

Femtosecond to microsecond tracking of the complete mechanism of a radical reaction cycle

Contact A.Orr-Ewing@Bristol.ac.uk

L. Lewis-Borrell

School of Chemistry
University of Bristol, Bristol BS8 1TS

M. Sneha

School of Chemistry
University of Bristol, Bristol BS8 1TS

V. Fasano

School of Chemistry
University of Bristol, Bristol BS8 1TS

A. Noble

School of Chemistry
University of Bristol, Bristol BS8 1TS

V.K. Aggarwal

School of Chemistry
University of Bristol, Bristol BS8 1TS

A.J. Orr-Ewing

School of Chemistry
University of Bristol, Bristol BS8 1TS

Introduction

Organic chemical reactions initiated photochemically by absorption of ultraviolet or visible light often follow complicated, multi-step pathways involving free-radical intermediates. If the designs of these reactions are to be optimized for use in the synthesis of important target molecules, their reaction mechanisms must be understood. Considerable mechanistic insight derives from direct observation of the reactive intermediates transiently formed in the reaction mixture, and the rates of their production and loss. The LIFEtime Facility at the Rutherford Appleton Laboratory offers the capability to make such observations using time-resolved infrared (TRIR) spectroscopy over the femtosecond to millisecond timescales that are needed to probe multi-step radical reactions from photoinitiation to completion. We have previously demonstrated this capability in studies of photoredox reaction cycles^{1,2} and radical addition reactions.³ Here, we report a recent study of the use of a versatile class of organoboron compounds developed for use in C-C and C-heteroatom bond-forming reactions.⁴ This chemistry can be used to synthesize organic molecules with complex three-dimensional structures of value in drug-discovery research.

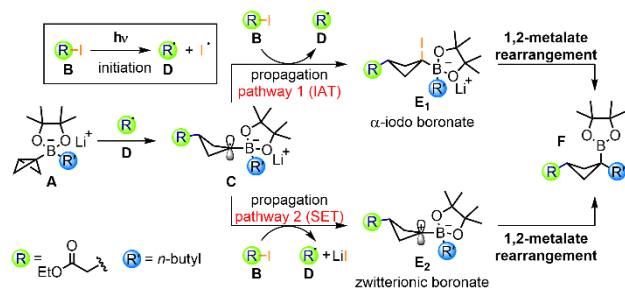


Figure 1: Proposed alternative mechanisms of a radical 1,2-metalation reaction via Iodine atom transfer (IAT) or single electron transfer (SET) pathways.

Figure 1 illustrates the reaction of an example boronate complex with an organic radical formed by photolysis of an organoiodide precursor. The chosen example involves radical (**D**) addition to a bicyclo[1.1.0]butyl boronate (**A**), followed by a 1,2-metalate rearrangement, the outcome of which is the formation of product **F** containing two new C-C bonds. Based on prior studies of this and similar reactions, two reaction mechanisms have been proposed to form an intermediate (E_1 or E_2) that undergoes the key 1,2-metalate rearrangement. One is an Iodine atom transfer (IAT) reaction of radical intermediate **C** to form the α -iodo boronate complex E_1 , and the other is a single electron transfer (SET) mechanism making zwitterionic boronate complex E_2 . Previous reports have favoured the SET

pathway, but they lacked direct experimental evidence for the participation of E_2 . The correct mechanistic distinction between the two pathways is important for design of stereoselective 1,2-metalate rearrangement reactions.

TRIR study of the radical induced 1,2-metalate rearrangement reaction

Mechanistic study of the reaction shown in Figure 1 is complicated by the multi-step radical reaction cycle proposed to drive the chemical transformation of **A** to **F**. This cycle is illustrated in Figure 2. The photodissociation of the precursor organoiodide **B** to make radical intermediate **D**, and any geminate recombination of **D** with its partner I atom to reform the starting compound **B** occur on sub-picosecond to few-ps timescales, whereas the subsequent bimolecular reaction propagation steps involving the regeneration of radical **D** extend over nanosecond to microsecond timescales. The build-up of product **F** is similarly expected to occur over timescales as long as microsecond to millisecond after the initial photoexcitation of **B**. In our studies, the radical precursor **B** is chosen to be ethyl iodoacetate because it contains a carbonyl group with a distinct IR spectrum. The IR spectral shifts of the carbonyl stretching band can be exploited in TRIR measurements to follow the reaction as ethyl acetate radical **D** forms and is incorporated first into intermediates **C** and E_1 / E_2 then into product **F**. Using the multi-probe capabilities of the LIFEtime Facility, all the steps in this complex reaction can be tracked by TRIR spectroscopy. The spectroscopic and kinetic deductions from the data unambiguously resolve the debate about IAT versus SET mechanisms.⁴

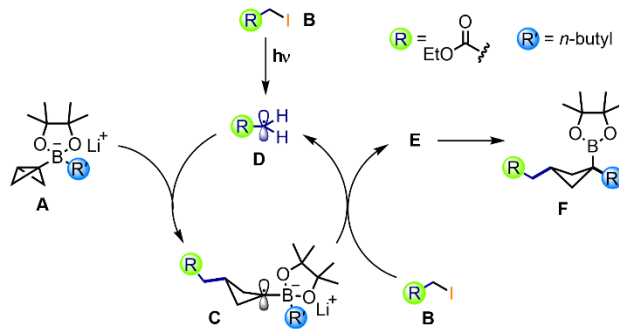


Figure 2. The reaction cycle studied by TRIR spectroscopy.

