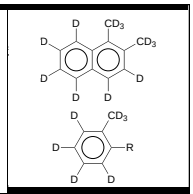
Hydrogen isotope exchange reactions involving C–H (D, T) bonds



CHEMICAL SOCIETY REVIEWS

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Exchange reactions involving the displacement of hydrogen bonded to carbon by its heavier isotopes are of interest for both mechanistic and product-orientated research. This review surveys practical strategies for the preparation of isotopically labelled compounds, discusses recent progress made in developing mild and regioselective exchange protocols, and summarizes the mechanistic aspects of C–H bond activation under homogeneous and heterogeneous exchange conditions.

1 Introduction

Exchange reactions involving the displacement of hydrogen bonded to carbon by deuterium or tritium are of interest to a broad variety of disciplines, including the preparative chemistry of isotopically labelled materials, fundamental studies of carbon–hydrogen bond activation processes, and study of the nature of catalysts. The interdisciplinary nature of this area has largely precluded the development of comprehensive literature sources specifically concerned with isotopic exchange procedures. After a period of intense research with a synthetic focus, which began approximately two decades ago, interest in hydrogen isotope exchange reactions subsided for a number of years. Recently, renewed attention for such reactions has been sparked by a general interest in catalytic C–H bond activation, as well as by an increased demand for labelled compounds as standards, reference materials, and special applications such as non-linear optical materials.[1] This trend is strongly supported by the emergence of analytical methods which simplify product analyses, including the availability of bench top mass spectrometry, ^{2}H and ^{3}H NMR spectroscopy in solution and in the solid state as readily accessible tools.[13] Deuterium is available at low cost and in high isotopic purity, facilitating H → D exchange experiments. Furthermore, D and T labels can be introduced into organic substrates post-synthetically, in contrast to ^{13}C and most other isotopic labels. This can greatly reduce efforts involved in preparing isotopically labelled materials, if conditions can be found which satisfy our expectations in terms of regioselectivity, chemical and isotopic purities.

2 H → D *vs.* H → T (D → T) exchange reactions

Obviously, hydrogen–deuterium exchange and hydrogen–tritium exchange reactions share many characteristics; consequently, we will focus on deuterium exchange and imply its extension to tritium exchange unless stated otherwise. Preparatively, however, the requirements for deuteration *vs*. tritiation reactions differ significantly. For practical purposes, it is generally desirable to obtain deuterated compounds in high isotopic purities, and the introduction of multiple labels is often required. Thus, exchange conditions which introduce labels in low abundance may be well suited for the preparation of tritium labelled compounds, but not for the preparation of deuterated analogues. Furthermore, exchange protocols specifically suited for H → T exchange include microwave-induced processes, substrate treatment with solid tritium near absolute zero, and decay-induced labelling, which have been reviewed mechanistically.[2]

3 General considerations

We can distinguish between three types of H → D exchange reactions. Acid catalysed exchange is initiated by the addition of acids to a mixture of a deuterium source and a substrate. Typically, this reaction is applied to aromatic or heteroaromatic substrates, even though other electron-rich substrates (*e.g.* alkenes) have been employed successfully. Eqn. (1) depicts the acid-catalysed deuterium exchange in benzene *via* formation of an aromatic π complex as a prototype example of this reaction,

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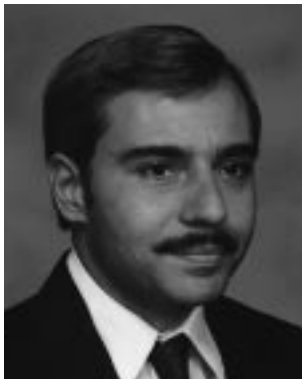

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which was introduced as a synthetic method several decades ago (high temperature dilute acid or HTDA procedure).[3]

$$C_6H_6 + DX \rightarrow (\pi\text{-}C_6H_6)D^+ + X^- \rightarrow C_6H_5D + HX \quad (1)$$

This approach has been extended to include various Lewis acids and organic substrates under protic or aprotic conditions, and has retained a dominant role in the preparation of isotopically labelled compounds. Current research is focused primarily on improvements in regioselectivity, the development of catalytic systems with broadened scope, and the suppression of chemical side reactions.

