Interactive Organic Reaction Trajectory Animation iPhone Application (iORA) and Website (webORA)

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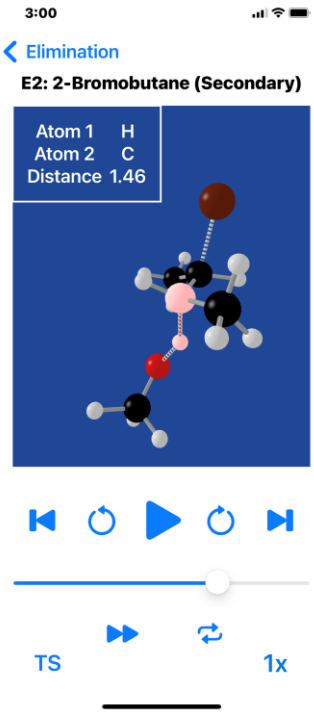
ABSTRACT

Organic reaction trajectories show atomic motion and molecular reorganization of reactants during a single product-forming collision. iORA is a free (available from the Apple App Store), easy to use, highly interactive iPhone application that provides on-the-fly 3D rendering of organic reaction trajectories calculated with density functional theory (DFT) direct dynamics simulations. Visualization of trajectories using iORA enables qualitative and quantitative learning about organic reaction pathways. iORA users can interactively zoom, rotate, and translate the reaction animations. Users can track distances, angles, and dihedral angles. Other iORA features include buttons to jump to the transition state, control the animation speed, and 3D image display. Currently available reaction classes include Bronsted acid-base, alkyl substitution, alkyl elimination, alkene addition, alkyne addition, rearrangement, oxidation, reduction, carbonyl addition, acyl substitution, radical, and pericyclic. WebORA is a web-based site that also displays interactive DFT-based organic reaction trajectories simulations from these reaction classes. It can be used by all web browsers and operating systems. WebORA also offers brief trajectory descriptions.

GRAPHICAL ABSTRACT



KEYWORDS

Second-Year Undergraduate, Organic Chemistry, Computer-Based Learning, Internet/Web-Based Learning, Mechanisms of Reactions, Molecular Mechanics/Dynamics, Quantum Chemistry, Theoretical Chemistry

For many students imagining 3D structures of molecules and then mentally transforming them to understand organic reaction mechanisms can be difficult to impossible without the aid of 3D model sets. [1,2,3,4] 3D molecular models help students develop accurate imagery,[5,6,7,8] such as shapes of molecules, and can also have a positive effect on STEM-related achievement, attitudes, and motivation.[9,10] In second-year organic and graduate-level organic chemistry, the most often used 3D visualization tool is a plastic model kit.[11,12,13] While these physical models can be very useful for basic qualitative static structures (e.g. tetrahedral, trigonal planar, and linear shapes), they do not provide the capability to easily transform to view organic reaction mechanisms with transition states and reactive intermediate where significant changes in geometry occur. These model kits also do not contain any quantitative information (e.g. bond lengths) about reactants, transition states, or

intermediates. Additionally, in our own experience of teaching organic chemistry, for many students the cost and process of obtaining a physical model kit, as well as carrying it in their backpack, causes delays in student use or completely impedes its use. Therefore, it is highly desirable to have a smartphone-based 3D model to visualize ground-state structures, transition states, and reactive intermediates that is free, instantly accessible, easy to use, and highly interactive. This type of convenient and powerful visualization could also enable active learning.[14]

In the late 1990s Fleming and Savage pioneered one of the first software programs (called Organic Reaction Animations (ORA)) that displayed 3D renderings of organic reactions.[15,16,17,18] Contemporaneously, Lipshutz also developed a suite of organic reaction animations.[19] While the ORA program effectively displayed 3D animations in a variety of visualization options, it was not interactive or based on optimized structures, and is no longer able to run on modern operating systems. Recently, a few websites have been developed that animate 3D organic reaction pathways in the same spirit of Fleming and Savage's program. For example, Greeves' chemtube3d.com[20] website provides reaction animations based on the quantum-mechanically calculated intrinsic reaction coordinates (IRCs).[21,22] Attesting to the excitement about 3D visualization of organic reaction animations this website reports greater than four million visits to the website.[23] A related website is Champagne's visualizeorgchem.com website with similar IRC-based animations.[24]

