The Michael Reaction

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Introduction

As chemical education has evolved, it has seen numerous trends become mainstay modes of teaching in the classroom. The use of computational chemistry is one example. Until the turn of the 21st century, the use of computational chemistry to explain phenomena in organic chemistry was reserved for individuals or institutions with access to specialized software. The use of computations and the visually stunning three-dimensional output from these calculations is now available to students in a growing number of textbooks (1). Two other prevalent trends in chemistry education are the emphasis on chemistry's relationship to the fields of biology and medicine (2), and the incorporation of research data and results into lectures and laboratory experiments (3). As students become more accustomed to these methods of presenting chemical concepts, instructors will need to find more examples that allow them to incorporate these modes of presentation into their daily lectures.

While introductory organic chemistry possesses a fair number of topics that have already benefited from computational treatments, biologically and medicinally relevant stories, and significant research examples, there are many topics yet to be enriched by such approaches. We present herein a concise review of a staple reaction in the organic chemistry curriculum, the Michael reaction. Included are examples of its use in chemical research, an illustration of its biological and medicinal relevance, and detailed instructions for educators who wish to use a computational approach to present this reaction to their students.

Short Biography

This reaction is named after Arthur Michael, born in Buffalo, NY, in 1853. Although he was self-taught and never formally took a degree, he had training with Bunsen (Heidelberg), Hofmann (Berlin), Wurtz (Paris), and Mendeleiev (St. Petersburg). He took his first academic post at Tufts, and in 1887 discovered the reaction for which he is remembered. After a short stint at Tufts, Michael took a three-year break for private research on the Isle of Wight. He then returned to Tufts, where he eventually retired in 1907. After five years of private research at Newton Center in Massachusetts, he was appointed Professor of Chemistry at Harvard University. Michael died in 1942, leaving a record of a highly innovative and productive career (4).

Overview of Reaction

The broad view of the Michael reaction may be most readily summarized by "1,4 addition" or "conjugate addition" to an α,β-unsaturated carbonyl compound. However, there is the obvious competitive reaction, where we see the 1,2-addition reaction already familiar to us in carbonyl chemistry (Scheme I). How can these two modes of attack be reconciled, and further, is it possible to predict products of a new reaction? As it turns out, this is easily rationalized by way of modern computational methods.

Computational Approach

Mendez and Gazquez (5) have discussed chemical reactivity in terms of hard–soft acid–base theory (6). They state, "the regions of a molecule where the Fukui function is large are chemically softer than the regions where the Fukui function is small, and by invoking the HSAB principle in a local sense, one may establish the behavior of the different sites with respect to hard or soft reagents." They define, using a finite difference approximation, the Fukui function

\[ f^+(r) = \rho_{N+1}(r) - \rho_N(r) \]  

for nucleophilic attack. In this analysis, \( \rho_N \) is the electron density at a point \( r \) in space around the molecule. The \( N \) corresponds to the number of electrons in the molecule. Thus, \( N + 1 \) corresponds to an anion, with an electron added to the LUMO of the neutral molecule. All calculations are done at the ground-state geometry. These functions can be condensed to the nuclei by using an atomic charge partitioning scheme, such as Mulliken population analysis

\[ f_{A_k} = q_{A_k}(N_A + 1) - q_{A_k}(N_A) \]  

for nucleophilic attack, where \( q_{A_k}(N_A) \) is the Mulliken charge on atom \( k \) for \( N_A \) total electrons.

While the user can obtain values for the condensed functions by hand, the difference plotting capabilities of Spartan \(^1\) for UNIX systems can be used to obtain 3-D grid representations of the Fukui function. These are done by running the appropriate calculations of the \( (N + 1) \) state using the same geometry and subtracting the resulting density volumes.\(^2\)
Simplified Computational Approach

An easy graphical display technique based on the Fukui functions can also be achieved. Instead of calculating the molecular orbitals for the neutral species, cation, and anion, one can just add or subtract electrons from the molecular orbitals of the neutral species. This procedure isn’t as good as the one described above, but it does give a quick graphical display of the susceptibility of the molecule to different kinds of attack. So rather than being a definitive calculation of a molecular property, freezing the molecular orbitals to those for the neutral molecule gives a useful graphical technique that can be rapidly applied. To use the frozen orbitals approach for nucleophilic attack:

1. Build and minimize your molecule. Only the neutral molecule is needed for this approach.
2. Enter the Expert mode of the Volumes setup. Define the following volume in the Volume setup dialog box:
   \[ \text{volume} = \text{density}[\text{EADD} = \text{LUMO}] . -. \text{density} \]
3. Use resolution=med and submit your job with a single point MO calculation.