Base catalysed exchange, in contrast, constitutes a viable option for the exchange of sufficiently acidic protons [eqn. (2), (3)]. This family of reactions includes the reversible metallation of organic species in deuterated aprotic media (*e.g.* liquid ND_3), suitable for the exchange of protons with low acidities. The latter method is of limited practical interest, however, as suitable deuterated solvents are poorly accessible.

$$RR'R''\text{–}CH + B^- \rightarrow RR'R''\text{–}C^- + HB \quad (2)$$
$$RR'R''\text{–}C^- + DB \rightarrow RR'R''\text{–}CD + B^- \quad (3)$$

Exchange in carbonyl compounds and related species follows established methods, and will not be discussed in further detail. Several remarkable developments in this area include the introduction of base catalysed supercritical and near-critical exchange processes, and the emergence of methods based on solid phase catalysts including alkali metal fullerides and naturally occurring clays.

Finally, hydrogen isotope exchange reactions can be carried out in the presence of homogeneous or heterogeneous metal catalysts, notably those containing Group VIII elements. A representative example for homogeneous metal catalysis, depicting the chloroplatinate(II) catalysed H–D exchange of benzene *via* a dissociative π-complex mechanism is shown in [eqn. (4) and (5)].

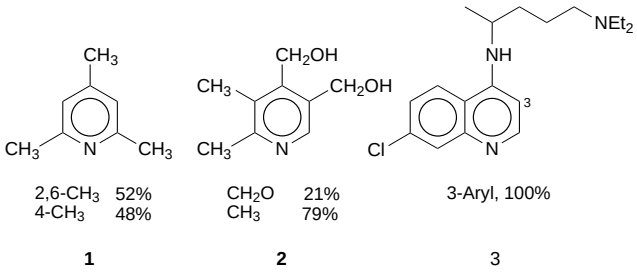
$$C_6H_6 + PtCl_4^{2-} \rightleftharpoons (\pi\text{-}C_6H_5)PtCl_3^- + H^+ + Cl^- \quad (4)$$
$$(\pi\text{-}C_6H_5)PtCl_3^- + DCl \rightleftharpoons C_6H_5D + PtCl_4^{2-} \quad (5)$$

Homogeneous transition metal catalysed exchange reactions involving naturally occurring heterocyclic substrates (thiazoles, imidazoles, histidines and purines) are of particular significance, as models for C–H bond activation in biological systems.

4 Lewis acid catalysed exchange reactions

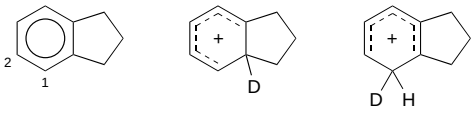
Classical Lewis acid catalysed exchange conditions have been studied since the 1960s. The most commonly employed catalysts include concentrated or hot dilute mineral acids, alkylaluminium dihalides, boron trifluoride and perfluorocarboxylic acids. Unfortunately, inconveniences are encountered when using these reagents. Thus, alkylaluminium dihalides are pyrophoric and are deactivated by amines, and HTDA catalysed exchange procedures require acid-resistant pressure vessels.[4] None of these approaches are regiospecific. Recently, polymer-supported acidic catalysts, notably the sulfonated fluoropolymer Nafion, were introduced for the deuteration and tritiation of a variety of aromatic and heteroaromatic substrates.[5] Thus, 2,4,6-trimethylpyridine **1**, pyridoxine **2**, and the antimalarial agent chloroquine **3** were tritiated at temperatures between 80 and 120 °C. Chloroquine was labelled in the 3 position only, in contrast to the poor regioselectivity achieved with other commonly used Lewis acid catalysts. Remarkably, isotope exchange in α positions was observed for both **1** and **2**, which indicates that polymer-supported acid catalysts exhibit regioselectivities which differ from those observed in the homogeneous acidic phase. Acid catalysed isotope exchange in alkyl side chains of aromatic compounds is uncommon, the perdeuteration of 2,9-dimethylphenanthrene being the only other known example.[6]

