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Short Research Article

Tritium chemistry: history, current status and future developments; a brief review†

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History and current status

Tritium was first produced[1] by McMillan at the Lawrence Berkeley laboratory in the USA, but misidentified as ^{10}Be. Subsequently, trace amounts were deliberately produced[2] by Rutherford and Oliphant in the Cavendish laboratory at Cambridge, UK, though the nuclide was first prepared in significant quantities by Alvarez and Cornog, again at Berkeley, by deuteron bombardment of D_2O.[1]

The organic chemistry of tritium was first codified by Evans[3] at the Radiochemical Centre, UK, who identified the major routes for labelling organic compounds as: (1) acid- and base-catalysed exchange; (2) metal-catalysed exchange; (3) tritiodehalogenation; (4) multiple bond reduction with T_2; (5) active metal tritide reduction; (6) hydrolysis of metal alkyls/aryls with T_2O; (7) biochemical labelling; (8) Wilzbach labelling; and (9) recoil labelling (now little used). Most of these approaches, or their subsequent developments, are still in use today, and the reader is pointed to excellent, more comprehensive, reviews of the current status of these and other more recent methods.[4,5]

Evans's group also developed palladium-catalysed tritium gas exchange in solution for the labelling of benzylic compounds, carbohydrates, and nucleics,[6a,b] a technique subsequently extended to histidines and histidine-containing peptides by Brundish *et al.*[6c,d] An alternative Group VIII metal-catalysed solution exchange of a wide range of compound classes with isotopic water was also developed by Garnet *et al.*[7a,b] More recently, a solid-state exchange approach has been developed by Myasoedov *et al.*,[8a–c] and applied to the labelling of a wide range of compounds and compound classes, including: amino acids and peptides, nucleosides, nucleotides and their deoxy-analogues, xanthine bases, psoralens, sterols, gibberellins, fatty acids, biotin, ATP, GMDP, indoleacetic acid, kinetin, a range of drugs including: dimethomorph, cyprofloxacin, cymoxanil, opamocarb, ribavirin, alprazolam, zeryamycin and AZT and even proteins such as: galactosidase, glucosidase, lichenase and collagen.

Many other acid-, base- and metal-catalysed exchange methodologies have been developed over the years[4] and creatively applied to the rapid tritiation of pharmaceutical agents.[9]

Perhaps the exchange methodology most used at present is metal-catalysed *ortho*-exchange. Initially developed with a tritium oxide isotope donor in dipolar aprotic solvents,[10a–f] the approach was later extended to tritium gas in dichloromethane.[11a–e] The subsequent discovery that the commercially available Crabtree catalyst was also effective[12a,b] in this latter exchange gave particular impetus to the technique. Investigations of *in situ* catalyst preparation and labelling regiochemistry,[13a–d,14a–d] the development of dendrimeric and solid-phase catalysts,[14a–d] further studies of ligand effects, cyclometallation constraints and extensive kinetic studies followed.[13e,15] Meanwhile, the solvent limitations of the process were addressed by the application of ionic liquids[16] or the development of catalysts, with new directing group specificities, which were active in dipolar aprotic solvents such as DMF or DMA.[17a–c]

More recently another type of reversible C–H activation catalyst[18a–e] has been under development using Bergman chemistry. These Ir(III) catalysts have labelling regiochemistries defined by a combination of electronic and steric effects. Though they show good potential for future use, their widespread utilization is limited at present by the need for multi-step precursor synthesis and by various degrees of air sensitivity.

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The development of new non-catalytic approaches has been hampered by the closure of the US National Tritium Labelling Facility at Berkeley. This facility proved to be key in the development of a range of tritium reagents,[4,5] particularly in the area of active tritides[4,19a–c] which was explored in detail in conjunction with the Novartis group of Voges and Andres. The latter in particular collaborated in a thorough investigation of the preparation and use of a wide range of tritides. These ranged from the precursor tritides LiT, NaT and KT, through the nucleophilic species $LiEt_3BT$, $LiAlT_4$, $LiBT_4$ and $LiPh_3BT$ to the softer nucleophiles such as $NaBT_4$, KBT_4, $Na(OMe)_3BT$ and $Na(OAc)_3BT$ which will tolerate hydroxylic solvents and, in some cases, acid. A range of stannanes and silanes including Bu_3SnT, Ph_2SiT_2, Et_3SiT, Hex_3SiT, TMS_3SiT were also investigated as was the preparation of the Schwartz reagent Cp_2ZrClT, and a number of electrophilic alkyl boranes and alanes. Thus, routes were opened to a whole range of selective reductions, polar hydrogenations, tritiodeoxygenations, radical additions, radical translocations and alkene additions. Other researchers have developed the use of borotritide in conjunction with transition metal salts and complexes to provide simple one-step tritiodehalogenation procedures.[19d,e]

Possible future developments

The identification and development of new and specific tritiation and deuteration catalysts have been greatly facilitated by the availability of high-throughput NMR and MS analysis methodologies for deuterium,[14b,c,20] as has the availability of the small-scale parallel hydrogenation equipment.[21a–c,22d] With the recent availability of similar commercial systems further advances are anticipated.[21b,c] In addition, the convenience of modern automated microwave systems[23] promises to revolutionize radiochemical preparations and speed up the search for new labelling catalysts.[17b,24] An interesting area with potential applications in tritium chemistry is that of microreactors,[25a,b] though these have so far only been applied to deuterium and β^+ emitters.[26]

Of key importance to tritium chemistry is the availability of sensitive analytical techniques. Since tritium is the most detectable NMR nuclide and has only a vanishingly small natural abundance, further developments in the area of ^{3}H-NMR are to be expected. One such development, the ^{3}H-cryoprobe[22a,b] is now commercially available and shows a sensitivity improvement of between 4- and 5-fold over conventional probes.[22c,d] Further sensitivity improvements via active signal processing, possibly based on QRI,[22e] can be expected.

Although lagging behind its ^{14}C-counterpart, tritium accelerator mass spectrometry[27a–c] has great potential, and even at this early stage sensitivities of <1 dpm have been achieved.

All these developments will generate large quantities of raw data and will make available a wealth of new information about labelling reactions, with a consequent requirement for appropriate data processing and information technology applications. Some such applications are currently under development.[28]

In addition, the new sensitive analytical techniques will enable a reduction in the amount of tritium needed to obtain good-quality experimental information.

Another development which will reduce tritium disposal is the recycling of tritium by GE Heathcare (Amersham) at their Cardiff site, though whether this will be commercialized is uncertain.

New applications of the tritium isotope are also particularly likely, and one with great potential for biological applications is microscopic autoradiography,[29a–c] which exploits the short range of tritium β-particles to report of sub-cellular distributions of the isotope, information which is key to target identification and validation in the pharmaceutical and agrochemical areas.

Conclusion

Seventy years since its accidental preparation by McMillan the chemistry of this fascinating nuclide continues to develop apace and the future for tritium looks as bright as ever.

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