

# Computational Investigations for Undergraduate Organic Chemistry: Modeling Markovnikov and anti-Markovnikov Reactions for the Formation of Alcohols

Rita K. Hessley<sup>†</sup>

Department of Chemistry, Rose-Hulman Institute of Technology, Terre Haute, IN 47803; [Rita.Hessley@uc.edu](mailto:Rita.Hessley@uc.edu)

For the first course in organic chemistry in a setting that stresses collaborative or interactive learning, the applications of molecular modeling are many and they can be rewarding for students and teachers alike (1). All students at Rose-Hulman Institute of Technology have personal notebook computers. Students majoring in chemistry or chemical engineering are required to purchase PC Spartan-Plus molecular modeling software (2) and it is used routinely in Organic Chemistry in class, for out-of-class assignments, and in the laboratory. In our experience students learn the various building and computational setup processes readily, and even students who transfer into the course during the term do not exhibit any lag in participation or in performance after their introduction to the software. We have found that introducing the use of the software during the first laboratory session is a valuable use of that time period. Previously the first lab session was used only for desk assignment, consideration of the laboratory syllabus, and safety training. In a 2–3-hour period students can build structures and acquire some of the computational data that will be used as the term progresses. This extended session gives everyone a simultaneous opportunity to become familiar with the software and gives the instructors insight about any needs that arise for the class as a whole.

This paper describes how molecular modeling can be used to illustrate the effect of structure on the electron distribution and the thermodynamic properties for 3 reactions used to form alcohols from alkenes: acid-catalyzed hydration, oxymercuration–demercuration, and hydroboration–oxidation. It proposes that because molecular modeling promotes students' involvement in their learning and visualizes structure–reactivity relationships, it is a valuable tool with which to counter the common belief among students that memorization is the best way to learn reaction mechanisms. The exercises described here are assigned as homework about one day before the in-class discussion. Students are encouraged to do the modeling assignments together and to compare and pool their data. They bring their computers to class and participate by displaying their version of the structure under discussion and contributing the relevant data from their computations. As we tabulate data together and look for variations and any “outliers”, I can easily move around the room to see that each student has the assignment, and I can sense the extent of un-

derstanding from the discussions and questions that arise. Because students must also deal with the interpretation and application of computational data working alone on exams, there is little concern that a few students are doing the actual work and others just copying their files. Using more than one example of any particular structural type permits students to compare data for similar structures, and having several students work with the same structure often exposes variations and vagaries that arise in using the software. These include building or computational setup errors and nuances of the software itself, such as effects of molecular conformation on the data (“local minima”). By using molecular modeling in this way I am attempting to use the visual experience to reinforce the notion that there are recognizable trends in computed properties associated with observed structural features and that taken together, these structures and properties govern the progress of chemical reactions. Over and against my claim that these relationships preclude any need for memorization, students can see for themselves that even without my experience *they* are making the connections and drawing conclusions long before they have had time to memorize.

## Pedagogical Considerations

Reactions involving electrophilic addition to alkenes are introduced, commonly, as the second major category of organic synthesis reactions in a full-year organic chemistry course (generally at the sophomore level), typically after reactions using nucleophilic reagents, substitution, and elimination of alkyl halides (3). Additions to alkenes illustrate important syntheses for the formation of a carbon–oxygen bond (or a carbon–halogen bond, using HX). Students' ability to master this material may vary as a function of academic major, personal inclination toward chemistry, and skill of instruction. However, there is anecdotal evidence that even at this early stage of the course, the perception among students is that successful completion of the course will depend in large part on their ability to “just memorize” the growing set of complex reactions, reagents, reactive intermediates, and mechanisms. “Flash cards” for each reaction can often be seen sprouting among students at about this point in the course.

