Isotope Effects in C-H Bond Activation Reactions by Transition Metals

Dongqi Wang

Zhao Group Meeting

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Entering the Deuterated Age

1929 Giauque and Johnson discover heavy oxygen isotopes ^{17}O and ^{18}O.

Urey

1932 Urey and coworkers reported the first spectroscopic evidence for a Heavy isotope of hydrogen.

1933 Gilbert Lewis and coworkers isolated a pure sample of heavy water.

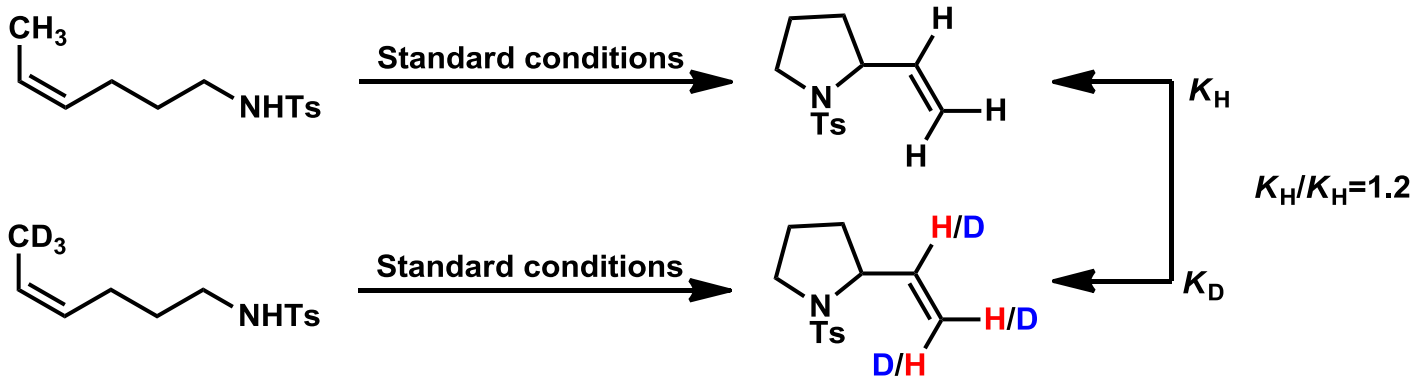
1934 Eyring and Polanyi independently and correctly postulate that protonated and deuterated compounds should react at different rates based upon differences In zero-point energies.

Eyring

1934 Interest and the availability of deuterated compounds lead to an explosion of research into isotopically labelled molecules.

KIEs in C-H Bond Activation

- **Case 1**



X. Ye, G. Liu, B. V. Popp, S. S. Stahl, *J. Org. Chem.* **2011**, *76*, 1031 – 1044

- ***WHAT*** **is Kinetic isotope effects?**
- ***WHY*** **should we carry out the KIE experiments?**
- ***HOW*** **do we carry out the KIE experiments?**

WHAT is Kinetic Isotope Effect

Kinetic Isotope Effect (KIE) is the ratio of reaction rates of two different isotopically labeled molecules in a chemical reaction.

---------- Wikipedia

- **Interpretation of the rate differences provides information on the nature of the rate-determining step.**

- **There are several different classifications for KIEs.**

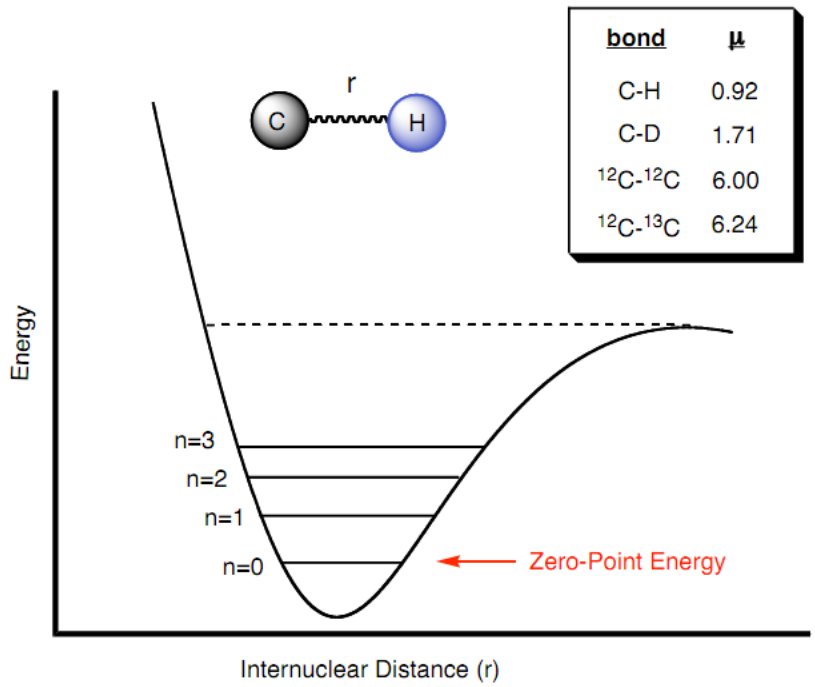
Primary isotope effect: Occurs when labelled bond is made or broken in RDS

