Editorial

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Metal-catalysed hydrogen isotope exchange labelling: a brief overview

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An overview is given of this Special Issue of the *Journal of Labelled Compounds and Radiopharmaceuticals* dealing with the subject of metal-catalysed hydrogen isotope exchange labelling. In addition to summarizing the areas covered by the contributed papers, the overview also adds some historical information and gives short reviews of those areas and metals, not specifically covered by the contributed papers.

INTRODUCTION

This Special Issue of the Journal had been in conception for several years before taking its final form over the last year or so. It was conceived during discussions with many isotopic chemists who had come to recognize the increasingly important role being played by hydrogen isotope exchange in the pharmaceutical, fine radiochemical supply, and related industries. Many of those chemists have contributed papers to this issue. They are all active chemists who utilize the techniques they describe in their daily synthetic activities. This has given the issue a very practical flavor, which was one of our initial intentions. In this context, it is worthwhile to remember the oft-quoted J. B. S. Haldane ''If you want an expert opinion ask the person who did the work, failing that ask his immediate supervisor, after that there *are* no appropriate persons''. We believe that we have followed his advice in the construction of this issue.

METAL-CATALYSED HYDROGEN ISOTOPE EXCHANGE A BRIEF HISTORY

The development of metal-catalysed isotope exchange methodology has been a truly international activity with significant contributions from private industry, from universities and from government research organizations. Extensive reviews of the area have recently been published and the reader is referred to these for more detailed consideration of all the chemistries involved.[1a,b]

Platinum-catalysed exchange

The earliest investigations concerned heterogeneous catalysis by platinum group metals. Foremost among these were a series of studies by the group led by J. L. Garnett at the Commonwealth Scientific and Research Organisation (CSIRO)/University of New South Wales in Australia. These defined the major aspects of heterogeneous platinum-catalysed exchange of simple aromatics with isotopic water[2] *via* a long series of kinetic and regiochemical investigations beginning around 1960 and carried out over more than 20 years. Other academic groups helped to further investigate the process.[3] The above studies resulted in a novel, and more predictable, labelling approach than the Wilzbach technique,[4] which was in common use at the time.

The advantages of the new platinum-catalysed exchange technique were rapidly exploited by a newly-formed group under the leadership of E. A. Evans at the Radiochemical Centre in the United Kingdom (RCUK). By further developing the technique and by employing higher specific activity tritiated water, this group was able to label various classes of biologically important compounds,[5] many of which were crucial in developing our current understanding of fundamental biochemical pathways and of xenobiotic metabolism.

In addition to the work with heterogeneous platinum group metals, the Garnett group discovered that chloro-complexes of these metals could also catalyse isotopic exchange between aromatics and isotopic water. The studies were subsequently extended to saturated hydrocarbons by Shilov *et al.* at the N. N. Semenov Institute of Chemical Physics in Russia,[6a–c] and to phenylalanine, tyrosine and derivatives by Kanska in Poland.[7]

Tetrachloroplatinate(II)[8], hexachloroiridate(III),[9] and rhodium(III) chloride trihydrate [10] were all shown to be catalytically active by the Garnett group, and their reactions were subjected to varying degrees of kinetic analysis. Labelling specificity varied depending on the catalyst, and model studies were carried out by the group to investigate the regiochemistry of the labelling process in each case. However, conclusive quantitative information on the labelling selectivity of these catalysts awaited the development and application of ^{3}H-NMR by J. R. Jones, J. A. Elvidge, J. Bloxsidge *et al.* of the University of Surrey.[11] These workers carried out many studies of catalytic tritium exchange using the new technique, accurately defining, for the first time, the specificity of labelling for many catalytic reactions and for many important tritiated radiochemicals.[12]

Subsequent ^{3}H-NMR studies by M. A. Long (one of Garnett's early collaborators, and by then leading the group) and P. G. Williams, at the University of New South Wales, analysed the specificity of the heterogeneous platinum system with a range of model substrates over supported catalysts.[13] Long continued work with platinum catalysis throughout his career, investigating metal blacks[14] and metals in aluminophosphate molecular sieve, zeolite, mordenite and microcrystalline ALPO5 matrices[15] in addition to metal-based Lewis acid catalysts.[16] Williams, after a short spell with Jones at the University of Surrey, would go on to found the National Tritium Labelling Facility at the E. O. Lawrence Berkeley National Laboratory in the USA, along with another Jones student M. Saljoughian. This facility was to play a leading role in the development of many new tritium-labelling techniques during the 1990s.[17]

More recently, a group at Kyoto University in Japan have applied hydrothermal methods,[18] while hydride-activation and microwave conditions have been applied by groups at Sanofi-aventis.[19] Platinum catalysis techniques therefore continue to develop and this approach remains in common use (Atzrodt and Derdau; Sajiki *et al*., this issue).