The ORA program and these newer IRC-based animation websites do not show instantaneous atomic motion and molecular reorganization during individual reactive collisions, which are called trajectories and contain vibrational, rotational, and translational motion. Similar to Tantillo who recently reported a website/database for organic reaction trajectories,[25] we believe that the details of individual reaction trajectories have the potential to enhance student learning. Martinez has also disclosed the InteraChem program that provides virtual reality type visualization of molecular dynamics simulations.[26,27]

Here we describe our easy to use, highly interactive iPhone application that provides 3D visualization of organic reaction trajectories based on density functional theory (DFT) direct dynamics simulations. The iPhone application is called interactive organic reaction animations (iORA) and can be freely downloaded from the Apple App Store.[28] Additionally, we describe a website called webORA[29]

that also displays interactive DFT-based organic reaction trajectories. The iORA iPhone application and webORA provides the ability for users to qualitatively and quantitively (i.e. reacting atomic distances) interact with individual organic reaction trajectories.

INTERACTIVE ORGANIC REACTION ANIMATIONS (IORA) IPHONE APPLICATION

Brief overview of trajectories and iORA animation

An organic reaction trajectory describes time dependent atomic and molecular reorganization during an individual chemical transformation. One method to generate organic reaction trajectories is to use Newton's equations of motion combined with atomic and molecular forces calculated at each timestep, which is referred to as direct dynamics simulations.[30,31,32] The iORA iPhone application provides on-the-fly 3D rendering and interactive visualization of organic reaction trajectories calculated DFT direct dynamics simulations. Figure 1 displays iORA trajectory snapshots of the S_N2 reaction between cyanide and ethyl chloride. There are two frames that occur prior to the transition state, the transition state frame, and two frames that occur after the transition state.

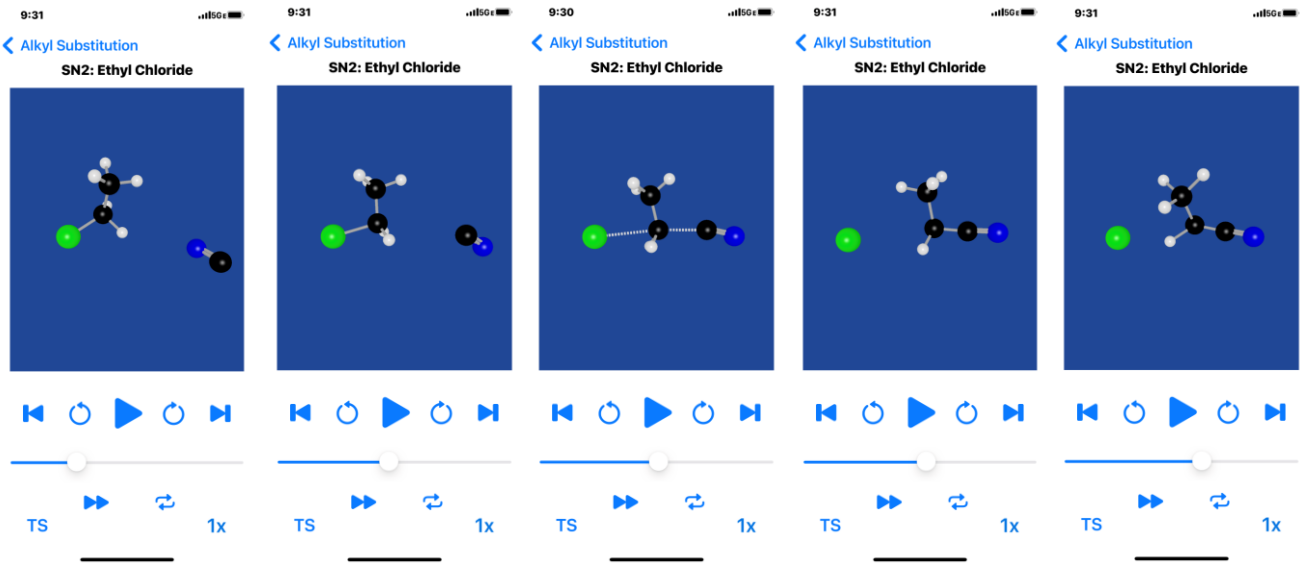


Figure 1. iORA snapshots of the dynamics trajectory for the S_N2 reaction between cyanide and ethyl chloride.