Improved regioselectivity has remained one of the primary objectives in the development of novel acid catalysed exchange



1 **2** 3

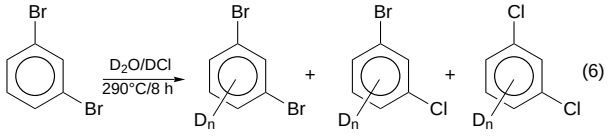
procedures. In earlier experiments, Sakhabutdinov *et al.*[7] achieved limited regiocontrol of H → D exchange in the series tetralin, indane **4** and 2-xylene, by employing either sulfuric



4 **5** **6**

acid or trifluoroacetic acid as exchange catalysts. Relative exchange rate increases in the 1 position of indane in sulfuric acid only were explained by the formation of an initial *ipso* substituted intermediate **5**, which underwent rearrangement to **6**. This approach, though moderately successful in producing regioselectively labelled products, indicates that improved regiocontrol may be achieved with non-polymeric acidic catalysts.

Drastic exchange conditions, while generally undesirable, nevertheless can offer solutions to specific problems. Recently, we investigated the exchange behaviour of polyhalogenated aromatics in an effort to perdeuterate these substrates in high isotopic purities. As expected, the addition of halogen atoms exerted electronic effects which required increasingly drastic conditions in order to achieve isotopic equilibration. Remarkably, 1,2,4,5-tetrachlorobenzene, which remained essentially inert at 310 °C, underwent smooth H → D exchange with no significant decomposition at 410 °C under supercritical conditions in 5% DCl–D_2O. In media containing other halides, substantial quantities of substrates were lost to halogen exchange reactions. Thus, products resulting from halogen exchange became dominant during the attempted preparation of 1,3-dibromobenzene under the conditions shown in eqn. (6).



5 Base catalysed exchange processes

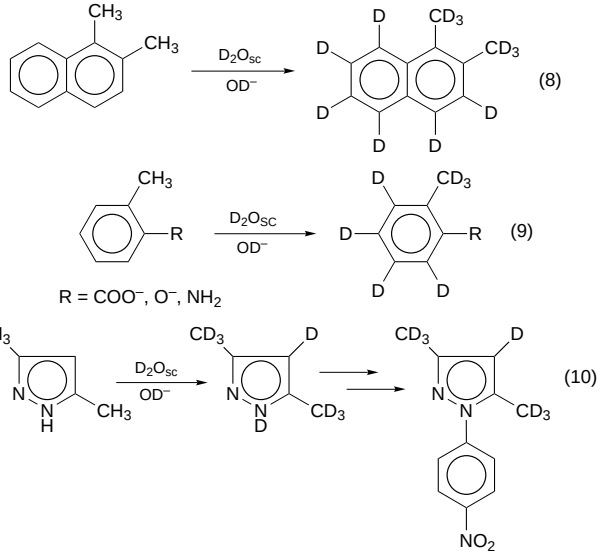
Not surprisingly, acidic protons are readily displaced by base catalysed H → D exchange procedures, even in cases where equilibria strongly favour the protonated species. The specific α labelling of carboxylic acids is representative of this strategy [eqn. (7)].

$$R\text{–}CH_2\text{–}COO^- + D_2O \rightarrow R\text{–}CHD\text{–}COO^- + DHO \quad (7)$$

This method recently was applied to prepare deuterated analogues of various antiinflammatory 2-arylpropionic acids[8] and requires relatively mild conditions (5% NaOD–D_2O, ≈ 100 °C).

