal compromise between computational accuracy and cost is an ever-moving target. Time-resolved experimental techniques allow understanding reactivity on the fly, accessing increasingly exotic and increasingly unstable species with even transition states³ and, more recently, hilltops on potential energy surfaces⁴ succumbing to experimental scrutiny. This is a productive interplay. Experiments are important for benchmarking and testing theory,⁵ whereas theory is useful in guiding and streamlining experiments.

1.3 The birth of stereoelectronic concepts in organic chemistry

Initially, even the simple 3D description of molecules was a controversial idea. In fact, Van't Hoff's 1874 book *La chimie dans l'espace* was ridiculed by such eminent chemists as Adolph Kolbe, the editor of the *Journal für Praktische Chemie*, who stated:

A Dr. H. van't Hoff of the Veterinary School at Utrecht has no liking, apparently, for exact chemical investigation. He has considered it more comfortable to mount Pegasus (apparently borrowed from the Veterinary School) and to proclaim in his "La chimie dans l'espace" how the atoms appear to him to be arranged in space, when he is on the chemical Mt. Parnassus which he has reached by bold flight.⁶

However, the situation had already changed drastically before the early 1950s when important stereochemical concepts had already permeated the fabric of organic chemistry. In 1954, the term "stereoelectronic" was born in a paper by Hirschmann et al.⁷ who disclosed a remarkable coordinated ring contraction/expansion in rockogenin (Figure 1.3).⁸ The authors stated that "the stereoelectronic requirements are fulfilled only in the case of the natural C₁₂- β -configuration. The significance of this geometrical factor is reflected in the extraordinary ease with which this rearrangement occurs." The unprecedented rearrangement to a new ring system took place instead of the more mundane methyl migration or elimination without rearrangement.

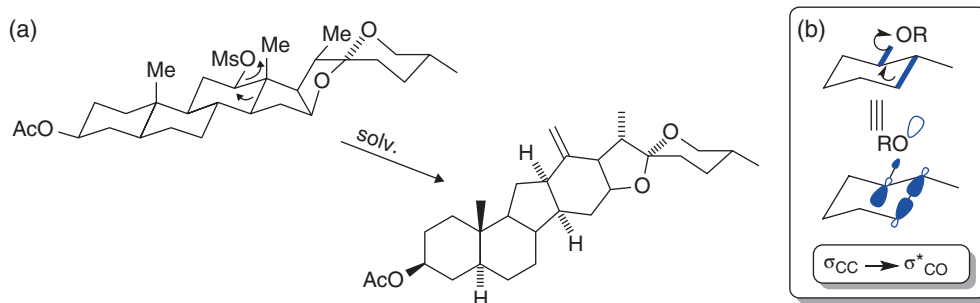


Figure 1.3 (a) Rearrangement of rockogenin as reported by Hirschmann (Source: Hirschmann 1954 (7). Reproduced with permission of American Chemical Society). (b) Orbital interactions involved in the bond reorganization.

Two years later, in 1956, E. J. Corey, a young professor at the University of Illinois used "stereoelectronic" in the title of a paper ("Stereoelectronic Control in Enolization-Ketonization Reactions").⁹ In this paper, he associated the faster loss of axial hydrogen in enolization and the faster gain of axial hydrogens in ketonization with the more favorable orbital overlap of the carbonyl π -system with the axial C-H bonds relative to the equatorial C-H bonds (Figure 1.4).

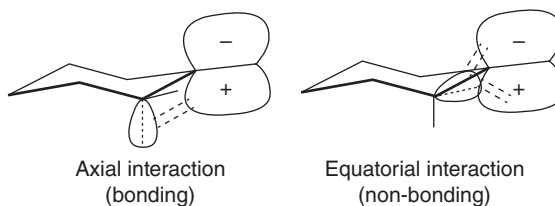


Figure 1.4 Early comparison of the carbonyl π -system overlap with the axial and equatorial C-H bonds. (Source: Corey 1956 (9). Reproduced with permission of American Chemical Society.)

The evolution of stereoelectronic concepts was further catalyzed by steroid synthesis and rapid development of conformational analysis recognized by the 1969 Nobel Prize to Barton and Hassel. However, it was not until 1983, that an organized treatise dedicated to stereoelectronics was published (the important books by Deslongchamps and Kirby).¹⁰

What does the future hold, or “Are we living on an oblate spheroid”? To take the Earth analogy even further, one can illustrate that the basic stereoelectronic concepts are likely to have their own limitations as well. Further refinements of our understanding of chemical structure are unavoidable. For example, stereoelectronic concepts discussed in the following sections are still just an approximation of the exuberant variety of bonding patterns created by the chemical cornucopia known as the periodic table. There are systems so delocalized that starting with a Lewis structure is simply too far off for arriving to a useful description. For such highly delocalized structures, the Lewis approximation is just too crude, and the perturbative approach, which we refer to as resonance, is not able to correct this deficiency. In such cases, it is more productive to describe a molecular system from an MO perspective. Striving to delocalization, transition states and unstable reactive intermediates defy the limitations imposed by the classic two-center two-electron bond: the Lewis structure’s line between atoms. Odd-electron systems are incapable of perfect electron-pairing by their nature. Aromatic and antiaromatic molecules, inorganic clusters, and multicentered bonding in reactive intermediates are examples that further emphasize the primary importance of electronic delocalization.

