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Video Demonstrations of a Benzene Derivative Reaction from Its Optimized Intermediate Structure

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Abstract – A number of researchers have performed studies on the application of chemical reaction visualization by means of computational chemistry techniques for the purpose of teaching and learning chemistry at secondary and higher education levels. However, on practical grounds, the presented approach thus far was generally unattainable for teachers due to the time-consuming process of finding the transition states. This research offers a less time-consuming computational chemistry technique for producing organic reaction-modelling videos upon which the students may sufficiently build their understanding of fundamental concepts of chemical reactions. The technique being proposed here consists of (1) intermediate structure modelling, (2) reactant-wise and product-wise optimizations of the intermediate structures without the search for transition states, and (3) visualizations of the optimized results. The application of this technique has managed to produce a video demonstration of an organic reaction of benzene derivatives that may serve as modelling videos in chemistry lessons at secondary education or undergraduate degree levels.

Keywords: video demonstration; organic reaction; benzene derivative; computational chemistry

INTRODUCTION

The development of technology for visualizing atoms, molecules, and chemical reactions has made great strides in the era of information technology. No longer just a digital alternative to Molymod®, molecular visualization software has become a vital tool in a wide range of computational chemistry applications, from predicting molecular characteristics to simulating the interactions of enzymes with their ligands. Among the visualization software that has continued to be developed to this day are MOLDEN 2.0 (Schaftenaar et al., 2017), WebMO (Polik & Schmidt, 2022), Jmol (Cohlberg, 2021), molUP (S. Fernandes et al., 2018), and Avogadro (Hanwell et al., 2012).

A number of studies, primarily by Ikuo & Ogawa (2014) as well as Ikuo et al. (2006, 2009, 2011, 2013), have explored the use of computational chemistry calculations in the innovation of chemical teaching aids, from video demonstrations of reactions to digital laboratory modules. This innovation will be very helpful for chemistry education in the era of disruption that is currently sweeping Indonesia's educational world. However, there are at least three challenges that Indonesian teachers must face before they can apply these innovations, namely: (1) the relatively long duration of intrinsic reaction coordinate mapping by computation, which typically requires a search for the transition state (TS), (2) software that is less economically accessible, and (3) technical publications on the application of computational chemistry in the development of chemical teaching aids that are not yet relevant to Indonesian chemistry education.

Therefore, this study was designed to present an alternative technique for creating a video demonstration of an organic reaction of benzene derivatives from the optimization of intermediate

structures of the reaction without going through a search for the transition state using the ORCA-Avogadro software tandem. This study offers an alternative technique based on the optimization of intermediate structures without a search for the transition state to reduce the computational cost. The topic of organic reactions of benzene derivatives was chosen because, regardless of the constantly changing curriculum, benzene and its derivatives are almost always discussed in Chemistry textbooks for grade 12 of high school or its equivalent (Mendera, 2020; Nursanti, 2020; Putri, 2016; Rahayu, 2009; Wardiyah, 2016). The ORCA-Avogadro software tandem was chosen because ORCA can be obtained for free with an academic license (Neese et al., 2020) while Avogadro and Avogadro 2 are also available for free with a GPL2 license (Hanwell et al., 2012).

METHODS

This research adapted the approach used by Ikuo & Ogawa (Ikuo & Ogawa, 2014) in the development of a video demonstration of organic reactions with a number of adjustments as previously discussed. In general, the standard intrinsic reaction coordinate (IRC) mapping method (Cramer, 2004) and the alternative method offered in this study were applied and then compared in terms of their qualitative and quantitative performances from the perspectives of computation and visualization results.

Specifically, the computational stages of the standard method consist of: (1) prediction of the transition state structure, (2) optimization of the transition state structure, (3) calculation of the vibrational frequency of the optimal transition state structure, and (4) intrinsic reaction coordinate mapping (Lewars, 2016; Neese et al., 2020). Meanwhile, the computational stages of the alternative method offered in this study include (1) prediction of the intermediate state structure, (2) optimization of the intermediate state structure and (3) optimization of the intermediate state structure towards the reactant or product with the help of constraint parameters. The prediction stage of both methods was carried out using Avogadro and Avogadro 2, followed by the next stages using ORCA 5.0 at the B3LYP/6-31++G** theory level (Omer et al., 2020).