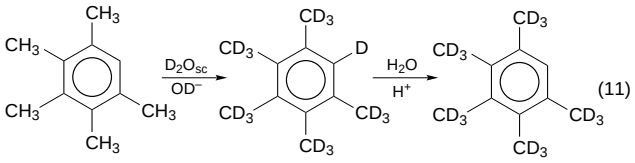
A recent, striking development is the deuteration of organic substrates in near-critical and supercritical aqueous media. Supercritical fluids have properties which differ distinctly from those under subcritical conditions. Thus, pure water at its

critical point (374 °C, 221 bar) is characterized by a low relative permittivity ($\varepsilon \approx 6$), complete miscibility with organic substrates, and a reduced self-ionization constant ($pK \approx 16$) when compared to room temperature values.[9] Its properties are highly dependent on pressure and density changes of the reaction medium. Thus, a density change from 0.16 to 0.65 g ml^{-1} results in a change of the self-ionization constant by nine orders of magnitude. Supercritical deuterium oxide, D_2O_{sc}, has analogous characteristics. Hydrocarbon acid dissociation constants increase in supercritical water with increasing temperature from approximately 10^{-43} under ambient conditions to 10^{-19} at 400 °C.[10] Thus, even extremely weak acids can be deprotonated by the deuteroxide anion under supercritical conditions. This results in the rapid deuterium incorporation into aromatic, heteroaromatic, and selected aliphatic positions. Eqn. (8)–(10) show representative examples for the OD^-

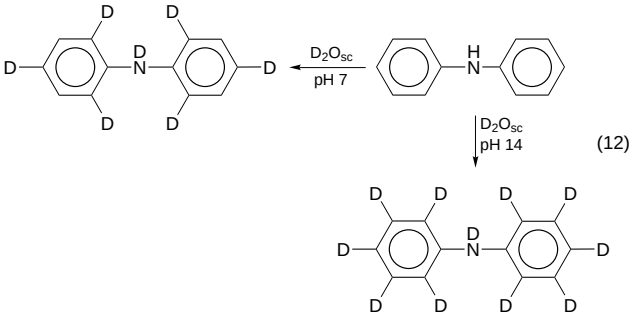


catalysed deuteration of homo- and hetero-cyclic substrates in D_2O_{sc}.[11,12] The practical utility of this approach extends to a variety of functionalized aromatic and heteroaromatic compounds with sufficient thermal stability. Thus, we recently demonstrated rapid access to deuterated pyrazoles of practical interest as non-linear optical materials, as shown below in eqn. (10).[1,14]

It is remarkable that indications for deuterium incorporation into aromatic hydrocarbons under aqueous basic conditions had been observed decades ago, but found limited interest.[15] Base catalysed methods are characterized by an absence of isomerization reactions typically observed in the presence of Lewis acids, and the introduction of labels into α positions of alkyl side chains in aromatic substrates. In conjunction with other exchange methods, labels can be introduced regiospecifically [eqn. (11)]. Mechanistically, this reaction is not fully under-



stood. In most cases, exchange rates can be expressed in terms of proton acidities. Deuteration is suppressed, greatly reduced, or observed with altered regioselectivity in the absence of a base. Thus, diphenylamine was perdeuterated at pH 12, while *meta* positions remained unexchanged under neutral conditions [eqn. (12)].[16] However, an unusual exchange pattern inconsistent with expected proton acidities was reported for di-*n*-butylamine, which exchanged preferentially at carbons 1 and 3 when reacted with 0.06 M NaOD for 20 min at 400 °C. No



satisfactory explanation was presented for this result.[10] Furthermore, evidence was found that phenols and amines underwent deuteration by a mechanism better described as electrophilic substitution. Several byproducts observed during base catalysed supercritical exchange (*e.g.* formation of bibenzyl from sodium phenylacetate) also suggest the formation of radical species under these conditions. It is likely that several, competing mechanisms occur depending on the choice of substrates and reaction conditions, including protonation–deprotonation, radical, and electrophilic substitution reactions.