Learning which reagents lead to Markovnikov chemistry, which signal anti-Markovnikov, and what reaction site is the “right” one are examples of the demands students face in coming to grips with memorization versus conceptual understanding of a reaction mechanism. My approach to dealing

<sup>†</sup>Current address: College of Applied Science, University of Cincinnati, Cincinnati, OH 45206; [Rita.Hessley@uc.edu](mailto:Rita.Hessley@uc.edu).

with this is to try to provide sufficient exposure to the concept of structure–reactivity relationships to convince students that memorization is unnecessary and, in this particular instance, to dissuade them from the entire notion of an anti-Markovnikov reaction. I avoid using that terminology in spite of its common occurrence (3). I prefer to have my students understand that the so-called anti- mechanism does *not* occur by a process contrary, or opposite, to its companion reaction. Instead, I emphasize acid–base, electrophile–nucleophile interactions in a manner similar to that found in Ege’s text (3a). Those concepts permit me to describe most mechanisms in terms of a (relatively more) nucleophilic moiety interacting with a (relatively more) electrophilic species. Since an alkene has two C sites associated with the double bond, both seem equally reactive. The structures of alcohols formed with each of the reagents reveal that one reaction site is preferred. Students can be drawn to see that the locus of the question about mechanism is identified: What is the effect of the electrophile–nucleophile interaction on the initial structure of the substrate that leads to the observed products? This leads to the notion that a sufficiently uneven distribution of electron density between reagents produces one intermediate species that is more thermodynamically stable than the alternative, resulting in the preferred (observed) product. This supports the prediction regarding the regioselectivity for the reaction that is borne out by experiments credited to Markovnikov.

## Implementing Modeling

### Electrostatics

For modeling the Markovnikov mechanism, I select structures to illustrate primary, secondary, tertiary, benzylic, and allylic carbocation sites. Students build and carry out geometry optimization for each ion using the semiempirical AM1-level computation (4) and map the electrostatic potential onto the density surface. It is important to stress that the  $\Delta H_f$  values obtained do not agree with experimental values but that the *trends* observed for a set of structures can be relied upon to be indicative of the relative stability of the species, and the reliability can be tested experimentally. The electrostatic potential map can be used to reinforce the concept that electron delocalization promotes stability. For treatment of the hydration reaction, propene is a suitable example for an unsymmetrical alkene. Although other molecules may be more interesting or have more practical appeal, computational time increases markedly with the number of atoms in the molecule (and with the number of computations being carried out simultaneously) (1h).

### Thermodynamics

Students refer to  $\Delta H_f$  values to draw conclusions about the thermodynamic stability of the primary and the secondary carbocation for this substrate. The electrostatic potential map illustrates the greater electron density surrounding the  $\pi$  system, and it helps me reinforce the notion that electron-rich species react preferentially with electron-poor moieties. I also use it to provoke discussion about the inductive effect of the methyl group on the secondary cation site. These data lead naturally to discussion of the nucleophilic character of the  $\pi$  bond, the reactive center between an alkene and an electrophilic reagent. For hydration we use the relative  $\Delta H_f$

Table 1. Typical Computational Data for Propene and Its Carbocations

Molecule	$\Delta H_f / (\text{kcal mol}^{-1})$
$\text{CH}_3\text{CH}=\text{CH}_2$	7.868
$\text{CH}_3\text{CH}_2-\overset{+}{\text{C}}\text{H}_2$	217.944
$\text{CH}_3\overset{+}{\text{C}}\text{H}-\text{CH}_3$	191.862

Note: Computations done with PC Spartan-Plus, AM1 level (2).

values for 1° and 2° carbocations to postulate the most reactive (“attractive”) site for protonation in the first step of the reaction (hence the need for a proton catalyst to achieve hydration, but not HX addition). Table 1 displays some typical data determined by this computation.