The benzene derivative reaction that is the focus of this study is the acetylation of aniline by acetic anhydride through 1 intermediate, as shown in Figure 1 (Koreeda, 2011), which is classified as an electrophilic substitution reaction where one of the hydrogen atoms on the aniline amine group is substituted by an acetyl group. The results of the standard and alternative computation methods are compared quantitatively with each other and their compatibility with the reaction mechanism diagram in Figure 1.

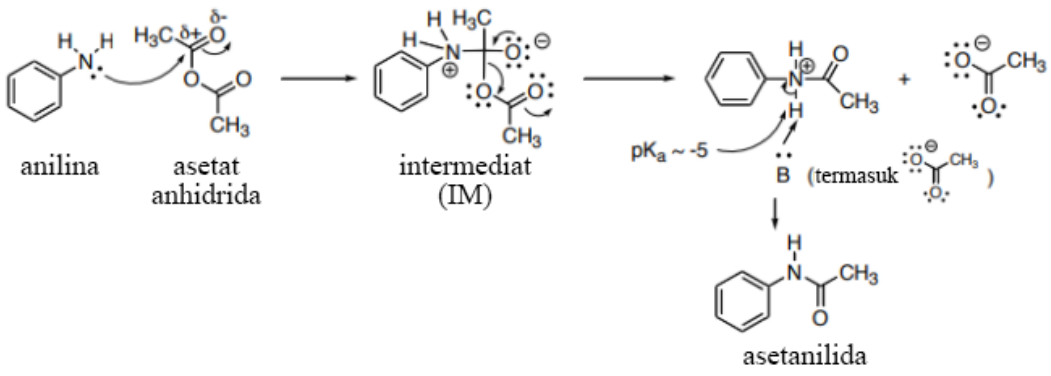

Figure 1. Mechanism of aniline acetylation reaction (Koreeda, 2011).

For the purpose of comparing the compatibility with the reaction mechanism diagram as well as a proof-of-concept video demonstration, the computational results were visualized. For the standard method, the IRC mapping results were visualized, while for the alternative method, the results of optimization towards the reactant and the product sides were visualized. The visualization stage was carried out using Avogadro 2 alone with FFmpeg because (1) Avogadro on Windows® cannot export visualizations to video format due to technical constraints that are considered known issues, (2) even if it were to succeed, the available video format would only be AVI which cannot be played directly in modern web browsers, and (3) the development of Avogadro had been retired by its own developers. This study used Avogadro together with Avogadro 2 for structure prediction because Avogadro is still commonly used by computational chemistry researchers in Indonesia.

RESULTS AND DISCUSSIONS

This section is hereby presented in four sections. The first section covers the overall result and performance of the standard method. The second section covers the same scope with respect to the alternative method. The third section compares the performance of both methods in terms of computation and visualization results. The fourth section discusses possible implementation scenario alternatives for this novel approach.

Standard Method

Based on the computation using the standard method, the IRC of the aniline acetylation reaction was obtained as shown by the energy curve in Figure 2a. The IRC computation results provide the energy of each structure conformation on the IRC in hartree (Eh) and kilocalorie per mole (kcal/mol) units, making it easier to determine the reaction enthalpy. In the case of aniline acetylation by acetic anhydride, a reaction enthalpy of -3.865 kcal/mol was obtained.

From the visualization of the IRC, a video demonstrating the change from the reactant system, consisting of aniline and acetic anhydride, to the product system, consisting of acetanilide and acetic acid, with a focus on the dissociation and formation of important bonds, was obtained. The IRC visualization product from the computation results of the standard method is free from molecular movements that do not directly contribute to the reaction.