Several applications of the above platinum-based approaches are described in this special issue (Figure 1). They include: the preparation of the tritium-labelled carcinogen, 3-methylcholanthrene (1) at 2.4 Ci/mmol and tyramine (2) at 13.6 Ci/mmol using heterogeneous platinum and tritiated water (Filer); the toxin ouabain (3) at 15–50 Ci/mmol, using platinum on charcoal and tritiated water (Chappelle and Hawes); and deuterated fluoren-9-one-4-carboxylic acid (4) and ferroquine (5) using tetrachloroplatinate-catalysed exchange of 3-chloroaniline (Atzrodt and Derdau). In addition, the preparation of Schering-Plough research pharmaceuticals (6 & 7) containing [*meta*/*para*-^{3}H]phenyl-labelled and [^{3}H]furo[3,2-c]pyridine-labelled moieties via heterogeneous platinum exchange with tritiated water is described (Hesk).

Palladium-catalysed exchange

Although palladium was investigated by the Garnett group along with the other platinum group metals, it acquired its current prominence as a result of studies, carried out using tritium gas as donor, by the Evans group at the RCUK. By simply stirring a solution of the substrate at room temperature with the metal (in unsupported or supported form) and tritium gas, a wide range of sugars,[20] nucleics,[20,21] compounds containing benzylic hydrogen (including oestrogens) [20,22a,b] and some heterocyclics,[20,23] could be labelled, often with good specific activity and with predictable regiochemistry, as confirmed by ^{3}H-NMR.[23] The range of structures amenable to labelling in this fashion was subsequently extended to include histidine and histidine-containing peptides.[24a,b]

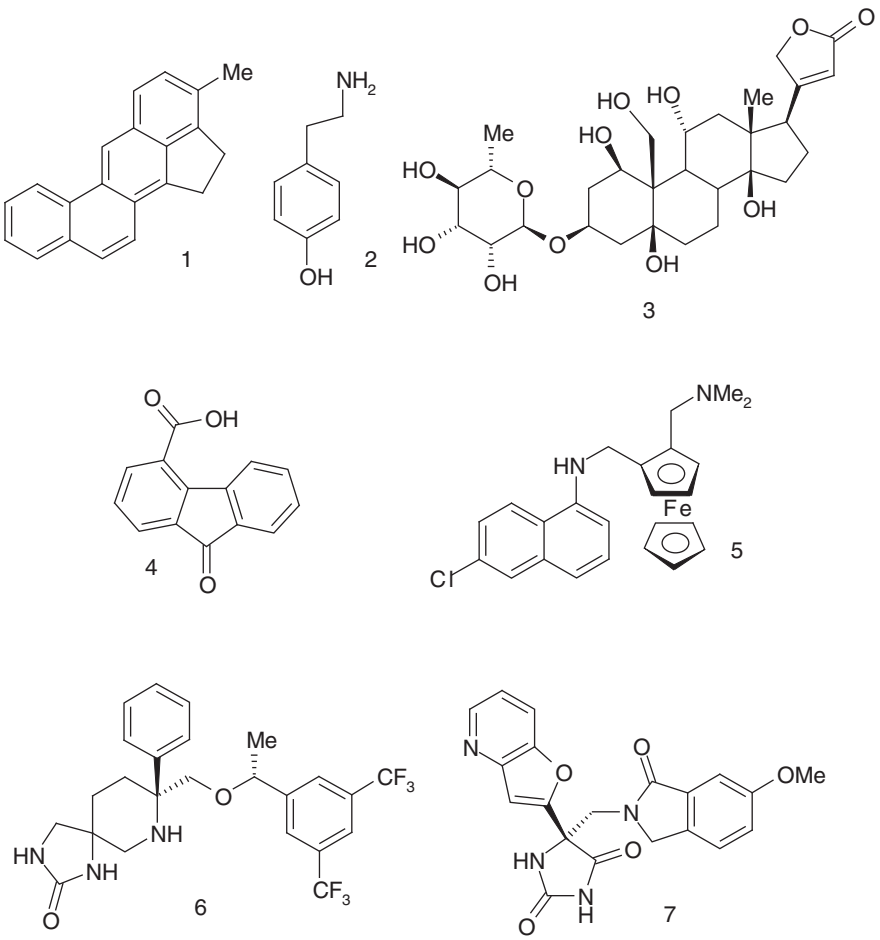

Figure 1. Some examples of compounds labelled with hydrogen isotopes using platinum catalysis in this special issue.

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Subsequently the technique has been developed and modified initially by the group of Buchman, Pri-Bar & Shimoni in Israel,[25a–d] more recently by Sajiki *et al*. in Japan[26a–e] and by Derdau *et al.* in Germany.[19]

It is worth noting that platinum and palladium catalysts can be utilized together,[27] often producing a synergy in the labelling efficiency (Atzrodt and Derdau; Sajiki *et al*.).

Several applications of the use of the palladium catalysis approach are described in this special issue. They include: the tritium labelling of staurosporine (8) at 17.2 Ci/mmol using 5% palladium on barium sulphate (Filer); of ribavirin (9) at 24 Ci/mmol using palladium oxide on barium sulphate in basic phosphate buffer (Hesk) and of tocopherol in the range of 30–70 Ci/mmol using 10% palladium on charcoal in acetic acid (Chappelle and Hawes; Figure 2). The deuterium labelling of valpromide, caffeine, theophylline and trimethoprim using 10% palladium on carbon and deuterium oxide is also described (Sajiki *et al*.).