### Conceptualization

As this exercise progresses students are actually developing their own formulation of the Markovnikov rule (ideally without yet reading it in the text); an articulation can be coaxed out of the class that emphasizes electrophile–nucleophile interaction and thermodynamic stability, *regardless of what reagents are used*. This discussion also provides the necessary tools so that students can be asked to formulate hypotheses about what product(s) will form for any substrate that might be provided them in lab for acid-catalyzed hydration (e.g., 1-hexene, cyclohexene, or 1-methylcyclohexene). I use that extension of this assignment as a prelab exercise. After completing the lab experiment students use their experimental data on the identity of their product to draw conclusions about the validity of their hypothesis and the reliability of their theoretical data.

The oxymercuration–demercuration reaction is less amenable for an undergraduate lab than is acid-catalyzed hydration, so molecular modeling is especially useful for conveying this mechanism. First, students need to understand that the reactive electrophile is the  $^+\text{Hg}(\text{OAc})$  species. If, as in some textbooks (5), the reaction is described as involving a “blocked carbocation” when the  $\pi$  electrons bond to the cation, the exercise becomes a trivial example of the chemistry already modeled in the previous example. However, the utility of the molecular modeling program is that the alternative reactive intermediate, the 3-center ring species analogous to the 3-atom halonium ion, can be readily constructed and analyzed. One good way to do this is to build the symmetrical 3-center ion, optimize the geometry, and determine the  $\Delta H_f$  value for this structure as a reference. Two additional structures can then be compared to that symmetrical reference structure. In one, the C–1–Hg bond length, in the other the C–2–Hg length, can be constrained at some arbitrary but logical, *longer*, distance. This represents partial bond cleavage from one C center or the other, approximating how electron distribution in the electrophilic mercury–alkene complex might “shift” to accommodate the nucleophilic water molecule.

### Steric Considerations

In addition to illustrating how steric effects might influence the stereochemistry of this reaction, the structural

modifications are reflected in the relative  $\Delta H_f^\ddagger$  values. Differences among some typical values shown in Table 2 are small, but they do permit students to suggest that bond cleavage can be predicted to allow *developing positive charge* to occur preferentially at the 2° site, the predictable Markovnikov site. Skeptical or industrious student can repeat the computations using more widely varied bond lengths at one position and more fully explore the impact of thermodynamic properties on the progress of this reaction.

For the hydration reaction of an unsymmetrical alkene with diborane followed by oxidative cleavage to yield the alcohol, molecular modeling is equally applicable and useful especially because the observed regioselectivity is opposite that of the previous two reactions. This reaction is also modeled easily using propene. Students can start the exercise without any additional information other than that the  $\text{BH}_3$  moiety does not dissociate (discussion of the monomer-dimer species is optional). Although borane,  $\text{BH}_3$ , is a trivial structure to build using this software, it is useful to display the electrostatic potential map and see that atomic charge values do show that the hydrogen atoms bear greater electron density (Table 3). This is also an excellent structure for introducing students to molecular orbital displays. The LUMO for  $\text{BH}_3$  shows the empty p orbital of the boron atom, emphasizing the electron deficiency at that site. Students who recall Lewis structures will recognize the electron-deficient character of the boron atom even without computational data, and will be able to suggest C-1-B or C-2-B formation for the first step. Once the electrophilic site is identified, students sometimes assume the mechanism is governed by the thermodynamic preference for electron deficiency at C-2 by virtue of carbocation formation, as previously. If experimental evidence for the concerted, syn, addition is introduced prior to the discussion of the mechanism, carbocation formation is obviated but steric considerations are not.

The use of molecular models for the various species involved in this reaction is particularly helpful for reminding students not to slip into the mindset that memorizing an "exception" is called for. Whether the 4-center transition state is emphasized (*3c,f,g*) or not (*3a,h*) can be determined by each situation. Regardless of the amount of detail included in the discussion, determination of  $\Delta H_f^\ddagger$  values for either the 4-center structures or the two  $-\text{CH}-\text{C}(\text{BH}_2)-$  structures leads to the same conclusion: the observed reactivity need not be explained as an *exception* ("anti"-Markovnikov); it can be explained by *logical extension* of the Markovnikov rule to include conditions of partial, or tendency toward, electron deficiency. Table 3 shows some typical values obtained for this set of computations. In addition to text examples to support the results of this modeling exercise, laboratory experiments for both macroscale and microscale experiments are available (*6*).