6 Heterogeneous metal catalysis

Noble metal catalysed isotope exchange has been known for decades but traditional noble metal catalysts (Pt, Pd) give rise to numerous byproducts resulting from hydrogenation, dehalogenation, and other catalytic processes. The heterogeneous noble metal catalysed exchange of alkanes is commonly considered to involve three fundamental steps, the dissociative adsorption of hydrogen or its isotopes, the dissociative monoadsorption of the alkane, and the formation of an α,β-diadsorbed species [eqn. (13)–(15)].

$$D_2 + M \rightleftharpoons 2\ D^* \quad (13)$$

$$-CH_2-CH_2- + M \rightleftharpoons -CH_2-CH^*- + H^* \quad (14)$$

$$-CH^*-CH_2- + M \rightleftharpoons -CH^*-CH^*- + H^* \quad (15)$$

In practice, the processes resulting in isotope exchange were shown to be quite complex. Takehara *et al.*[17] employed 2,2-dimethylbutane as a mechanistic tool for the characterization of isotopic exchange catalysed by rhodium/silica gel. They experienced extreme variations by a factor of 330 of the observed turnover frequencies, and of exchange regioselectivities as a function of catalyst pretreatment conditions. The presence of at least eight different types of catalytic sites was postulated, some of which likely involved more than one rhodium atom.

For preparative purposes, many heterogeneously catalysed exchange reactions are carried out in solution. The resultant three-phase systems (catalyst, organic reactant dissolved in solvent, and gaseous deuterium–tritium) further add to the mechanistic complexity of heterogeneous exchange procedures. Not surprisingly, experiments of this type usually embrace the 'cook-and-look' approach, in which catalyst–substrate ratios, solvents, deuterium (tritium) partial pressures *etc.* are optimized empirically. Azran *et al.*[18] undertook a systematic investigation of the factors influencing $H \rightarrow D(T)$ exchange in benzylic substrates in organic solvents. Their results indicate that exchange under these conditions occurs along two simultaneous pathways, a rapid, associative π-complex mechanism and a slow, dissociative mechanism which involves transformation from an initial, aromatic π-complex to π-allyl complex which extends over the benzylic moiety and facilitates isotopic exchange. Kinetic measurements confirmed that C–D bond fission was the rate-determining step in all cases. Remarkably, exchange rates for bibenzyl were found to be nearly independent of the catalyst–substrate ratio above a specific threshold value.

Mechanistic questions not withstanding, heterogeneous metal catalysis has retained its important role as a preparative

tool. The high temperature solid state catalytic isotopic exchange (HSCIE) method represents an interesting example in this respect. The substrates, admixed with suitable platinum metal catalysts, are exposed to gaseous deuterium or tritium at temperatures ranging from 100 °C–150 °C. High levels of isotopic substitution were achieved by HSCIE for various organic substrates including amino acids and peptides. While labelling is uniform in most instances, some regiocontrol can be exerted by careful temperature control during the exchange.[19]

7 Homogeneous metal catalysis

In light of the difficulties encountered during attempts to gain a clear mechanistic understanding of heterogeneously catalysed H → D exchange processes, it is not surprising that increased attention is being given to homogeneous noble metal catalysis. First developed by Garnett and Hodges in 1976,[33] recent research efforts have focused on catalysts containing Pt, Ir, Rh and Re.

Chloro complexes of iridium in aqueous acetic acid were found to be active catalysts for hydrogen isotopic exchange in aromatic compounds carrying electron-withdrawing substituents, for which few alternative exchange methods exist. A series of experiments conducted by Lukey *et al.*[20] suggest the *in situ* formation of a solvated monomeric iridium(III) species as the active catalyst, which reacts with aromatic substrates to produce π-aryl complexes, as shown below for benzene as representative substrate [eqn. (16)–(18)].

$$2\ IrCl_6^{3-} + 6\ CH_3COOH \rightarrow [Ir_2Cl_4(OAc)_4(HOAc)_2]^{2-} + 4\ H^+ + 8\ Cl^- \quad (16)$$

$$[Ir_2Cl_4(OAc)_4(HOAc)_2]^{2-} \rightarrow 2\ [IrCl_2(OAc)_2(HOAc)]^- \quad (17)$$

$$[IrCl_2(OAc)_2(HOAc)]^- + C_6H_6 \rightarrow [(\pi\text{-}C_6H_6)IrCl_2(OAc)_2]^{2-} + H^+ \quad (18)$$