Alternative Method

Based on the computation using the alternative method, a rough picture of the aniline acetylation reaction was obtained, as shown by the energy curve in Figure 2b. The optimization results of the intermediate structure towards the reactant and product provide the energy of each structure conformation only in hartree (Eh) units separately, so the determination of the reaction enthalpy must be done by first extracting the energy data from the output file to a CSV file, then plotting it on a graph before finally calculating its reaction enthalpy. In this case of aniline acetylation, a reaction enthalpy of -8.918 kcal/mol was obtained.

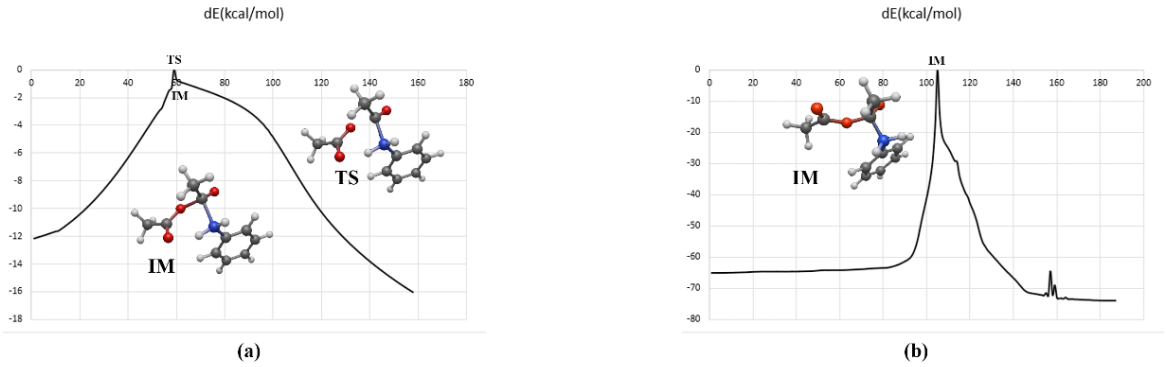

Figure 2. Energy level, dE, curves relative to the transition state (a, standard method) and the intermediate (b, alternative method).

From the visualization of the IRC, a video demonstrating the slow change from the reactant system, consisting of aniline and anhydride acetate, to the product system, consisting of acetanilide and acetic acid, through the intermediate structure was obtained. This visualization product of intermediate structure optimizations towards the reactant and the product sides as computed using the alternative method is filled with molecular movements that do not directly contribute to the formation and dissociation of bonds in the reaction, making it relatively unclear but still understandable because it still shows the sequence of bond dissociation and formation similar to that of the IRC visualization using the standard method.

Performance Comparison

In this research, the standard method resulted in the optimized transition state structure (TS), and the alternative method resulted in the intermediate structure (IM), as shown in the inset of Figure 2. The optimized transition state for the standard method was obtained from ORCA computations after a series of complicated and time-consuming trial-and-error processes. Meanwhile, the intermediate structure for the alternative method was obtained from auto-optimization with Open Babel via Avogadro or Avogadro 2.

For the reaction of aniline acetylation, ORCA optimization without constraints on the intermediate structure from Open Babel auto-optimization always produces a reactant system, while constraints on the C–N amide bond always produce a product system. This indicates that the intermediate structure (IM) and the transition state (TS) are likely very similar (concerted). This is then confirmed by the IRC computation results of the standard method, which show that the TS and IM structures are very similar with extremely close energy levels, as shown in the inset of Figure 2a.

Open Babel auto-optimization via Avogadro and Avogadro 2 does not show significant differences in results. In this auto-optimization, the difference between Avogadro and Avogadro 2 lies only in the implementation of Open Babel. In Avogadro, Open Babel is implemented as a native feature, while in Avogadro 2, Open Babel is implemented as a plug-in that must be installed separately.

The entire computation process for the standard method for the reaction of aniline acetylation by acetic anhydride takes 2.267 days. Meanwhile, the entire computational process in the alternative method without transition state search takes 0.752 days. These time measurements do not include the trial-and-error time spent in the standard or alternative methods. In the alternative method, the

trial-and-error time is much shorter than in the standard method because the computational starting point is the intermediate structure, which can be directly taken from the literature.

