

PRF# 55140-UR4

**Project Title:** Structural Effects on the Primary Isotope Dependence of Secondary Kinetic Isotope Effects in Hydride Transfer Reactions in Solution

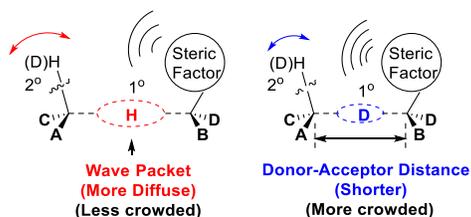
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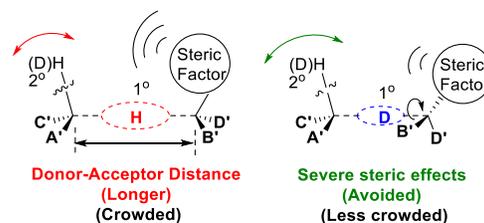
The hypothesis in the original proposal is that H-tunneling and D-tunneling have tunneling-ready state (TRS) structures of different donor-acceptor distances (DADs). We investigated the hypothesis by determining the effect of the 1° isotope on the 2° KIEs on the non-transferring (“in-place”) 2° H/D. Since the DAD is shorter for the tunneling of a heavier D isotope, the resulting more crowded TRS would suppress the 2° H/D vibrations and thus decrease the 2° KIE value (Scheme 1). The pronounced effect of the 1° isotope on 2° KIEs is expected to be observed in the sterically hindered H-tunneling systems. In Year 1 we designed several systems and determined the 1° isotope effect on 2° KIEs. Results supported the hypothesis and were published. In Year 2 we investigated more systems and found two important results that were not expected: (i) in addition to the steric effect, the electronic factor can also affect the 1° isotope dependence of the 2° KIEs, and (ii) the 2° KIEs at remote positions can also be sensitive to the 1° isotope. The results were submitted for publication. Publication was recommended, but major revision was required. We are still working on collecting additional results to support the discussion and conclusions in that manuscript. The new experiment involved the development of a competitive KIE measurement method to determine the KIEs. This became part of our work in Year 3.

In Year 3 we proposed an extension to the DAD hypothesis — the shorter DAD could also make the interfering neighboring steric factor lead away from the targeted 2° H/D to avoid the otherwise unbearable overall steric effect at and/or near the reaction center, possibly increasing the 2° KIE value (Scheme 2). We investigated the hypothesis.

**SCHEME 1. The hypothesis in the original hypothesis: the shorter donor-acceptor distance (DAD) in D-tunneling induces greater steric effect on the vibrations of the 2° H/D leading to a smaller 2° KIE value.**



**SCHEME 2. The extended hypothesis in Year 3: the shorter DAD in D-tunneling could also decrease the steric effect on the vibrations of the 2° H/D to avoid the otherwise severe steric effect on the 2° H/D vibrations increasing the 2° KIE value.**

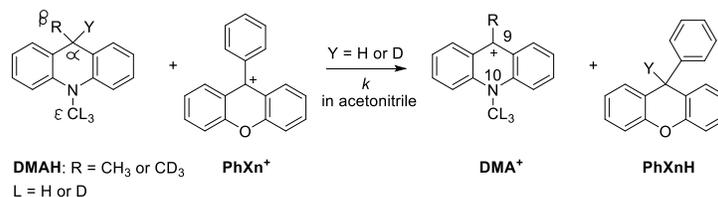


The details of the Year 3 study are as follows:

A. *Development of the competitive KIE measurement method to determine 2° KIEs for hydride transfer reactions in solution*

In this type of experiment, both isotopologues of known concentrations react in the same container and the KIE can be determined from the relative amounts of unreacted starting materials after a certain time. This experiment ensures that reactions of both isotopologues occur under exactly the same conditions. We chose a system that was in the above-mentioned manuscript to develop the method (Scheme 3).

**SCHEME 3. The system that we used to develop the competitive KIE measurement method, the resulting KIEs are expected to be the same with those from the UV-Vis spectroscopic measurements.**



We used a known mixture of CH<sub>3</sub> and CD<sub>3</sub> isotopologues reacting with PhXn<sup>+</sup> of limiting concentration and measured the isotopic fractionation of the leftover isotopologues. We used mass spectrometry to determine the concentrations of CH<sub>3</sub> and CD<sub>3</sub> at time = 0 and time = t, and used the following known equation to calculate the KIE.<sup>1</sup> The preliminary KIE result for the hydride-isotope transfer process is close to the one obtained from the spectroscopic measurement. The study is currently in progress (supported by NSF).