Trajectories for iORA were generated using the quasiclassical formulation of direct (Born-Oppenheimer)[33,34] molecular dynamics simulations. Transition-state structure or reactant initialization sampling was performed using a microcanonical (*NVE*) vibrationally averaged distribution of structures and atomic velocities based on zero-point energy and thermal vibrational energy. Trajectories were

either initialized/sampled using either our Milo program,[35] which provides atomic velocity only sampling, or with Gaussian 16[36] that provides sampling of the molecular structure (potential energy) and atomic velocities. Trajectories were then propagated with a timestep of 0.5 femtoseconds (fs) using the M06-2X density functional with the def2-SVP basis set, which provides accurate description of organic reactions.[37] Trajectories were propagated using the Gaussian 16 program. For the S_N1 reaction, because there is no transition-state stationary point, we used the metadynamics molecular dynamics technique in ORCA.[38] After trajectories were calculated their structures at each timestep were loaded into iORA for 3D shape rendering and visualization.

iORA was coded in the Swift language[39] and provides on-the-fly rendering of 3D structures for each trajectory reaction step. SceneKit[40] graphics framework was used to define shapes, which minimizes the impact on the iPhone processor and streamlines the application flow despite handling many 3D objects at a time and performing several calculations (distance, angles, dihedral angles) at each frame of the animation, which provides the ability for user interrogation of these values. iORA contains our own bond interpolation algorithm in the same spirit as Open Babel[41] that allows display of partial full bonds between atoms.

Interactive features and adjustable parameters

While the animation is playing or paused a user can interactively zoom in or zoom out, rotate, and translate the 3D animation. Clicking on two atoms begins tracking a distance. Clicking them a second time stops tracking. Clicking on three or four atoms begins or ends tracking an angle or dihedral angle. There is a reaction progress slider to rapidly scrub through frames, a speed control button (from 0.25X to 10X), and one-click jump forwards or backwards buttons. There is also “TS” button to jump directly to the transition state frame. iORA includes the ability to change atom sizes, bond sizes, lighting direction, background color, and use colored or translucent bond types.

Reactions included in iORA

iORA currently contains 14 different organic reaction classes as well as conformations. Reaction classes are arranged in the order they generally appear during a second-year undergraduate organic chemistry course. For example, Bronsted acid-based reactions are first followed by alkyl substitution, alkyl elimination, alkene addition, alkyne addition, and rearrangement reactions. Table 1 lists a few

representative examples of trajectory animations that are currently available. In addition to the classic model type chemical reactions, such as the S_N2 reaction of cyanide with ethyl chloride, there are also more sophisticated reactions. For example, in the alkyl substitution class there is the reaction between tetramethylammonium with methyl sulfide. It is noteworthy that iORA also provides animations of non-productive collisions where the reactants do not achieve the transition state. This is probably best illustrated by the non-productive S_N2 collision between cyanide and ethyl chloride. Additionally, in some trajectory aminations we have included an initial non-productive collision followed by a second productive collision. This is probably best illustrated by the reaction of cyanide with acetone in the carbonyl addition reaction class.

Table 1. Representative examples of reaction trajectories currently available in iORA. Approximate simulation times are rounded to the nearest 100 fs.