The above solution phase approaches have been widely utilized; however, the platinum group metals may also be employed in solid-phase labelling procedures using tritium gas as the isotope donor. This technique has been extensively developed by the Myasoedov group in Russia [28a,b] and their work is reviewed and thoroughly referenced in this special issue (Shevchenko, Nagaer and Myasoedov); hence, it will not be described in detail here. The method, which involves exposing an intimate mixture of the solid substrate and catalyst to tritium gas, usually at elevated temperature, has been utilized for the labelling of a wide variety of substrates, ranging from small biologically significant molecules to large proteins and polymers. Under the right conditions, which must be optimized for each substrate, compounds can be labelled at very high specific activities and often with a good degree of regioselectivity and stereoselectivity. A typical application of the technique, the preparation of gabapentin (11, Figure 3) labelled with tritium at 150–200 Ci/mmol by solid-phase exchange over palladium black, is also given in another paper in the issue (Chappelle and Hawes), whilst the technique has been used to label the aminoglycoside antibiotic amikacin (12) at 3.4 Ci/mmol using palladium on calcium carbonate (Filer).

Rhodium-, ruthenium- and nickel-catalysed exchange

This special edition contains extensive reviews of isotopic exchange over heterogeneous and homogeneous rhodium and ruthenium catalysts (Lockley and Hesk) and over nickel catalysts (Heys); hence, these catalysts will not be described in detail here.

In addition to these full reviews, some newer applications of the above catalysts are described in other papers in the issue. Thus, rhodium black in the presence of tritium gas was utilized for the α-labelling of a pyrazine-containing Schering-Plough

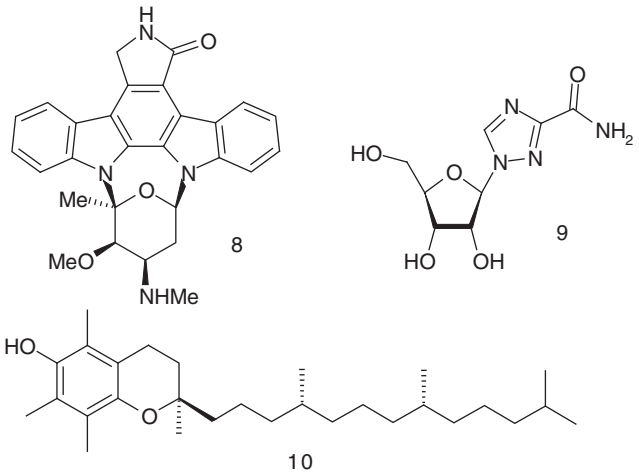

Figure 2. Some examples of compounds labelled with hydrogen isotopes using palladium catalysis in this special issue.

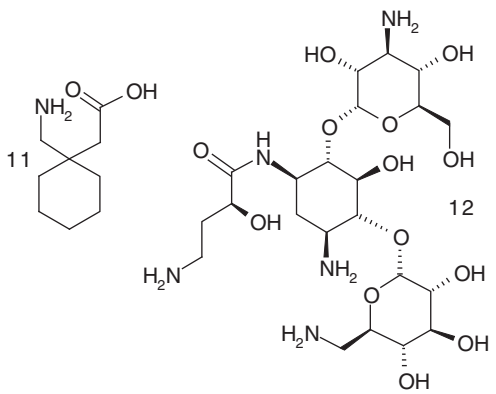

Figure 3. Examples of compounds labelled with tritium via solvent free tritium exchange in this special issue. For many more examples, see Nagaev, Shevchenko and Myasoedov.

pharmaceutical agent. The same paper describes the use of the homogeneous catalyst *tris*-(triphenylphosphine)ruthenium(II) dichloride for the labelling of three other pharmaceutical targets containing piperidine or piperazine groups (Hesk). Examples of the rapid labelling of drugs and intermediates via homogeneous rhodium(III) chloride trihydrate-catalysed exchange with tritiated water at both high and low specific activity are also given (Hesk; Wilkinson *et al*.).

Rhodium on alumina in combination with tritium oxide has also been used extensively for the tritium-labelling of a range of compounds including the cardiac glycosides digoxin (13, R = H) and digitoxin (13, R = OH) and the related toxin ouabain (3). The same catalyst was also used with a tritium gas donor to label the toxin bufalin (14, stereoisomer unspecified) at 4.1 Ci/mmol and a range of receptor agonists and neurochemicals at high specific activity. Similarly, the derivatized nucleoside N^6-cyclohexyladenosine (15) was tritiated at *ca.* 30 Ci/mmol, with the label present in the expected C2 and C8 positions (Filer), while tritiated water and rhodium on alumina labelled kaempferol (16) at 12 Ci/mmol (Chappelle and Hawes). Rhodium on a different support, this time charcoal, was also used, in conjunction with tritium gas, for the α-tritiation of a complex pyridine containing contract labelling substrate (Chappelle and Hawes; Figure 4).

In addition to many examples of ruthenium catalysis (Hesk; Hesk and Lockley), the use of Raney nickel and tritiated water as donor in the labelling of furo[3,2-c]pyridine- and 2-aminopyrimidine-containing Schering-Plough research compounds is also described (Hesk), whilst numerous examples of the use of nickel catalysts are given in the full review of nickel catalysis (Heys).

