

USE OF OXIDATION NUMBERS FOR PREDICTING REGIOSELECTIVITY IN ORGANIC REACTIONS

Maulidan Firdaus, Patiha

Sebelas Maret University, Indonesia

Abstract. The oxidation number concept is usually used to determine the relative electron density around atom, to balance chemical reactions, or to decide whether the chemical formula assigned to a compound is valid or not. Although rules for calculating oxidation numbers in organic molecules are available, they are rarely used in organic chemistry. In fact, this concept can be modified. Thus, we proposed a new approach for predicting regioselectivity in simple organic reactions.

Keywords: oxidation numbers, regioselectivity, carbon intermediate

A variety of approaches to the concept of oxidation and reduction (redox) appear in organic textbook and has been discussed extensively. Several articles give explanation about oxidation numbers as they are thought in basic chemistry courses (Calzaferri, 1999; Kauffman, 1986). Generally, the oxidation number concept is widely employed to determine the relative electron density around atom, to balance chemical reactions, or to verify on the validity of the assigned chemical formula. Different approaches have been reported in exploring oxidation and reduction in the field of organic chemistry. To only mention a few examples; Anselme (1997) introduced the use of electron density as an approach in helping students gain more theoretical understanding of redox in organic reaction; Menzek (2002) proposed the oxidation and reduction of compounds by assigning average oxidation numbers to all carbons in smalls or conjugated organic molecules or ions; Shibley, Jr. et al. (2010) introduced a simple approach concerning oxidation and reduction reactions in organic chemistry by calculating the total number of heteroatoms, π -bonds, and rings. Although variety of approaches involving oxidation and reduction in organic reaction have been described in the literature, to the best of our knowledge, there is still no report about the use of oxidation numbers in the prediction of regioselectivity in simple organic reactions. Thus, the use of oxidation numbers to explain the stability of carbocation, carbanion, and alkyl radical intermediates are discussed. Also, a new approach in the modification of oxidation number to predict regiochemistry in electrophilic aromatic substitutions, alcohol dehydration, and hydrogen halide addition are proposed.

Assigning the oxidation numbers of a carbon

Before we discuss about the use of oxidation numbers for regiochemistry prediction, it is helpful to first learn how to assign the oxidation numbers of a carbon. Generally, the oxidation numbers are determined by a set of rules (Jørgensen, 1969). Although it is helpful, it is ambiguous when they are used in the determination of oxidation numbers of atoms in a molecule having two or more atoms without specific rules. For example, in HCN, the oxidation state of N could be -5 or -3 , depending on the oxidation state of C, whether it is $+4$ (as in CO_2) or $+2$ (as in CO). On the other hand, the oxidation number of C could be $+2$ or $+4$, if the oxidation number of N is -3 or -5 , respectively. If possible, an oxidation number should be assigned by applying a set of as few rules as possible, which should be simple and unambiguous leading to clear and reasonable results (Calzaferri, 1999). An oxidation number is a hypothetical charge associated with relative electronegative difference between atoms. Atom which is more electronegative is assumed to have all the bonding electrons and it has the possibility negative charge. On the other hand, if it is less electronegative, an atom is assumed to lose electron(s) and bear positive charge. The guideline for calculating the oxidation numbers of a carbon are given below (Hoffman, 2004): (1) every bond between carbon and another carbon does not affect the oxidation numbers, regardless the number of bonds (single, double, or triple); therefore, it has an oxidation number of zero; (2) a bond between carbon to hydrogen or a more electropositive element will decrease its oxidation number by 1 - on the contrary, if a more electronegative element (e.g., N, O, F, Cl, Br, I, and S) bond to carbon, its oxidation number will increase by 1; (3) multiple bonds to an element count as multiple single bonds to that element; thus, the oxidation number of carbonyl group is equivalent to a carbon atom with two single bonds to oxygen originating from it; (4) for carbon bearing positive charge, the oxidation number will be counted as $+1$; (5) a pair of electrons on carbon contributes -1 to the oxidation number.