Quantum tunneling Furthermore, the assumption that nuclear motion is slow enough to be separated from the motion of electrons (the Born–Oppenheimer approximation) and the expectation, that one can always assign distinct connectivity to a molecule, are also only approximations. In the world of quantum phenomena, the whole system of electrons and nuclei can take advantage of Heisenberg’s uncertainty principle and “miraculously” morph into a different molecule with different connectivity even under conditions approaching absolute zero, as long as the barrier separating the two molecular structures is relatively narrow (“quantum tunneling”)¹¹ – Figure 1.5.

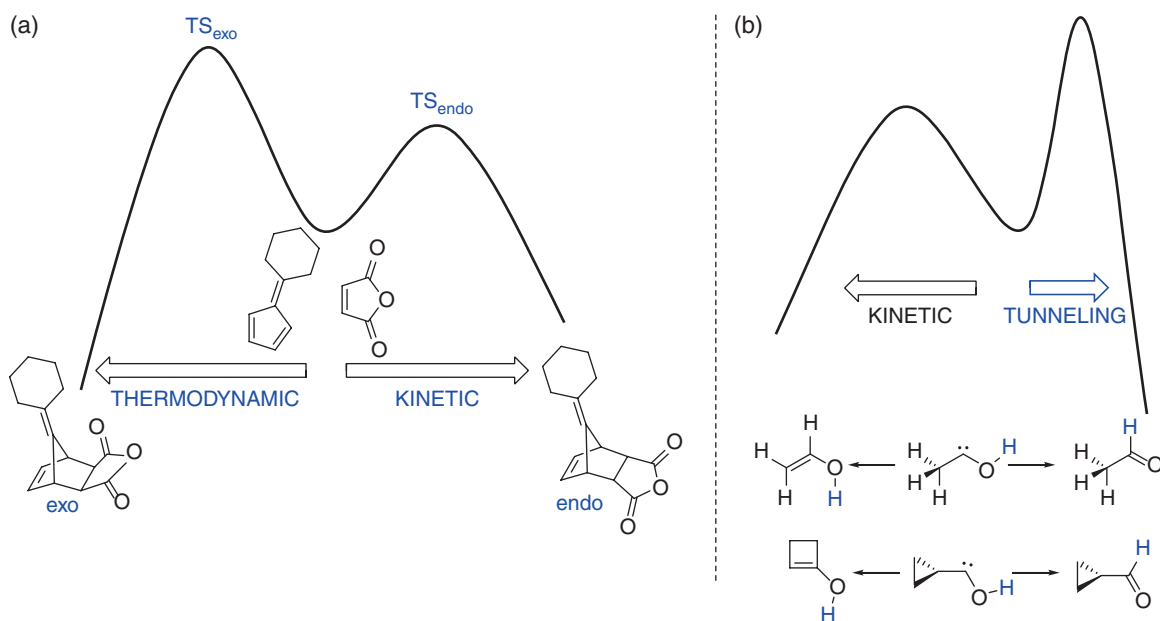
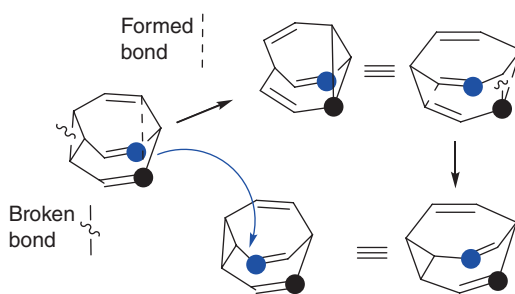


Figure 1.5 Three regimes of reaction control. (a) kinetic vs. thermodynamic control¹² (b) kinetic vs. tunneling control.¹¹

Molecular trajectories Further conceptual limitations of our understanding of chemical reactivity are illustrated by the simple notion that even the exact knowledge of energies and structures of every stationary point at the potential energy surface for a chemical system is not sufficient for accurately predicting the distribution of products for a given set of starting materials. One has to know the shape of the TS region in the 3N–6 dimensional space and the forces that affect a N-atom molecular system that traverses this region on its route from reactants to products.¹³

“Shapeshifting molecules” Not just the position of atoms but also molecular connectivity can be dynamic in the most unusual ways. In so-called fluxional molecules, the whole concept of a single Lewis structure fails at a different level. In these systems, *nuclear* structural reorganization and bond breaking/bond reforming are fast on the chemical timescale.¹⁴ For example, the 10 carbon atoms of bullvalene have identical bonding environment at 140 °C. Both the proton and the carbon NMR spectra show single signals (at 4.2 and 86.4 ppm, respectively), indicating that every carbon atom experiences the identical surroundings and that 10!/3 or 1,209,600 contributing Lewis structures interconvert in this unique “molecule”. There are no permanent C-C bonds in bullvalene, but every atom is equally connected to any other atom! As stated by Doering: “all ten carbon atoms [must] inevitably wander over the surface of a sphere in ever changing relationship to each other”.¹⁵ In the presence of several substituents, each bullvalene molecule becomes a “dynamic library” of compounds¹⁶ – Figure 1.6.

Transposition of atoms via sequential Cope rearrangements



The blue atom moves away from the black atom in the array of seemingly identical structures

Figure 1.6 Part of the extended reaction network connecting multiple isomers of bullvalene via degenerate Cope rearrangements. Although the structure seems to remain unchanged, note that the blue carbon atom moves away from the black atom.

The future of chemistry is full of surprises and, as the boundary with the unknown parts of the chemical universe continues to expand, we need to refine our models as we move deeper into the rich world of fuzzy objects at the subnanoscale.

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