Iridium-catalysed exchange

Iridium(I) systems

The area of isotopic exchange over homogeneous iridium(I) catalysts has undergone a huge expansion since the inception of the technique in the early 1990s.[29a,b] No less than four of the papers in this special issue address detailed theoretical or practical aspects of the technique (Salter; Nilsson and Kerr; Herbert; Lockley) while many of the other papers give specific examples of its application in labelling target compounds.

The popularity of the technique arises from a fortuitous combination of factors: as an exchange technique, there is no need for the preparation of a specific labelling precursor; the methodology can be used with tritium gas which is less prone to produce radiolysis than high specific activity tritium oxide; the specific activity of the exchanged product can approach the maximum; the exchange mostly places the label in sites *ortho* to a directing group which for steric reasons are unlikely to be involved in metabolic transformations; judicious choice of ligands can give some control over the regioselectivity of the labelling; the equipment necessary for the technique is simple, and routinely available in isotopic chemistry laboratories.

The simplicity of the technique has enabled many investigational studies designed to elucidate the mechanism of the reaction, to explore the role of ligands, or to optimize the labelling conditions. These studies are summarized in two of the review papers (Salter; Herbert). In addition, the subject has been broadened by the introduction of new classes of ligands (Kerr and Nilsson) or of new ligands amenable to isotopic water and isotopic hydrogen gas donors (Lockley).

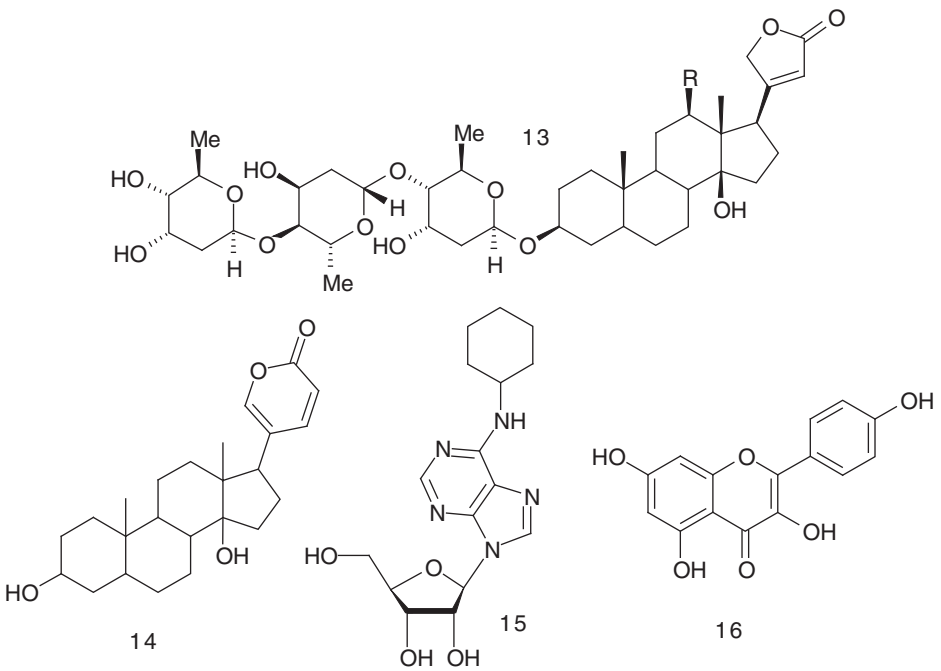

Figure 4. Examples of compounds labelled with tritium via rhodium-catalysed exchange in this special issue (for more examples see the papers from Hesk; Hesk & Lockley, Heys and Wilkinson *et al*.).

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Many examples of the use of homogeneous iridium(I) systems are cited in the other papers in this issue. The labelling of the formyl proton of aldehydes, facilitated by the Crabtree catalyst, is a general reaction[30a,b] and examples are given of this reaction, together with the labelling of paclitaxel (17), an anti-cancer agent, at *ca.* 70 Ci/mmol (Chappelle and Hawes). Roflumilast (18), an anti-inflammatory phosphodiesterase type 4 inhibitor, was tritiated at 77 Ci/mmol also using the Crabtree catalyst (Filer). Seven examples are given of the labelling of Schering-Plough research compounds using the Crabtree catalyst and tritium gas, while the use of cyclooctadienyliridium(I) hexafluoroacetylacetonate with tritiated water to label research compounds containing benzylamine, aryloxazole, phenylsulphonamide, urea and carboxylic acid groups is also described (Hesk; Wilkinson *et al.*). The utility of a solid-phase iridium(I) catalyst, COD.(polystyrene-$(PPh_2)_2$.Ir PF_6 (CH_2Cl_2 solvate), in the labelling of the anti-inflammatory drug tolmetin (19) and other target compounds is reported, as is the tritiation of the screening-ligand (20) using the closely related homogenous analogue [COD.Ir.$(PPh_2Me)_2$]PF_6 (Wilkinson *et al.*). The use of Salter's catalyst, COD.(R)-1-(SP)-2-[bis(4-methoxy-3,5-dimethylphenyl)-phosphino]ferrocenylethyldicyclohexylphosphine)Ir PF_6, has a clear advantage over the Crabtree catalyst in the tritiation of a proprietary compound (partial structure 21, Chappelle and Hawes). In addition, the utility of the new iridium(I) carbene catalysts in drug labelling is illustrated by the facile labelling of niclosamide (22), an anthelmintic drug, under *ortho*-direction by both the amide and the nitro-groups (Kerr & Nilsson; Figure 5).

