HYDROGEN ISOTOPE EXCHANGE: LATE-STATE FUNCTIONALIZATION STRATEGIES FOR ISOTOPIC LABELLING

Reported by Vincent Kassel April 9, 2019

INTRODUCTION

Hydrogen isotope exchange (HIE) is the replacement of a bonded hydrogen atom with a heavier isotope (i.e. deuterium or tritium). In the context of C-H bonds, hydrogen isotope exchange is among the most fundamental of all C-H functionalization processes.[1] Reactions that effect HIE generally fall into three broad classes. Namely, acid/base-mediated exchange, exchange by heterogeneous catalysis, and exchange by homogeneous catalysis.[2]

The field of HIE witnessed rapid development after the initial discovery of deuterium, culminating in extensive research in the 1960's and 1970's. In the mid-1990's, a "renaissance of H/D exchange" took place, driven in large part by contemporary interests in C-H activation.[3] Today, a range of exchange methods are being reported for both site-selective and global incorporation of hydrogen isotopes into complex molecular architectures. These methods are often amenable to late-stage functionalization and have a broad number of downstream applications.

APPLICATIONS

Methods for site-selective HIE enable mechanistic insights into chemical and enzymatic processes, particularly through kinetic isotope effects (KIE). Furthermore, incorporation of deuterium into drug candidates can significantly alter absorption, distribution, metabolism, and excretion (ADME) behavior. Deuteration of tetrabenazine, used for the treatment of chorea in Huntington's disease, demonstrated similar efficacy with lower dosing and an increased duration of action.[4] The outcome of this study was the first FDA approved deuterated drug molecule in 2017 (Austedo®).[5]

Stable isotopically labelled internal standards (SILSs) for mass spectrometry enable quantification of analytes in complex biomedia by way of similar chemical and physical properties between the analyte and internal standard. The application of SILSs can be advantageous in liquid chromatography coupled with tandem mass spectrometry, which is notably applied in the development of pharmaceutical drugs to understand toxico- and pharmacokinetic properties of the parent drug and subsequent metabolites.[4]

The use of tritium labelling in radioligand binding assays is also paramount to current biomedical research and drug discovery. Methods for high degrees of tritium incorporation are desired, as specific activities in the range of 50-100 Ci/mmol are required to detect low density binding sites.[6a]

METHODS FOR HYDROGEN ISOTOPE EXCHANGE

Methods for both global and site-selective HIE are needed depending on the end application (vide supra). A landmark method demonstrating a high degree of isotopic incorporation for both deuterium and tritium was reported by Chirik in 2016.[7] Isotopic incorporation proceeded under mild conditions (45°C, 0.15-1.0 atm gas) to afford labelled active pharmaceutical ingredients (APIs) by use of a homogeneous iron catalyst. Notably, the labelled APIs exhibited orthogonal site-selectivity to existing iridium catalysts. Later, MacMillan demonstrated that photoredox-catalyzed hydrogen atom transfer could deuterate and tritiate APIs at α-amino sp^3 C-H bonds with levels of incorporation adequate for ligand-binding assays and ADME studies.[8] In subsequent publications,[6a,b] Chirik has demonstrated that nickel catalysts are competent to promote HIE under similarly mild conditions. Strikingly, by designing a novel dimeric nickel hydride catalyst, Chirik was able to achieve unprecedented specific activities.[6a]

Several site-selective labelling methods have also been recently reported showing exquisite regioselectivity. For example, Bandar reported equilibrium-driven α-deuteration of styrenes using base-catalyzed reversible addition to effect >94% α-selectivity.[9] McNally has demonstrated the previously unknown *para*-labelling of pyridines and diazines using intermediate phosphonium salts.[10] Lastly, Kerr et al. have reported the formyl-selective deuteration of aldehydes.[11]

References:

1. Atzrodt, J. et al. *Angew. Chem., Int. Ed.* **2018**, *57*, 3022.
2. Junk, T.; Catallo, W. J. *Chem. Soc. Rev.* **1997**, *27*, 401.
3. Atzrodt, J. et al. *Angew. Chem., Int. Ed.* **2007**, *46*, 7744.
4. Atzrodt, J. et al. *Angew. Chem., Int. Ed.* **2018**, *57*, 1758.
5. Schmidt, C. *Nat. Biotechnol.* **2017**, *35*, 493.
6. (a) Chirik, P.J. et al. *J. Am. Chem. Soc.* **2019**, *141*, 5034. (b) Chirik et al. *ACS Catal.* **2018**, *8*, 10210.
7. Chirik, P.J. et al. *Nature* **2016**, *529*, 195.
8. MacMillan, D. et al. *Science* **2017**, *358*, 1182.
9. Bandar, J.S. et al. *J. Am. Chem. Soc.* **2019**, *141*, 1467.
10. McNally, A. et al. *J. Am. Chem. Soc.* **2018**, *140*, 1990.
11. Kerr, W. et al. *Angew. Chem., Int. Ed.* **2017**, *56*, 7808.