Example TRIR spectra are shown in Figure 3 together with band assignments. The strong, negative-going feature at 1736 cm^{-1} arises from photochemical depletion of the ethyl iodoacetate **B** and its partial recovery by geminate recombination within a few picoseconds. Over longer timescales, this depletion grows in depth as the radical cycle

shown in Figure 2 consumes additional **B** molecules. At the same time, radical **D** forms, as shown by a characteristic IR band at 1656 cm^{-1} which initially decays because of geminate recombination, and then recovers and reaches steady state as the cycle shown in Figure 2 converts **B** to **D**. In the same spectral window afforded by the broadband IR probe pulses from LIFEtime, product **F** is seen to grow on timescales up to $100\ \mu\text{s}$. Importantly for the desired mechanistic studies, a weak band is also observed at 1640 cm^{-1} that is assigned to intermediate **E** (either **E**₁ or **E**₂) based on its observed kinetics of growth and decay. Computational predictions of the frequency of the carbonyl stretching mode in either **E**₁ or **E**₂ do not definitively rule out either the IAT or SET pathway. However, these two proposed reaction mechanisms can be distinguished by further computational predictions of the kinetics of decay of **E**₁ and **E**₂ and growth of **F**.

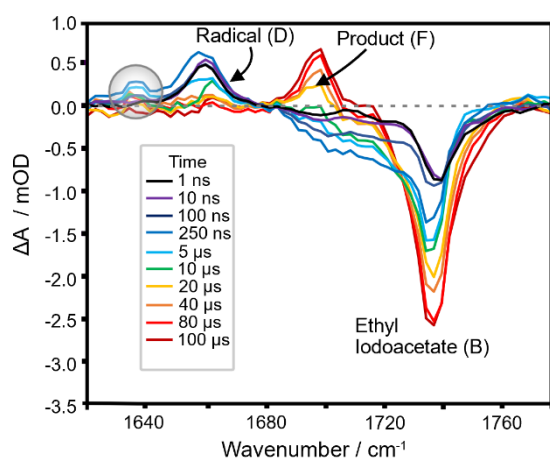


Figure 3: TRIR spectra of the photoinitiated reaction of bicyclo[1.1.0]butyl boronate **A** with ethyl acetate radical **D** produced by photolysis of precursor **B**. The weak band at 1640 cm^{-1} highlighted by a grey circle is assigned to intermediate **E**₁.

Computational studies of the 1,2-metalate rearrangement

The structures and energies of the transition states for IAT and SET reactions are amenable to calculation using quantum chemistry methods. From these computed properties, Transition State Theory can be used to predict the reaction rate coefficients at ambient temperature. Such calculations were performed for the conversion of **E**₁ or **E**₂ to **F**, and the predicted rate coefficients were compared to the experimentally derived kinetics from analysis of TRIR data such as the spectra shown in Figure 3. Conversion of **E**₂ to **F** is computed to be barrierless, and therefore to have a rate significantly greater than the experimental observation from analysis of the band at 1640 cm^{-1} . In contrast, a computed Gibbs energy of activation of 35.7 kJ mol^{-1} for conversion of **E**₁ to **F** predicts a rate coefficient within a factor of 10 of the experimental determination. The experimental data, supported by computational chemistry calculations, therefore point to the dominance of the IAT pathway. The SET pathway might appear favorable because of the barrierless conversion of **E**₂ to **F**, but it can be understood not to contribute to the reaction if the formation of **E**₂ is a bottleneck that makes this pathway uncompetitive.

Conclusions

The mechanisms of complex, multi-step organic photochemical transformations of synthetic utility are now amenable to direct study using TRIR over extended timescales from sub-picosecond to microsecond or millisecond. The observation of spectroscopic signatures of each intermediate in the reaction

exploits the structural sensitivity of TRIR spectroscopy. Mechanistic models can be fitted to the time constants for growth and decay of each intermediate to extract kinetic parameters which further inform about the reaction mechanism. This methodology is applicable to synthetic strategies of growing popularity including free radical cycles,³ photoredox catalyzed reactions,^{1,2} and reactions initiated using triplet energy transfer from a photosensitizer.

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