Iridium(III) systems

Iridium(III) systems for the labelling of organic compounds[31a–c] were first described in 2001. Since they are not the subject of any specific paper in this special issue they will be dealt with in some degree of detail in this overview.

Although labelling via the above iridium(I) catalysts usually gives labelled products with an isotope distribution which can be rationalized by the formation of metallocyclic intermediates, the corresponding examples of labelling by iridium(III) species show quite different regiochemistries. Here the distribution of the isotope between alternative sites is generally determined by steric factors rather than by chelation or electronic factors, though a neighbouring group effect of fluorine and hydroxyl substituents leading to somewhat enhanced labelling *ortho* to the substituent has also been reported.[32a]

Complexes, such as [$Cp^*Ir(PMe_3)(Me)$] $B(Ar_f)_4$ where (Cp∗ = pentamethylcyclopentadienyl and $Ar_f = 3,5\text{-}(CF_3)_2C_6H_3$), will label a range of substrates when used under stoichiometric conditions with an isotopic hydrogen gas donor.[32a–c] In addition to steric suppression of labelling, inhibition by strongly coordinating groups such as amino or thio is observed. It should also be noted that the preparation and use of the complexes is not trivial, requiring an inert atmosphere and strictly anhydrous conditions.

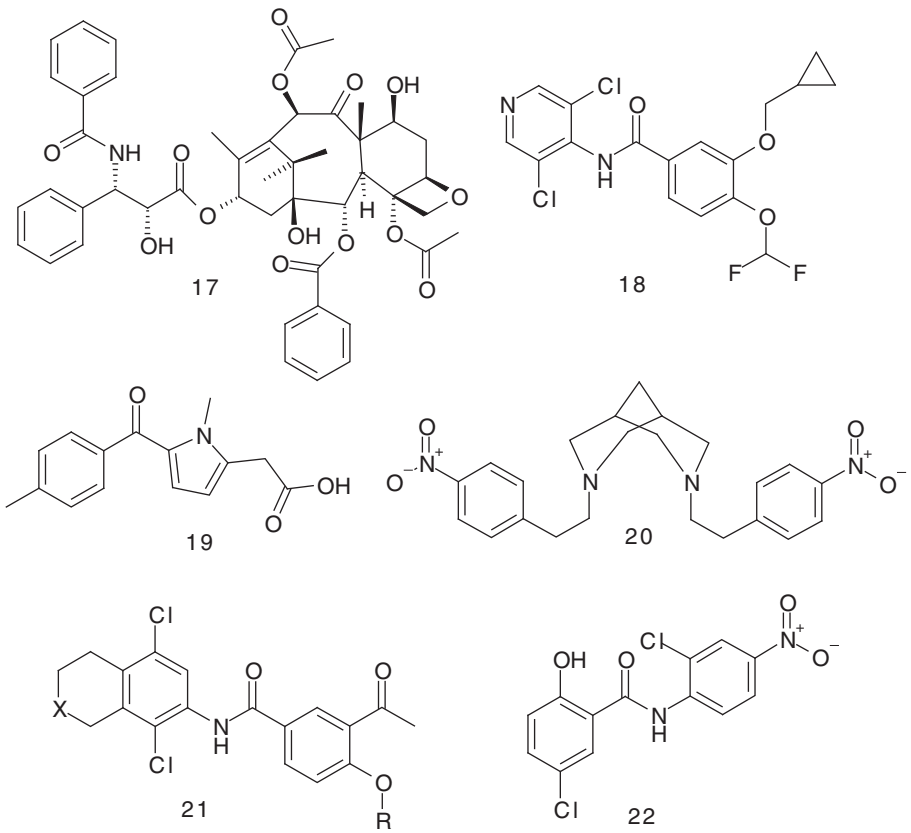

Figure 5. Selected examples of pharmaceuticals labelled with tritium via a range of iridium(I) exchange catalysts. Many more examples are quoted throughout the special issue.

The approach has been utilized with deuterium and with high and low specific activity tritium gas. However, at the time of writing, the reactions are essentially stoichiometric rather than catalytic, though the method may be capable of development in this direction. Examples of the labelling possible with this approach are given in Figure 6.

In contrast, the use of $Cp^*(PMe_3)IrCl_2$ in deuterium oxide is truly catalytic, though even here the catalyst is prone to deactivation at the temperature (135°C) used. Examples of the labelling achieved [33] are given in Figure 7.

Although the use of iridium(III) in isotopic exchange labelling is still in an early phase, the labelling regiochemistry of the complexes is complementary to that of the iridium(I) catalysts and hence there is much potential in the further development of these systems.

Other metals

In recent times, no other metals have been utilized as extensively as those above for the purpose of isotopic labelling.