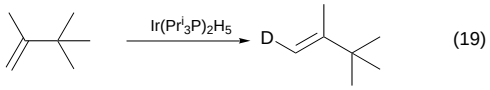
These π-complexes subsequently rearrange to σ-bonded species, in analogy to exchange reactions catalysed by platinum(II) species. It appears likely that this mechanism extends to catalysis involving other homogeneous platinum, iridium and ruthenium species. Experimental results include isotopic exchange reactions for a series of aromatic substrates which are known to undergo little or no exchange over heterogeneous transition metal catalysts, thereby eliminating the possibility that the formation of small quantities of Ir metal can account for the observed results (Table 1). Deactivation in *ortho* positions was noted for most substrates, consistent with a dissociative π-complex exchange mechanism.

Previously, it had been shown that homogeneous iridium catalysts are also effective catalysts for the stereoselective vinylic C–H activation of sterically hindered olefins.[21] Thus, 2,3,3-trimethylbut-1-ene and other alkenes carrying bulky substituents were exchanged stereoselectively in the *trans* positions [eqn. (19)]. Mechanistically, this process involves reversible insertion of the catalyst into an olefinic C–H bond, and constitutes one of three observed reaction pathways resulting in olefinic C–H exchange. Other known mechanisms include metal deuteride addition, followed by β-hydride elimination, and reversible allylic proton abstraction to form an η^3-allyl complex of a metal deuteride. Iridium catalysts have demonstrated excellent regioselectivity in isotopic exchange

Table 1 Deuteration of selected substituted benzenes in the presence of Na_2IrCl_6

Substrate	% D after 24 hours at 160 °C
Fluorobenzene	12.5
Chlorobenzene	12.1
Bromobenzene	13.0
Nitrobenzene[a]	1.7
α,α,α-Trifluorotoluene	4.7

[a] At 130 °C.



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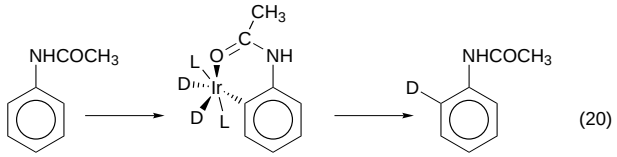
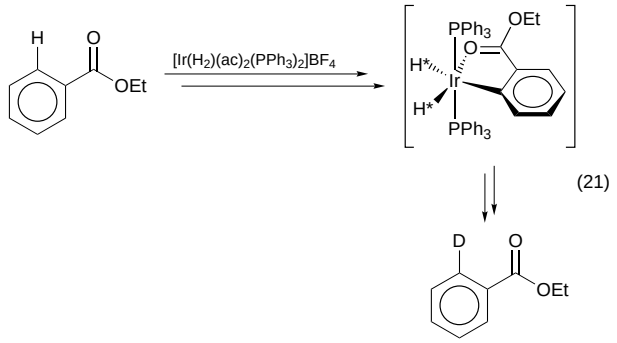
reactions of acetanilides and other substituted aromatic substrates.[22] Thus, catalysis with the commercially available complex [Ir(COD)(Cy_3P)(Py)]PF_6 (Crabtree's catalyst,[23] COD = 1,5-cyclooctadiene, Py = pyridine) offers convenient access to specifically *ortho*-labelled products, as shown in eqn. (20). The six-membered metallocycle shown here was not



(20)