Secondary isotope effect: Occurs when labelled bond is not made or broken in RDS

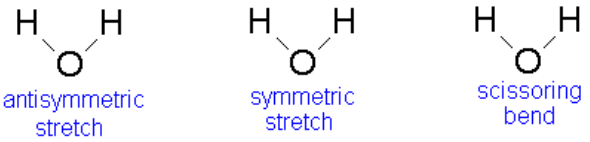
Normal isotope effect: Occurs when K_H/K_D is greater than 1

Inverse isotope effect: Occurs when K_H/K_D is less than 1

Quick Review of Vibrational Spectroscopy



Molecular Vibrational Motions:



Two Main Techniques:

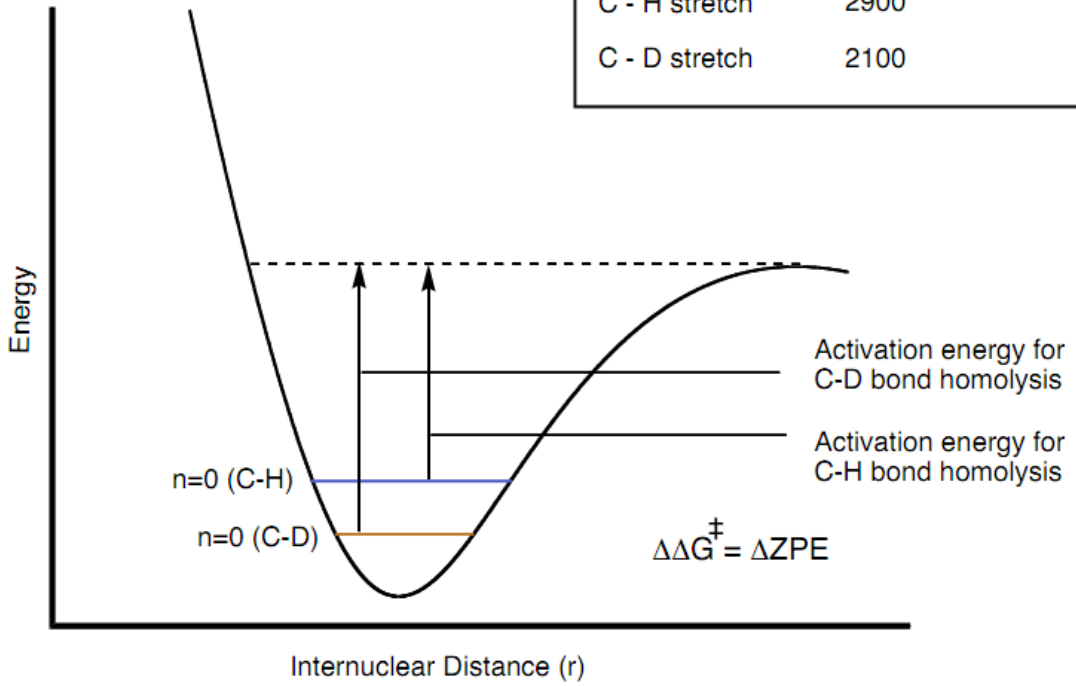
- Infrared spectroscopy
- Raman spectroscopy

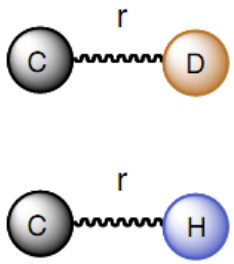
The picture comes from R. Knowle's talk on MacMillan group meeting adn chemwiki

General theory

Eyring's theory for reaction rates:
the reactants are in equilibrium with an "activated complex" or "transition state," and that this complex subsequently decomposes, in the rate-controlling step of the overall process, into products.

	frequency (cm^{-1})	ZPE (kcal/mol)	rel. rate (300 K)
C - H stretch	2900	4.15	~6.9
C - D stretch	2100	3.00	1.0





The kinetic isotope effect obtains only when a bond to a hydrogen atom is broken (or formed) in the rate-controlling step of a reaction.