However, studies of the gas-phase isotopic exchange reactions of small hydrocarbons on a wide range of transition metals have been carried out over many years for the purpose of characterizing the catalytic activity of the metal surfaces. The literature on this area is very extensive; however, it is only indirectly relevant to the preparation of labelled compounds; hence, it will not be covered here.

Cobalt, copper, chromium and iron

First row transition metals, with the exception of nickel, have not been extensively utilized for isotopic exchange. Nevertheless, isotopic exchange between D_2O and the α-positions of coordinated ligands have been observed for *N*-heterocyclic ligands with cobalt,[34a–c] while exchange into the vinylic bonds of coordinated olefins from perdeuterobenzene is also noted for this metal.[35] Indeed the facile *ortho*-labelling of the phenyl groups in the triphenylphosphine ligands of $HCo(N_2)(PPh_3)_3$ formed one of the first examples of this type of directed exchange.[36]

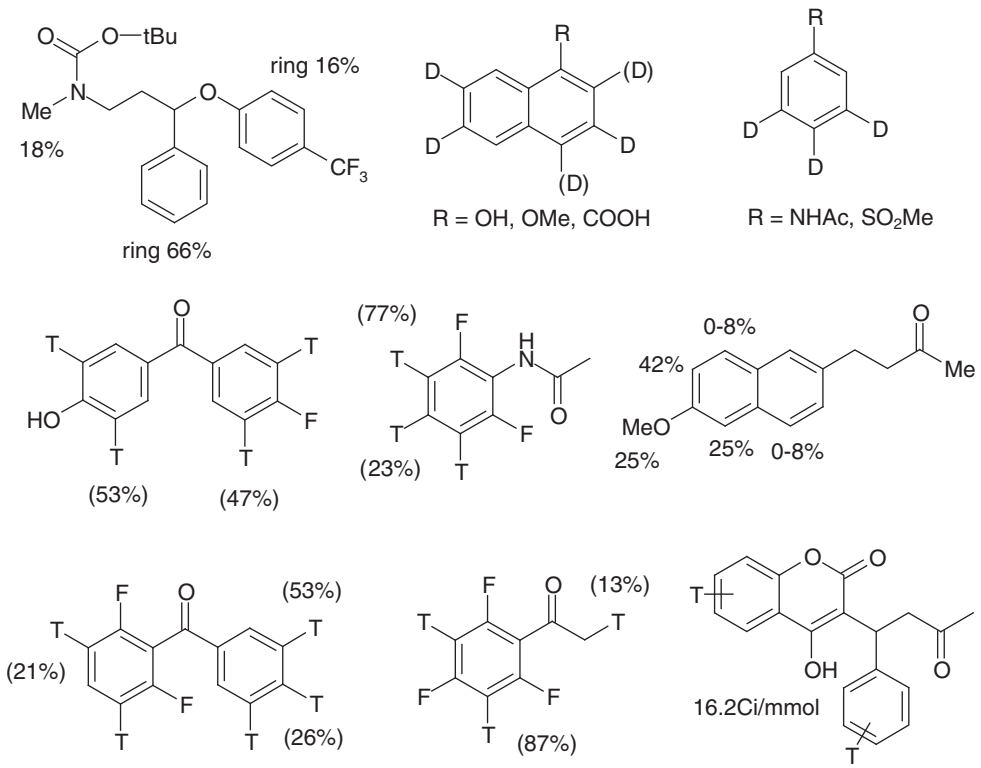

Figure 6. Labelling of various substrates by Ir(III) complexes.

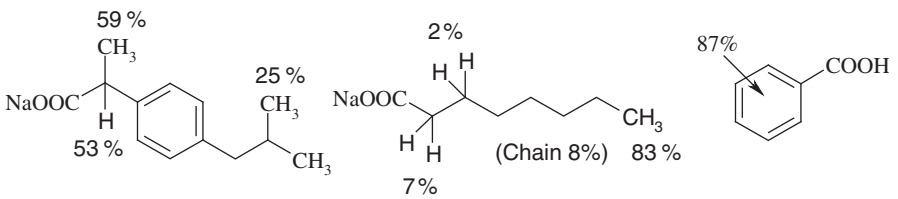

Figure 7. Catalytic exchange labelling of various substrates by $Cp*(PMe_3)IrCl_2$.

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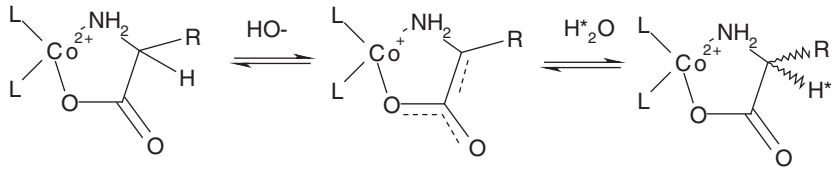

Figure 8. α-Labelling of amino acid cobalt(III) complexes.

Isotopic exchange into the α-positions of *N*-heterocyclics by heterogeneous cobalt at 130°C in D_2O has also been utilized for the labelling of pyridine, picolines, lutidines, pyridazine and isoquinoline.[37]

The exchange of benzylic hydrogen for deuterium by Raney cobalt and alkaline D_2O has been known for some time[38] and emphasizes the similarity between the chemistry of nickel and cobalt, though the former is much more active as an exchange catalyst.