A new approach to predict regioselectivity in organic reactions

A relatively simple approach to teach students how to predict regiochemistry in simple organic reactions is to calculate the oxidation number of carbon on their intermediate forms. In organic reaction, an intermediate is a molecular entity formed from the reactants, which then quickly reacts further being more stable molecule and yields the directly observed products. If a reaction yields two possible products, the relative stability of intermediate could determine whether a product is major or minor. There are three kinds of carbon intermediates i.e. carbocation, carbanion, and alkyl radical and their relative stability can be explained by calculating their oxidation numbers. Three

kinds of simple carbon intermediates that demonstrate this approach are shown in Fig. 1. A carbanion is an intermediate that possess an unshared pair of electrons and bears a negative charge. Therefore, it should have negative oxidation number. In this approach, it is assumed that the more negative oxidation number, the more stable the carbanion is. In Fig. 1, the oxidation number of primary (1°), secondary (2°), and tertiary (3°) carbanion intermediates is -3 , -2 , and -1 , respectively. Therefore, the order of stability in simple carbanion is $1^\circ > 2^\circ > 3^\circ$. A carbocation is an intermediate that loses electron and is therefore bearing a positive charge. In Fig. 1, the oxidation number carbocation is $+1$, 0 , and -1 for 3° , 2° , and 1° , respectively. In the same manner as in carbanion, in this approach it is assumed that a carbocation will be more stable, if the oxidation number is more positive. Thus, the relative stability of a simple carbocation is $3^\circ > 2^\circ > 1^\circ$. A radical is an intermediate that contains one or more unpaired electrons. An atom in the radical form has the same electron as in the ground state. Therefore, a radical should have zero oxidation number. As shown in Fig. 1, the oxidation number of 3° , 2° , and 1° alkyl radical is 0 , -1 , and -2 , respectively and is therefore the order of stability $3^\circ > 2^\circ > 1^\circ$.

There are various factors affecting the stability of carbon intermediates (Smith & March, 2001). For example in carbanion, the increased stability is due to certain structural feature such as conjugation of the unshared pair with an unsaturated bond, an increase in the amount of s character at the carbanionic carbon, field effects, stabilization by an aromatic ring, and stabilization by nonadjacent π bond. In case of carbocation, besides electronic effect, it is also influenced by inductive, hyperconjugation, field effects, and resonance stabilization. All these factors are beyond the scope of this approach.