This 301.6% faster working speed of the alternative method compared to its standard counterpart comes with a compromise on other aspects. From the energy level curves shown in Figures 2a and 2b, it is visible that the energy curve of the alternative method is very imprecise compared to that of the standard method. In addition to the overall shape of the curve, this is also apparent from the enthalpy values obtained from each curve. From the alternative method, the enthalpy of the acetylation of aniline is 230.7% larger than that obtained from the standard method. In addition, the activation energy value from the alternative method is 534.4% higher than that obtained from the standard method.

The compatibility between the results of the alternative method and the standard method only lies in: (1) the general thermal properties of the reaction and (2) the relative position between the energy of the reactant, the energy of the intermediate, and the energy of the product. In this case, both methods provide results that indicate that the product of the acetylation of aniline by anhydrous acetate has a lower energy level than its reactant, so it is known that the reaction proceeds exothermically. In addition, both methods also provide an intermediate energy level that is higher than the reactant and product, which is in accordance with the literature (Lewars, 2016).

As for the visualization results, it is clear that the visualization of the standard method results was very focused on bond dissociation and bond formation, so important moments of the reaction, including (1) the formation of a bond between the carbonyl carbon from the acetyl group of acetic anhydride and the nitrogen from the amine group of aniline, (2) the dissociation of the acetyl group from acetic anhydride, and (3) the transfer of one hydrogen atom from the newly formed amide functional group to the acetate anion, could be easily observed. Meanwhile, for the alternative method, although the visualization was not as focused as that of the standard method, the three crucial moments of the reaction were still displayed clearly and in order.

In terms of technical production, the visualization of the standard method results only required a compilation stage. This was possible thanks to the Avogadro 2 visualization sequence exporter feature, which can save all the IRC mapping frames into separate PNG files, which were then compiled into a single video file using the FFmpeg command syntax. As for the alternative method, because it could not involve IRC calculations, its visualization must go through a compilation stage with Avogadro 2 and FFmpeg, followed by editing with additional software. The optimization towards the reactant was visualized in a single video file. The optimization towards the product was also visualized in another single video file. These two video files were then combined in such a way as to represent the referenced reaction mechanism. Therefore, in terms of visualization, the alternative method required at least two more stages than the standard method: first, because the trajectory compilation must be done twice, and second because the two compilation results must be combined into a single, unified demonstration video file.

Implementation Scenario Alternatives

There are several possible implementation scenario alternatives that come to mind based on the aforementioned results. The first alternative is to use the videos as a simple demonstration tool in a classroom setup for showing how chemical reactions proceed. In chemistry, we know several explanations for how chemical reactions happen; one of them is the collision theory. The theory

states that for a chemical reaction to happen, not only collisions of adequate energy (Carey, 2000) but also those of appropriate orientation are needed (Levine, 2009). The videos and graphs obtained clearly show all of these factors in a readily-grasped visual representation.

The second alternative is to caption the videos and voice them over with explanations of the reaction for the students to watch as independent study material. Audio-visual materials are generally believed to be more helpful for beginners than static diagrams. The videos and graphs obtained may provide at least half of the raw materials needed for constructing such materials.

The third alternative is to open the computation output files in a more advanced visualizer software so teachers and students can interact with the graphs to see how each energy level corresponds with its respective structural conformation. An example of such software is wxMacMolPlt which is freely available and openly licensed for common operating systems (Bode & Gordon, 1998). There are, of course, many other alternatives teachers will find more suitable for their classes.

CONCLUSION

A simple visualization that shows the key moments in sequence for a benzene derivative reaction with a representative thermal property was produced with the alternative method offered in this research. Considering the quality and speed of visualization achieved, the results of this research can also be developed into an *in-silico* chemistry practice for use in computer labs to introduce the basic concepts of chemical reactions.

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