Perhaps, the most widely known application of cobalt(III) catalysis is in the α-labelling of amino acids,[39] as shown in Figure 8. This type of reaction is essentially a version of base-catalysis in which exchange via the α-carbanion is facilitated by the complexed metal, which has the effect of enhancing the carbon-acidity of the amino acid. As such it would be expected that the amino acid would be racemized. This is generally the case, though detritiation studies have shown that the nature of the complexed amino acid can affect the diastereoselectivity of the reprotonation step in the complex.[40] Indeed, diastereoisomeric complexes, such as [Co[Sal-(*S*)-2-^{1}H-amino acid]$_2$]Na (Sal = salicylidene), have been utilized for the preparation of (*R*)- and (*S*)-[2-^{2}H]amino acids via a separation of the Λ(*S,S*) and Δ(*S,S*) diastereoisomers on Al_2O_3, followed by base-catalysed α-exchange in D_2O. The resulting diastereomeric complexes after separation on Al_2O_3 give pure deuterated Λ(*R,R*) and Δ(*S,S*) complexes, then yield the (*R*)- and (*S*)-^{2}H-amino acids upon decomplexation via electrochemical reduction.[40,41]

Tritium studies of cobalt-mediated exchange have largely concerned the importance of cobalt-carbon bond homolysis in biological processes such as RNA synthesis where adenosylcobalamin functions as a cofactor.[42] This type of interaction has been studied with synthetic cobalt(III) complexes of imidazoles[43], where exchange of the C2 position is observed.

Little work has been carried out with copper. The metal, in Cu(I) form, has been shown to promote the reversible and regiospecific H/D exchange of a benzene-ring proton on a triaza-macrocyclic ligand in weakly coordinating deuterated acidic solvents, such as [$^2H_6$]acetone or [$^2H_4$]methanol.[44] Also in the Cu(I) form, as the complex benzene(copper(I)triflate)$_2$, the metal is highly active for the exchange of the methine proton in terminal alkynes.[45]

In metallic form, copper catalyses the deuteration of Et_3SiH and of *Z*- and *E*-1,2-dimethylsilacyclopentanes. In the latter silanes, the exchange is accompanied by retention of configuration at the silicon atom.[46]

The exchange of a range of aromatics complexed to the tricarbonylchromium tripod has been studies extensively under basic (ethoxide in ethanol) conditions[47a] and acidic conditions (trifluoroacetic acid with and without boron trifluoride).[47b] Moreover, rate constants and partial rate factors have been determined in many cases.[47a,b, 48a,b, 49] The orientation of the exchange varies with the aromatic, as expected, but the deactivating effect of the tripod is such that the variation in the rates are much less than in the uncomplexed aromatic, and this is also reflected in the corresponding partial rate factors. Thus, (anisole)$Cr(CO)_3$ in basic deuteroethanol at 100° exchanges only three times faster than (benzene)$Cr(CO)_3$. Moreover, the partial rate factors for the anisole ligand were *ortho* 4.9, *meta* 1.5 and *para* 2.4 showing a much reduced discrimination with respect to *meta*-labelling. Similar results were obtained by dedeuteration studies with deuterated toluene ligands.[49] The exchange of the benzylic protons of η^6-tetralin and *trans*-η^6-(octahydroanthracene)$Cr(CO)_3$ complexes has also been studied, and the conformation of the tricarbonylchromium tripod has been shown to determine the orientation of the exchange.[50]

A general method for the perdeuteration of a wide range of arenes, including polycyclics also utilizes chromium, this time as a solution of chromium metal in DCl at 300°C. Despite the forcing conditions, yields are generally good and isotopic incorporation is high.[51]

Iron has been little utilized for isotopic exchange of organics and the extant exchange studies with iron complexes have largely involved studies of iron containing reductases.[52a,b]

Silver, molybdenum, osmium, niobium, rhenium, tantalum and zirconium

Second and third row metals show more potential as exchange catalysts, but here the Pt, Pd, Ru, Rh and Ir species remain the metals of choice, and these are reviewed elsewhere in this special issue. Nevertheless, some interesting applications of the other metals from these groups are briefly reviewed below.

The properties of silver often mirror those of copper, as befits a second row group member, and so it is no surprise to find that, as with copper, the metal ion is able to catalyse the exchange of the methine proton in terminal alkynes.[53a] Studies of the dedeuteration of terminally deuterated alkynes show that the deuterated alkyne reacts faster than the protio-analogue, a fact ascribed to the increased p character of the terminal carbon in the rate-determining step. The rate of the deuterium exchange is predictable in that it is correlated linearly with the decrease in CH stretching frequency upon silver ion π-complexation.[53b]

Silver has also been noted as catalysing the H-D exchange of the methyl group of the coordinated ligand 2-methyl-6-nitrobenzothiazole in a silver complex in the presence of deuteromethanol.[54] It has also been utilized for the tritium labelling of the acetyl groups in polyol acetates via catalytic exchange with silver(I) fluoride in tritiated water/pyridine.[55] In this case, at least two neighbouring acetyl groups were required for the reaction, and polyol esters other than acetates did not exchange.