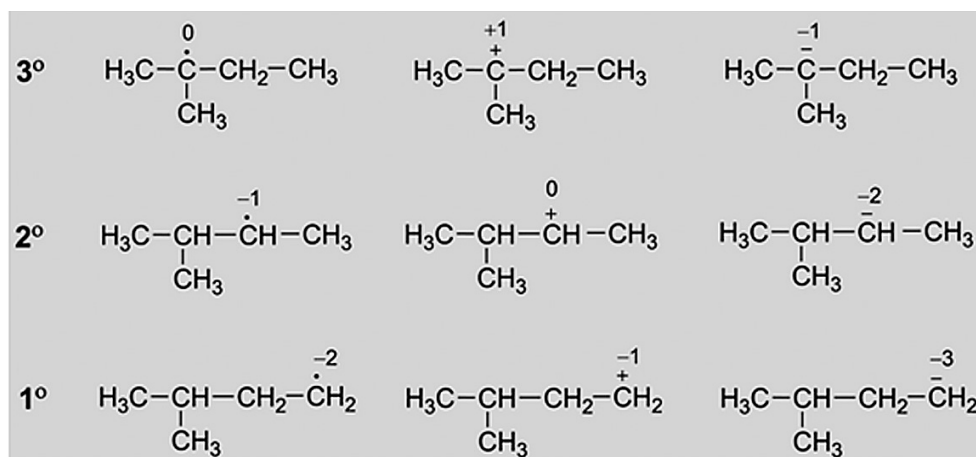


Fig. 1. Oxidation numbers in the carbon intermediates

Let us demonstrate this approach in a few simple organic reactions. In the electrophilic substitution, the occurrence of one substituent on an aromatic ring will direct the orientation of the second substituent added to the ring during a reaction. The first substituent will generally be either an ortho/para director or a meta-director. Using oxidation numbers, one can predict whether an existing substituent directs the second substituent in ortho/para, or meta position. Two examples of electrophilic substitution reaction, i.e., bromination of aniline and bromination of nitrobenzene that demonstrate the approach are chosen.

NH_2 group in aniline is an electron donating-group. The resonance forms of aniline is depicted in Fig. 2A. In structure **1**, C-2 has oxidation number -2.000 , whereas in **2** and **3** has oxidation number -1.000 . Since the resonance structure in aniline cannot be expressed by one single structure, the oxidation number of C-2 is assigned by calculating the average of oxidation number of all their resonance forms. Thus, the oxidation number of C-2 is -1.333 . In the same way, the oxidation number of C-4 and C-6 is -1.333 while C-3 and C-5 is -1.000 . This means that the electron density around C-2 and C-4 (ortho) and C-6 (para) is greater than that around C-3 and C-5 (meta). Bromination of aniline yields ortho or para bromoaniline as the major products. As an electrophile, Br^+ ion will be attracted to these positions, because it is where the electrophile encounter the highest amount of electron density.

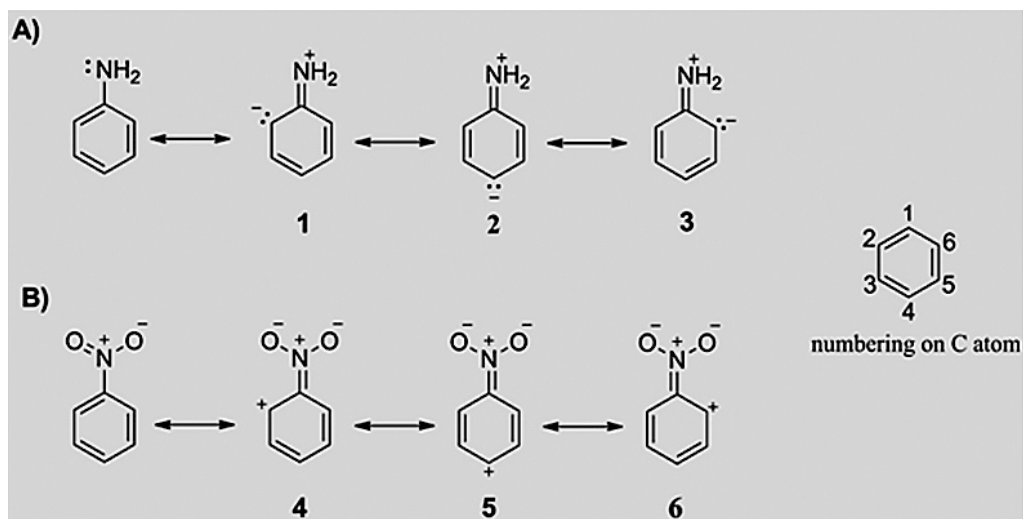


Fig. 2. The resonance form of aniline (A) and nitrobenzene (B)

Nitro group in nitrobenzene is an electron-withdrawing group. There are three forms of their resonance (Fig. 2B). C-2 in structure **4** has oxidation number 0.000 while in structure **5** and **6**, have oxidation number -1.000 . Thus, by calculating the average of oxidation numbers to C-2 – C-6, it can be obtained that the oxidation number of C-2, C-4, and C-6 is -0.667 while the oxidation number of C-3 and C-5 is -1.000 . The electron density of C-3 and C-5 (meta) is greater than that around C-2, C-4, and C-6 (ortho/para). In case of bromination of nitrobenzene, Br^+ ion approaching the ring will prefer to attack in the position with greater electron density. Thus, the only ring locations where the electrophile will encounter electron density is at the meta-positions. Therefore, aromatic electrophilic substitution of nitrobenzene occurs in the meta-position.