Reaction Class	**Reactants**	**Approximate Simulation Time (fs)**
Conformational Change	Butane (Anti to Gauche)	1500
Conformational Change	Ethane (C-C Rotation)	2000
Bronsted Acid-Base	Acetone + LDA	1000
Bronsted Acid-Base	Trifluoroacetic acid + Methoxide	500
Alkyl Substitution	S_N1: Tert-Butyl Iodide	500
Alkyl Substitution	S_N2: 2-Bromobutane + Methoxide	500
Alkyl Substitution	S_N2: Ethyl Chloride + Cyanide	2000
Elimination	E2: 2-Bromobutane + Methoxide	500
Elimination	E1cb: Alkyl Chloride + Methoxide	500
Alkene Addition	HX: HBr + Isobutylene	1000
Alkene Addition	Hydroboration: BH_3 + 1-Butene	700
Alkene Addition	Carbene: CCl_2 + Ethylene	500
Alkyne Addition	HX: HCl + 3-Hexyne	500

Rearrangement	Secondary to Tertiary Carbocation Shift	300
Oxidation	Epoxidation: Peracid + Trans-2-Butene	1000
Reduction	Hydride Reduction: LAH + Acetone	400
Carbonyl Addition	Acetone + Cyanide	400
Carbonyl Addition	Grignard: Propionaldehyde + MeMgBr	1400
Radical	Hydrogen Atom Transfer: CH_4 + Chlorine Radical	200
Pericyclic	Diels-Alder: 1,3-Butadiene + Ethylene	900
Pericyclic	1,3-Dipolar Cycloaddition: O_3 + Ethylene	1000
Pericyclic	Cope: 1,5-Hexadiene	800
Pericyclic	Electrocyclic: Cyclobutene	1500
Aromatic Substitution	Friedel-Crafts Acylation	1000

WEBORA

While the iORA application takes advantage of the native Apple iOS operating system it cannot be used as an application with Android and other non-iOS-based smartphones. Therefore, as a companion to iORA that can be used on all smartphones, including iPhones, we created the website webORA[29] that also displays animations of organic reaction trajectories (http://webora.chem.byu.edu/). WebORA uses Bootstrap as its framework to enable cross platform viewing compatible from a small smartphone screen to a large desktop monitor. Different from iORA, webORA provides a visual list of reactions that shows the curved arrow reaction mechanism. Clicking on the curved arrow mechanism provides a popup fully interactive animation. Figure 2 shows a screenshot of the Android curved arrow mechanism of the S_N2 reaction between methoxide and 2-bromobutane. Figure 2 also shows a screenshot of the trajectory animation that appears upon clicking on the curved arrow mechanism.