You can then set up slices or isosurfaces to display the results.

These results provide a very clear understanding for the course of the reaction. If we had simply looked at the electronic structure associated with the LUMO of methyl vinyl ketone (MVK), we would predict that the carbonyl carbon is most receptive to attack (Fig. 1). However, a Fukui analysis (Fig. 2) provides the necessary insight for the preferential conjugate addition. In general we note that soft nucleophiles will add in the Michael sense, whereas hard nucleophiles will add 1,2. A soft nucleophile can be considered one that is more diffused in its electrons. In the chemistry of the Sn2 reaction we readily appreciated that these nucleophiles include sulfide and iodide ion. We can expand this to include many enolate-type nucleophiles such as cyanide ion and Gilman reagents. Literature examples will show that hard nucleophiles such as alkyl lithium reagents and Grignard reagents tend to undergo chemistry at the carbonyl carbon, as do LiAlH4 and NaBH4.

The Michael Reaction in Organic Synthesis

The Michael reaction has been used widely in organic synthesis for its C–C bond-forming ability. It is employed in the traditional sense where an enolate reacts with an α,β-unsaturated carbonyl as seen in the work of Rubio et al. (7) for the synthesis of (−)-α-kainic acid (Scheme II).

The Michael reaction is also used in tandem with other reactions. Perhaps the best known of these is the Robinson annulation where the Michael addition occurs as the first step. This sequence of Michael addition followed by intramolecular Aldol condensation proved extremely important early on in the area of steroid chemistry as illustrated in Woodward’s synthesis of cortisone (Scheme III) (8).
Scheme IV. Synthesis of claenone.

Scheme V. Example of an intramolecular Michael addition.

Scheme VI. Michael reaction employing non-enolic carbon nucleophile.

Scheme VII. Example of nucleophilic oxygen used in the Michael reaction.

Scheme VIII. Example of nucleophilic nitrogen used in the Michael reaction.
Another useful application of a tandem Michael addition is seen in the total synthesis of the antimicrobial compound Clalenone (Scheme IV) (9). In this instance, Yamada and coworkers are able to construct a norbornane ring using two sequential Michael additions. In fact, the second step of Yamada’s synthesis, an intramolecular Michael addition, is frequently used to build complex ring systems. An interesting example is seen in Little’s use of the Michael reaction to form a tricyclic diketone (Scheme V) (10).

Although a majority of syntheses that utilize the title reaction involve an enolate as the attacking nucleophile, other types of nucleophiles have been effectively used in Michael reactions. Binns and coworkers (11) studied additions of phenylthioallyl anions to cyclopentenones and found the addition to be highly regioselective (Scheme VI). Kishi et al. used heteronucleophiles extensively in Michael reactions to synthesize complex natural products. In one example, Kishi used an oxygen anion to form a bridging ring in the steroid-like natural product (±)-batrachotoxinin (Scheme VII) (12). In another example, Fukuyama and Kishi use the negatively charged nitrogen of a thioacetal-bridged 3,5-piperazinedione to synthesize the antibiotic Gliotoxin (Scheme VIII) (13).

**The Michael Reaction in Nature**

The Michael reaction was found to play a crucial part in the mechanism for reactivity of the biomolecule, Calicheamicin (Scheme IX). Calicheamicin, a naturally occurring compound from the bacterium *Micromonospora echinospora*, is a novel antibiotic containing an enediyne functional group as the active part of its structure. Nicolaou and Sorensen, in their excellent book *Classics in Total Synthesis* (14), provide an intriguing story of the discovery and synthesis of this unique natural product.

![Calicheamicin and site of Michael addition](image)

**Scheme IX. Calicheamicin and site of Michael addition.**

We provide a short computer animation (15), based on the strategies developed in the text, to show this biological activity and the role played by a Michael reaction. One notes that sulfur is generally considered a soft nucleophile and it is not surprising that conjugate addition is observed.

**Summary**

In this short account we have provided computational insight for the observed conjugate addition associated with the Michael reaction, presented significant examples of the reaction in synthesis, and shown its relevance in the activity of a new type of drug.

**Supplemental Material**

Instructions for performing these calculations in various versions of Spartan for UNIX and other applications of Fukui surfaces are available in this issue of *JCE Online*. This article is also available with color figures in *JCE Online*.

**Note**


2. The Mac and PC versions of SpartanPro do not currently allow for Fukui function calculations. Detailed instructions for performing these calculations in various versions of Spartan for UNIX are available in this issue of *JCE Online*.

**Literature Cited**


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**[Links](http://www.OCHeM.com) (accessed Oct 2001); the animation can be accessed by first clicking on "Tutorials" and then "The Michael Reaction".**