The oxidation number approach could be employed in predicting regioselectivity of alcohol dehydration. Elimination of a tertiary alcohol (E1) such as 2-methyl-2-butanol [**7**] can proceed in two different directions which lead to two possible products (Fig. 3). In this reaction, a double bond can be generated between C-2 and C-3 or between C-1 and C-2. Under the normal reaction conditions, 2-methyl-1-butene [**8**] is the minor product, and 2-methyl-2-butene [**9**] is the major one (Carey, 2000). Usually, a major product from acid-catalyzed dehydration of alcohol can be easily predicted on the basis of the Zaitsev rule (Carey, 2000). The last step on the reaction mechanism of acid-catalyzed alcohol dehydration is deprotonation of the intermediate carbocation to form an alkene. In this step, an acid-base reaction in which the carbocation proceeds as a Brønsted acid, transferring a proton to a Brønsted base (Carey, 2000). In case of dehydration of **7**, water may remove a proton from either C-1 or C-3 from this carbocation. Carbocations are the conjugate acids of alkenes and readily lose a proton to form alkenes. Electron density around C atom affects deprotonation selectivity. The more negative electron density around C atom, the more difficult to remove a proton. The oxidation number of C-1 in **7** is -3 which is more negative than C-3. Thus, proton abstraction by Brønsted base (water) on C-1 is more difficult than C-3. Therefore, loss a proton from C-3 yields major product **9**.

In E1 elimination, some compounds follow Zaitsev rule, but others, for steric reason, give the non-Zaitsev product. Unfortunately, in this paper, the anti-Zaitsev product is outside the scope of the approach.

In the alcohol dehydration, under a certain circumstances, there is a possibility that not only elimination reaction has taken place, but also the arrangement of atom in alkene is different than in alcohol. There are many known examples of rearrangements of primary or secondary carbocations to tertiary. Elimination of H_2O from 3,3-dimethyl-3-pentanol [**10**] is an example of this rearrangement reaction (Carey, 2000). Let us compare two possible intermediate when **10** is treated with an acid (Fig. 4). The 2° carbocation in **11** formed by the releasing of OH^- will endure a methyl transfer to form more stable

3° carbocation [12]. The oxidation number of C-2 in **12** less negative than either the oxidation number of C-1 in **11** or C-4 in **12**. Thus, in the same manner as dehydration of **7**, hydrogen abstraction on C-2 in **12** much easily than in C-1 or C-4. Therefore, deprotonation of C-2 in **12** leads to the major product.

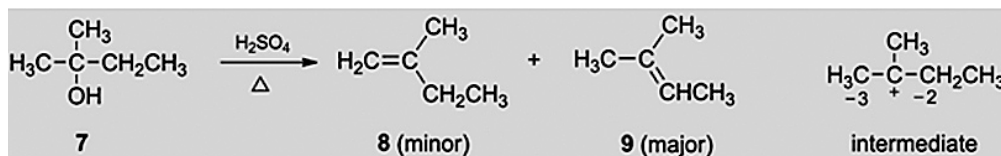


Fig. 3. Dehydration of **7**

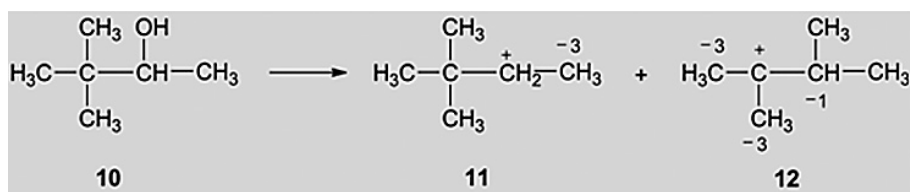


Fig. 4. Two possible carbocations formed in elimination of **10**

The oxidation number concept can also be used to predict regioselectivity of hydrogen halide addition. If hydrogen halide additions are carried out with unsymmetrical substituted alkenes, the product conceivably may add in two different ways. However, in practice, there is only one major product in accordance with Markovnikov's rule. An example of regioselective behavior in HBr addition to 2-methylpropene **13** is shown in Fig. 5.