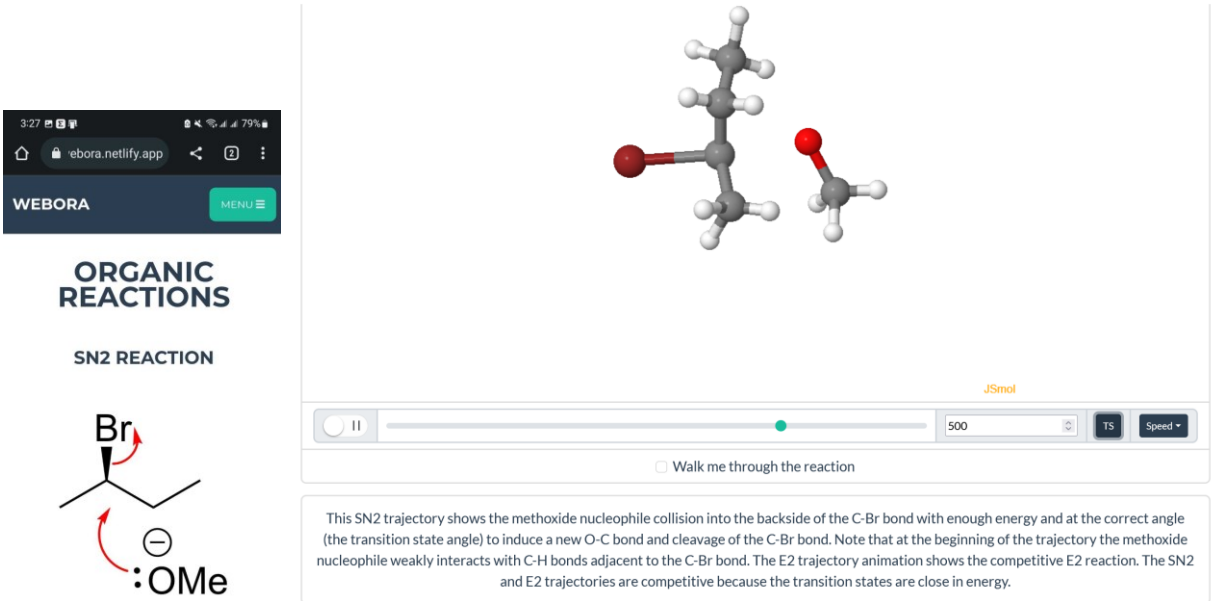


Figure 2. Left: Android view of webORA. Right: Snapshot of the webORA animation for the S_N2 reaction between methoxide and 2-bromobutane.

Similar to iORA, webORA is interactive (e.g. TS button, rotation, ability to track distances, angles, dihedral angles (when the animation is paused)) and provides all the same classes of organic reactions. The interactive aspect of webORA uses the same approach as Greeves' chemtube3d.com,[23] which is the JSmol API. However, a major limitation of webORA with the JSmol[42] API is that there is no ability to control and display partial bonds. WebORA provides a convenient platform for additional reaction trajectory details. For example, Figure 2 shows that webORA provides a short-written description of the trajectory.

PRELIMINARY USE IN A CLASSROOM SETTING

Developmental beta versions of iORA and webORA were briefly implemented in class while teaching a condensed one-semester organic chemistry course during Fall semester of 2022 (September through December) at Brigham Young University. After discussing the fundamental aspects of the S_N2 reaction mechanism using chalkboard images, such as the curved arrow mechanism and the reaction coordinate energy landscape, iORA and webORA tools were used for 3D visualization of a reactive S_N2 collision. Brief instructions were given on how to download iORA on iPhones and access webORA. Within a few minutes all students were able download iORA or access webORA. The students were

then allowed to spend five minutes using these programs to examine the S_N2 reaction between ethyl chloride and cyanide. Many students naturally began to explore other reactions. After a few minutes of exploring the S_N2 reaction on their own, students were instructed to use the TS button to examine the transition-state geometry and click on partial bond lengths and compare them to the reactant geometries. While there was no quantitative assessment, through a question-and-answer period it was observed that for many students the animation provided clarity about the carbon atom stereo inversion during the substitution reaction.

About one week after the initial use of the tools for the S_N2 reaction, the class then used iORA and webORA during the discussion of the E2 reaction mechanism. Specifically, the animation for the E2 reaction between methoxide and 2-bromobutane was used. After viewing the animation, the students were polled about the H-C-C-Br dihedral angle during the elimination reaction. The students were nearly unanimous with an answer of approximately 180° dihedral angle.

The third time iORA and webORA were used during the semester was for the Diels-Alder reaction. In this instance, after an in-class discussion on the cycloaddition reaction Ess instructed students to visualize the 1,3-butadiene-alkene reaction trajectory on their own in preparation for the homework, which required them to draw the transition-state geometry and the overlapping π bonding. Throughout the semester during office hours many students expressed that they continued to use iORA or webORA on their own.

CONCLUSIONS

IORA and webORA are new learning tools designed to visualize and interact with organic reaction trajectories calculated from DFT-based direct dynamics simulations. iORA is freely available through the Apple App Store and webORA can be found on the internet (http://webora.chem.byu.edu/). These animations of single molecular reaction reactive collisions enable qualitative and quantitative learning about organic reaction pathways. iORA and webORA currently have 14 reaction classes and we plan to continually update them with more reaction trajectories and reaction classes. Assessment of the utility of iORA and webORA as teaching tools is currently underway at several US-based institutions where instructors have volunteered to implement the tools in their classroom. Assessments include

attitudinal surveys, quiz scores, and data gathered from the visual perception skill tests. Results will be reported in due course.

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