The computations involving  $\text{BH}_3$  do reveal another of the nuances that arise in the use of molecular modeling. In some texts (*7*) the tetrahydrofuran (THF)-borane complex is shown as a fully charge-separated ion pair. The display of the electrostatic potential mapped onto the density surface for this structure does not show complete electron transfer. A comparison of the maps and atomic charges of relevant atoms for THF,  $\text{BH}_3$ , and the THF- $\text{BH}_3$  complex, does, however, adequately support the claim that oxygen donates electron density to the empty p orbital on boron (Table 3).

**Table 2. Values for 3 Transition-State Structures with Oxymercuration-Demercuration Using Propene**

Structure	Bond Length/Å		$\Delta H_f^\ddagger/(\text{kcal mol}^{-1})$
	C-1-Hg	C-2-Hg	
	2.291 computed	2.389 computed	105.292
	2.127 computed	2.800 constrained	103.693
	2.800 constrained	2.211 computed	109.034

Note: Computations done with PC Spartan-Plus, AM1 level (2).

**Table 3. Typical Computational Data for  $\text{BH}_3$  and for a Borohydride-Alkene Transition State**

Structure	Electrostatic Potential					
	Atom	Charge	Atom	Charge	Atom	Charge
$\text{BH}_3$	B	0.605	H	-0.202	-	-
THF	O	-0.402	C <sub>adjacent</sub>	0.126	H <sub>adjacent</sub>	0.037
$\text{BH}_3$ -THF complex	O	-0.243	B	0.142	H	-0.129

  

Structure	$\Delta H_f^\ddagger/(\text{kcal mol}^{-1})$
	40.817
	141.341
	-4.835
	-2.915

Note: Computations done with PC Spartan-Plus, AM1 level (2).

**Table 4. Typical Computational Data for Structures Showing Hydride Shift in 3-Methyl-1-butene**

Structure	Bond Length/Å		$\Delta H_f^\ddagger/(\text{kcal mol}^{-1})$
	C-2-H	C-3-H	
	-	-	166.479
	-	-	194.158
	computed values		
	1.115	1.154	179.460
	constrained values		
	1.7	1.17	183.882
	1.6	1.2	186.018
	1.4	1.4	187.170
	1.2	1.6	178.983
	1.17	1.7	175.041

Note: Computations done with PC Spartan-Plus, AM1 level (2).

### Carbocation Formation

Finally, use of molecular modeling can aid in illustrating carbocation rearrangements, a topic usually included in the unit on electrophilic addition. Because students already know about the relative thermodynamic stability of carbocations it is pedagogically easy merely to assert that hydride or methyl shifts govern the reaction by forming the more stable intermediate. However, having them construct a series of molecules in which a transfer is *partially* achieved and note the trend in  $\Delta H_f^\ddagger$  values provides both visual and computational reinforcement of the concept. Table 4 shows some typical data obtained for the progress of the hydride shift using 3-methyl-1-butene. This analysis may exceed the needs or the time constraints of the class but can be assigned as out-of-class work. Alternatively, it can be exploited in situations in which students are especially motivated to probe either reaction mechanisms or applications of molecular modeling more deeply.

### Conclusions

Taken as a whole, the instructional use of molecular modeling of reaction mechanisms as early as possible in the first course in organic chemistry seems to have very positive results. Not only does it serve as an instructional tool, it may allay many of the misconceptions and fears students have about the subject matter. Computer modeling makes 3-dimensional molecular structure visual and mobile in a manner hand-held models cannot. But the use of imagery in conjunction with group, or collaborative, learning is also emphasized, so there is greater potential to achieve deeper and more lasting understanding (1f, 8).