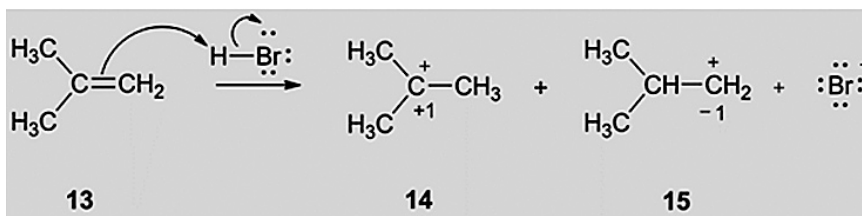


Fig. 5. Addition HBr to **13**

The oxidation number of C-2 in **14** is +1 and C-1 in **15** is -2. This means that the electron density around C-1 is greater than that of C-2. The more negatively charged that region becomes, the more it will repel Br⁻ ion. Therefore, the attack of the bromine atom to carbocation **14** will be obtained as the major product. An exception to this regioselectivity

happens when peroxides are present. The occurrence of peroxides along with HBr yields in anti-Markovnikov addition of HBr. This change in regioselectivity occurs because of a completely different mechanism. Thus, unlike ionic addition mechanisms, under free-radical conditions the regioselectivity is governed by addition of a bromine atom to give the more stable alkyl radical. However, the oxidation number concept still can be applied by predicting the most stable alkyl radical in similar manner as previously discussed.

Conclusion

In summary, regioselectivity in simple organic reaction i.e. electrophilic aromatic substitutions, alcohol dehydration, and hydrogen halide addition can be easily predicted by determining oxidation number to carbon intermediate.

REFERENCES

- Anselme, J-P. (1997). Understanding oxidation-reduction in organic chemistry. *J. Chem. Educ.*, 74, 69–72.
- Calzaferri, G. (1999). Oxidation numbers. *J. Chem. Educ.*, 76, 362–363.
- Carey, F. A. (2000). *Organic chemistry*. New York: McGraw-Hill.
- Hoffman, R. V. (2004). *Organic chemistry: an intermediate text*. Hoboken: John Wiley.
- Jørgensen, C.K. (1969). *Oxidation numbers and oxidation states*. Heidelberg: Springer.
- Kauffman, J.M. (1986). Simple method for determination of oxidation numbers of atoms in compounds. *J. Chem. Educ.*, 63, 474–475.
- Menzek, A. (2002). A new approach to understanding oxidation-reduction of compounds in organic chemistry. *J. Chem. Educ.*, 79, 700–702.
- Shibley, Jr., I.A., Amaral, K.E., Aurentz, D.J. & McCaully, R.J. (2010). Oxidation and reduction reactions in organic chemistry. *J. Chem. Educ.*, 87, 1351–1354.
- Smith, M.B. & March, J. (2001). *Advanced organic chemistry*. New York: John Wiley.

✉ **Dr. Maulidan Firdaus**

Department of Chemistry
Sebelas Maret University
Jl. Ir. Sutami 36A Surakarta 57126 Indonesia
E-mail: maulidan@mipa.uns.ac.id

✉ **Patiha, MSc**

Department of Chemistry
Sebelas Maret University
Jl. Ir. Sutami 36A Surakarta 57126 Indonesia
E-mail: patiha31@yahoo.co.id