The molybdenum complex Os(η-C_5H_5)($Me_2PCH_2CH_2PMe_2$)H_3 has been shown to catalyse the deuterium exchange in aryl and alkyl systems. Thus, photolysis of perdeuterobenzene solutions of aromatic hydrocarbons and of aliphatic ethers caused statistical exchange of hydrogen for deuterium. The same catalyst facilitated exchange in the arene ligands of organometallics, such as ferrocene and bis-η-toluenetungsten.[56] Similarly, the molybdocene complex [Cp′$_2$Mo(μ-OH)$_2$MoCp′$_2$](OTs)$_2$ (Cp′ = methylcyclopentadiene) was shown to catalyse the α-deuteration of alcohols in D_2O solution at 70–80°C. The catalytic species was shown to be the monomer [Cp′$_2$Mo(OH)(OH$_2$)]$^+$.[57]

Though osmium is rarely used for isotopic exchange, osmium polyhydrides can catalyse the isotope exchange into coordinated ligands. Thus, [$OsH_3(H_2)L_3$]$^+$ (L = PMe_2Ph or PPh_3) can reversibly dissociate deuterium gas, undergoing deuteration of the coordinated ligands in the process.[58] Similarly, with perdeuterotoluene and perdeuterobenzene as isotope donors, $OsH_6(iPr_3P)_2$ will catalyse the quantitative deuteration of the C4 and C5 positions of the coordinated vinylpyridine ligand in OsH_3(CH = CH-Pyr κC,κN)(iPr_3P)$_2$.[59] Hence, in common with a range of similar metal polyhydride complexes, the osmium polyhydrides show some potential for isotope exchange catalysis.

The pioneering work of the Parshall group[60a,b] on transition metal hydrides and polyhydrides is particularly noteworthy in this regard. The hydrides of niobium $NbH_3(C_5H_5)_2$, [$NbH(C_5H_5)(\mu$-$C_5H_4)]_2$, and iridium $IrH_5(Me_3P)_2$ were shown to catalyse the exchange between D_2 and aromatics, the relative rates of exchange of mono- and disubstituted benzenes increasing in the order p-Me_2 < Me ~ OMe < H < CF_3 ~ F < p-F_2. The mechanism advanced was one of alternating oxidative-addition/reductive-elimination steps, with the regiochemistry of the exchange subject to steric hindrance. The tantalum polyhydrides $TaH_3(C_5H_5)_2$,[60a,b] and $TaH_3(C_5H_4Me)_2$[60a] were also shown to catalyse the exchange between aromatics and D_2 as were the iridium polyhydrides $IrH_5(Me_3P)_2$,[60a,b] $(PhPEt_2)_2IrH_5$ and $(Et_3P)_2IrH_5$.[60a]

The exchange of borane/Lewis-base adducts ($BH_3 \cdot PMe_3$, $BH_3 \cdot NMe_3$ and $BH_3 \cdot PPh_3$ with perdeuterobenzene,[61a] catalysed by rhenium polyhydrides has been published and subsequently reviewed.[61b] Other examples include the dihydride $CpRe(PPh_3)_2H_2$ which proves to be a catalyst for H/D exchange between C_6D_6 and other arenes or alkanes,[62] and the anionic cluster complex $Re_3(\mu$-$H)_3(\mu$-$NC_5H_4)(CO)_{10}$, which contains an *ortho*-metalated pyridine bridge and undergoes a selective H/D exchange between the basal hydridic site and the α-position of the pyridine.[63]

Tantalum and zirconium alkoxides, at 180–220°C, have been shown to exchange the oxygen-bound deuterium of [*O*-^{2}H]ethanol for carbon-bound isotope. This reaction occurs by two separate mechanisms involving methyl group labelling and methylene group labelling, though the common intermediate may be the aldehyde.[64]

CONCLUSIONS

As the above discussion demonstrates, the technique of hydrogen isotope exchange labelling has undergone extensive development since the early days of Wilzbach *et al.*. In particular, the advent of powerful new analytical techniques, such as ^{2}H- and ^{3}H-NMR and LC/MS, in combination with parallel-chemistry optimization and catalyst screening approaches, have brought new understanding and control to what had previously been somewhat of a black-art. As detailed above, new, more efficient and more selective catalytic systems have been developed. The current situation is such that most target molecular structures can now be approached with one or other of the armoury of exchange-labelling techniques available to the isotopic chemist. Moreover, better understanding of many isotope exchange mechanisms has been achieved such that, whilst there are still some occasional surprises, the regiochemistry of most labelling reactions is reasonably predictable. Even the final specific activity or atom% abundance of the product may be estimated within an order of magnitude from literature precedents or, even more accurately, from high-throughput modelling reactions. Many types of institution, industrial and academic, have played their part in achieving this state of affairs. As a result, compounds labelled with isotopic hydrogen have played, and continue to play, an increased role as labelled tracers and standards in many fields of investigation. This special issue collates the experiences of many of the current contributors to the new isotope exchange techniques.

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