The opportunity for undergraduate students to comprehend organic chemistry is provided in a twofold way by the use of molecular modeling. First and foremost, modeling provides an effective explanation of the atomic (electronic) underpinnings for what is otherwise "factual" information *told* to students about the macroscopic world of chemical reactions. Second, it gives them a sound, if limited, basis for making their own predictions about chemical reactions they have not yet seen. Equally important is the value of using modeling for *pedagogy* at this level. Molecular modeling gives the

instructor a tool with which to focus students' attention away from memorization and toward solidly grounded structure-reactivity relationships.

### Literature Cited

- (a) Lipkowitz, K. B. *J. Chem. Educ.* **1989**, *66*, 275. (b) Simpson, J. M. *J. Chem. Educ.* **1989**, *66*, 406. (c) Lillie, T. S.; Yeager, K. *J. Chem. Educ.* **1986**, *66*, 675. (d) Bailey, R. A. *J. Chem. Educ.* **1989**, *66*, 836. (e) Blankespoor, R. L.; Piers, K. *J. Chem. Educ.* **1991**, *69*, 693. (f) Delaware, D. L.; Fountain, K. R. *J. Chem. Educ.* **1996**, *73*, 116. (g) DeKock, R. L.; Madura, J. D.; Rioux, F.; Casanova, J. J. In *Reviews in Computational Chemistry*; Lipkowitz, K. B., Boyd, D. B., Eds.; VCH: New York, 1990–1992; Vols. 1–3. (h) Hehre, W. J.; Shusterman, A. J.; Huang, W. W. *Wavefunction*: Irvine, CA, 1996;
- Wavefunction: Irvine, CA 92612; <http://www.wavefun.com/>.
- (a) Ege, S. *Organic Chemistry*, 3rd ed.; Heath: Lexington, MA, 1994. (b) Fox, M. A.; Whitesell, J. K. *Organic Chemistry*; Jones and Bartlett: Boston, 1994. (c) Hornback, J. M. *Organic Chemistry*; Brooks/Cole: Pacific Grove, CA, 1998. (d) Oullette, R. J.; Rawn, J. D. *Organic Chemistry*; Prentice Hall: Upper Saddle River, NJ, 1996. (e) Solomons, T. W. G. *Organic Chemistry*, 6th ed.; Wiley: New York, 1996. (f) Wade, L. G. Jr. *Organic Chemistry*, 3rd ed.; Prentice Hall: Englewood Cliffs, NJ, 1995. (g) Jones, M. Jr. *Organic Chemistry*; Norton: New York, 1997.
- Dewar, M. J. S.; Zoebisch, E. G.; Healy, Eamonn F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. See also, Dewar, M. J. S.; Storch, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 3398.
- Fox, M. A.; Whitesell, J. K. *Organic Chemistry*; Jones and Bartlett: Boston, 1994; p 350.
- Pavia, D. L.; Lampman, G. M.; Kriz, G. S. *Introduction to Organic Laboratory Techniques*, 3rd ed.; Saunders: Philadelphia, 1988; p 212. Holman, R. W.; Hessley, R. K. *Contemporary Microscale Organic Chemistry*; Kendall/Hunt: Dubuque, IA, 1991; p 243. Mayo, D. W.; Pike, R. M.; Trumper, P. K. *Microscale Organic Laboratory*; 3rd ed.; Wiley: New York, 1994; p 252.
- Ege, S. *Organic Chemistry*, 3rd ed.; Heath: Lexington, MA, 1994; p 306. Wade, L. G. Jr. *Organic Chemistry*, 3rd ed.; Prentice Hall: Englewood Cliffs, NJ, 1995; p 352.
- Casanova, J.; Casanova, S. L. *EDUCOM Rev.* **1991**, Spring, 31.