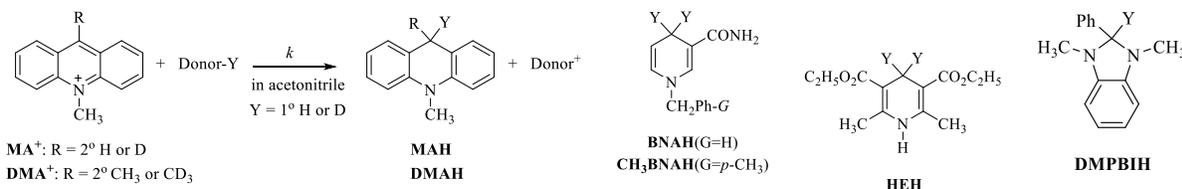
$$KIE = \frac{\ln(1-F)}{\ln\left((1-F) \times \frac{R_t}{R_0}\right)} \quad \text{where} \quad R_0 = \frac{[CD_3]_0}{[CH_3]_0}, \quad R_t = \frac{[CD_3]_t}{[CH_3]_t}, \quad F = \frac{[CH_3]_0 - [CH_3]_t}{[CH_3]_0}$$

We attempted to fit the observed 1° isotope dependence of 2° KIEs to the calculations to find the TRS structures. This study has gained preliminary results and is currently in progress (supported by NSF).

#### B. Study the steric effect on the 1° isotope dependence of 2° KIEs to test the hypothesis in Scheme 2

Hydride transfer reactions from a series of hydride donors with various steric requirements to MA<sup>+</sup> or DMA<sup>+</sup> in solution were designed to test this hypothesis. The 2° KIEs are those at the α-H/D position in MA<sup>+</sup> and the β-CH<sub>3</sub>/CD<sub>3</sub> position in DMA<sup>+</sup>. The steric effects are expected to increase from the reactions of BNAH/CH<sub>3</sub>BNAH, to HEH, to DMPBIH. It was found that the 2° KIE value accompanying D-transfer changed from smaller than, to similar to, and to larger than that with H-transfer as the steric effect increases, supporting the new hypothesis. The traditional 1°/2° H coupled motions model that could also interpret the smaller 2° KIE for the tunneling of a heavier isotope cannot explain the last “reversed” effect. Our NSF grant supports the further investigation of the hypothesis.

#### Donor-Y



#### Impact of the Research

This is a brand-new physical-organic-chemistry research direction that studies the *isotopologues*—DAD—TRS structures relationship for the H-transfer reactions. The significance of this project has multiple facets. First, the confirmed isotopically different DAD concept could not only support the activated H-tunneling model, but also provide a foundation for the development of other necessary models for H-transfer Chemistry. Second, the “DAD concept” will change our understanding of the nature of H-tunneling and the origin of 1° KIEs. Third, the “DAD concept” will also help understand the 1° isotope effect on the 2° KIEs that has been previously widely used to provide insights into the H-tunneling mechanism in enzymes. Fourth, the 1° isotope effect, i.e. the DAD effect, on the 2° KIEs at various positions gives information about the DAD—TRS structure relationship, which can assist the understanding of the DAD sampling coordinate of the H-tunneling reactions. This much-needed study is expected to change many traditional views about KIEs and H-transfer reactions, and a similar study in enzymes would help understand the H-transfer chemistry in biological systems. The published and preliminary results have been incorporated into a funded NSF proposal (starting August 1<sup>st</sup>, 2018). The three-year ACS-PRF project has assisted the PIs in progressing to make seminal contributions to the H-transfer chemistry.

Undergraduate and MS degree graduate students involved in this project learned basic organic synthesis, kinetic procedures, mechanistic analysis techniques, computational chemistry and the use of modern analytical instrumentation. With these research experiences students are prepared to enter professional schools and Ph.D. programs, to become teachers, and problem-solvers for chemical companies. For example, of the three MS graduate students who graduated summer 2018, Li Ma is in the University of Missouri as a Ph.D. candidate, Nader Sakhaee is teaching in two colleges in the St Louis area, and Nasim Salimrafter will start to work in October in Monsanto in St Louis.

#### Reference(s)

- (1) Singleton, D. A.; Thomas, A. A.: High-Precision Simultaneous Determination of Multiple Small Kinetic Isotope Effects at Natural Abundance. *J. Am. Chem. Soc.* **1995**, *117*, 9357–9358.