WHY: The Application of KIEs in C-H Activation

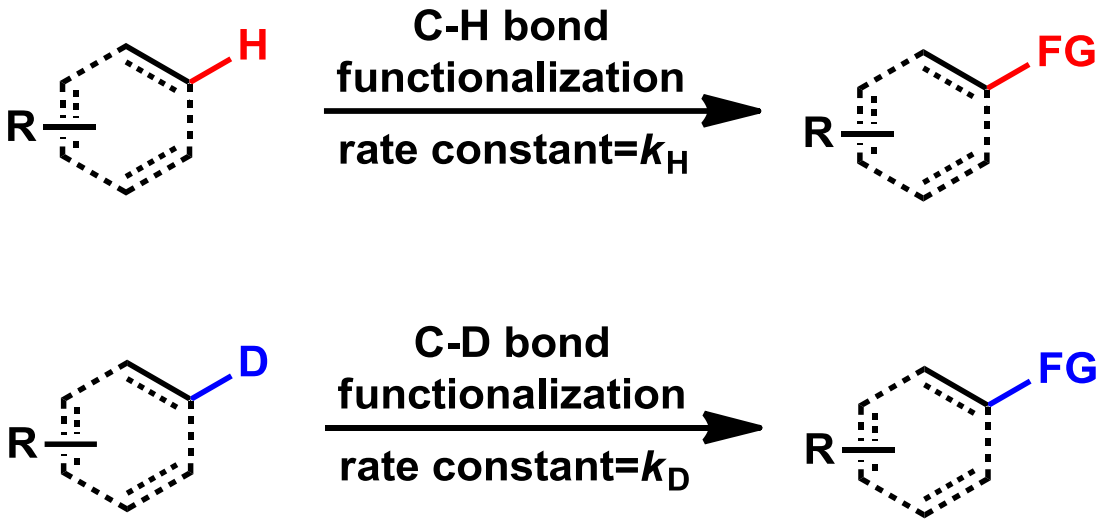
- **KIE experiments can provide important information about which bonds are broken or formed at different stages of a reaction**

- **C-H bonds do not generally undergo exchange in the absence of an external reagent or catalyst (in contrast to N-H and O-H bonds)**

- **Carbon-bound deuterium labels can be introduced by a variety of synthetic methods**

HOW: Three Types of KIE Experiments

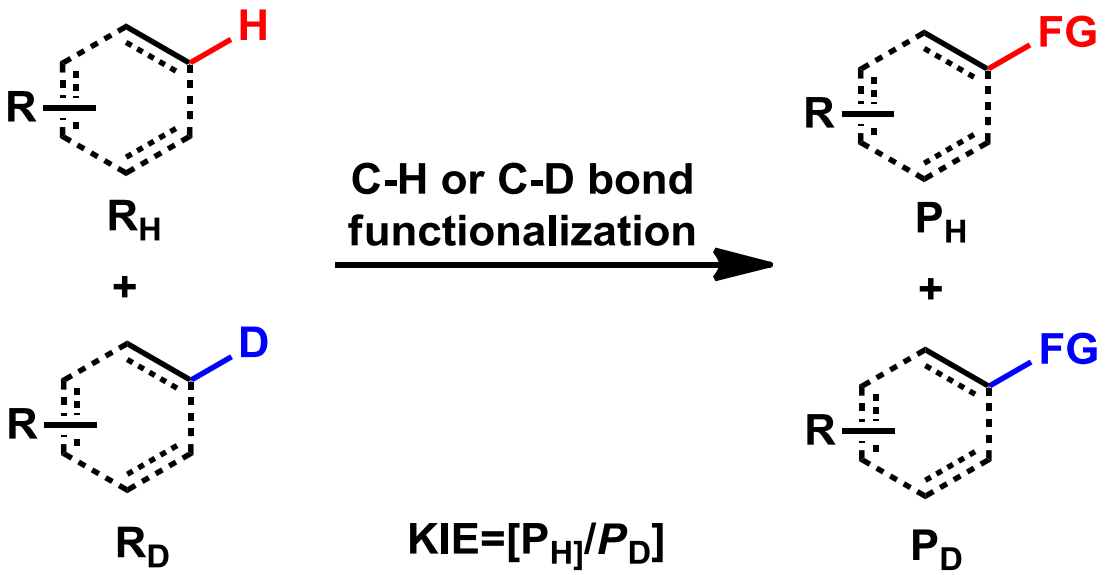
A) KIE determined from two parallel reactions



KIE=K_H/K_D

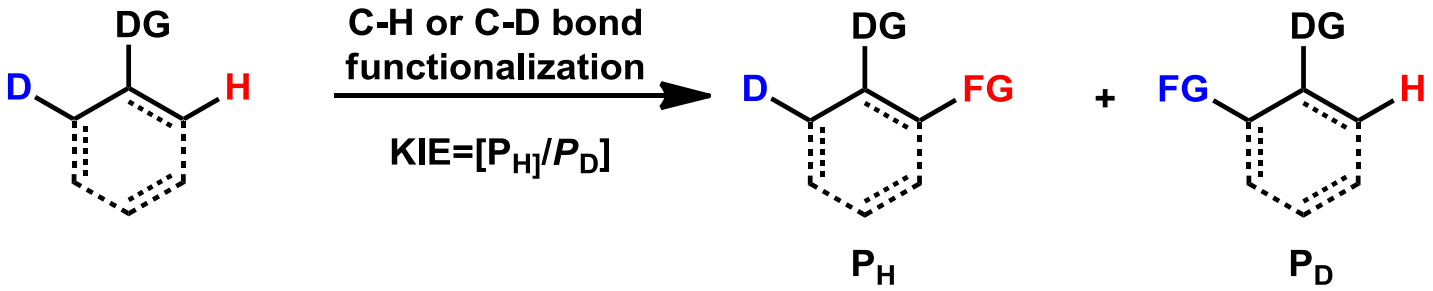
HOW: Three Types of KIE Experiments

B) KIE determined from an intermolecularcompetition



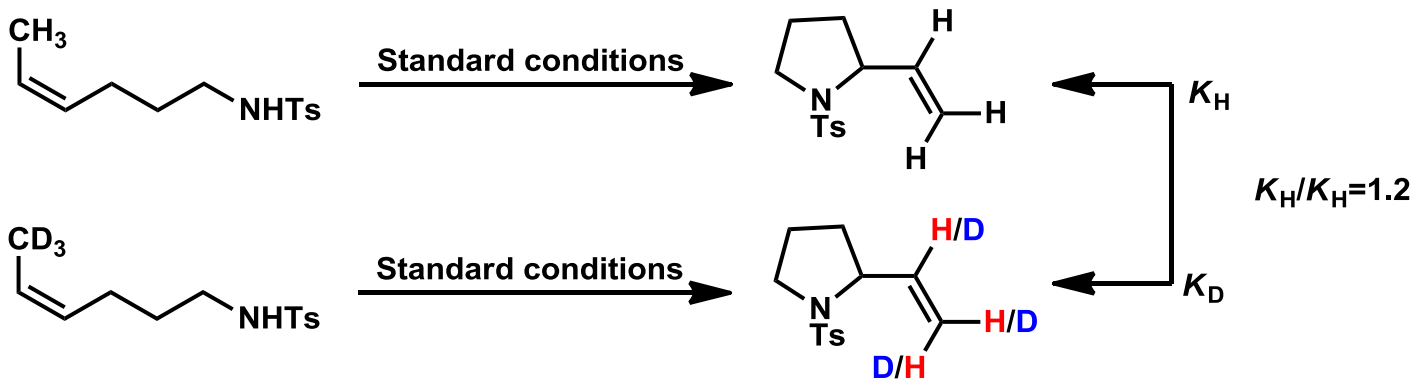
HOW: Three Types of KIE Experiments

C) KIE determined from an intramolecular competition



APPLICATION: The Answer of Case 1

- **Case 1**



The C-H Bond Cleavage is not the Rate-Determining Step

Thank You

Key Reviews:

E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 3066 – 3072
W. D. Jones, *Acc. Chem. Res.* **2003**, *36*, 140 – 146
F. H. Westheimer, *Chem. Rev.* **1961**, *61*, 265 – 273