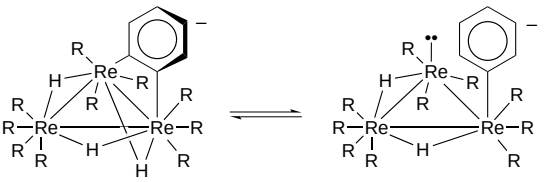
isolated, but its transient existence is implied by the observed exchange products. Selective *ortho* exchange involving homogeneous iridium catalysts is not limited to six-membered intermediate metallocycles. Thus, the efficient regioselective deuteration of aromatic substrates upon exposure to deuterium gas in the presence of [IrH_2(acetone)$_2$CO)$_2$(PPh_3)$_2$]BF_4 and structurally related catalysts was reported to proceed *via* the transient formation of five-membered metallocycles.[24,25] In this case, exchange occurred preferentially *ortho* to oxygen- and nitrogen-containing substituents including –CO_2H, –CO_2Et, –C(O)Et, and –NO_2, as shown by the example in eqn. (21).



(21)

Interestingly, 2-pyridylbenzene underwent rapid deuteration, while 2-pyridylphenylmethane, which requires the formation of a six-membered intermediate, was inert towards exchange. The body of data collected from these experiments was insufficient for a complete mechanistic interpretation; nevertheless, it is noteworthy that neither steric nor electronic impediments appeared to play a significant role in the outcome of these labelling experiments. Earlier, the homogeneous catalyst $RhCl_3$ was shown to achieve similar *ortho* selectivity in the tritiation of substituted carboxylic acids and benzylamines; however, it is noteworthy that this catalyst failed to tritiate acetanilide.[26] Again, experimental results indicated the transient formation of metallocycles.

Isotopic exchange *via* the reversible formation of metallocycles under mild conditions is not restricted to organic iridium species. Thus, the triangular cluster anion [Re_3(μ-H)$_3$(μ-Py)(CO)$_{10}$]$^-$ **7**, which contains an *ortho*-metallated pyridine molecule bridging a cluster edge, undergoes selective H–D exchange between the basal hydridic site and the α positions of the *ortho* metallated pyridine, with $k = 1.9(1) \times 10^{-6}\ s^{-1}$ at room temperature.[27] This result is easily accounted for by the reversible interconversion of structures **7** and **8**. Metal catalysed hydrogen isotope exchange reactions involving thiazoles, imidazoles, histidines, purines, and other heterocyclic structures



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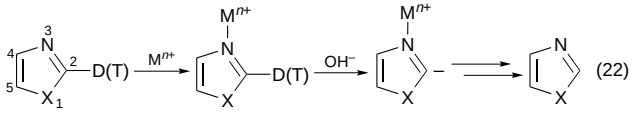
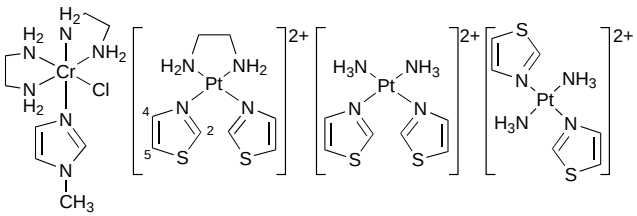
known to exist within biomolecules are of mechanistic interest in evaluating the physiological interactions of metal ions with biological substrates. For 1,3-thiazoles and imidazoles, the rates of acid catalysed C–H exchange serve as a benchmark for the determination of the degree of C(2,4,5)–H bond activation associated with metal complexation. A generalized C(2)–H exchange mechanism of this type, showing deprotonation as the rate-determining step, is depicted in eqn. (22). It should be noted



(22)

that C(4,5)–H exchange can be realized for imidazoles under acidic conditions in the absence of metal catalysts, but requires fairly drastic conditions not encountered in biological systems. Mechanistic studies of such complexes are often complicated by the involvement of multiple, stoichiometric equilibria. Thus, the determination of isotopic exchange rates constitutes one of the best approaches for their characterization. Recently, Buncel *et al.*[28,29] have accomplished the isolation and characterization of the substitution-inert chromium–imidazolyl and platinum–thiazolyl complexes *cis*-$[Cr(en)_2(MeIm)Cl]Cl_2$ **9**, $[Pt(en)(Th)_2]Cl_2$ **10**, *cis*-$[Pt(NH_3)_2(Th)_2](NO_3)_2$ **11** and *trans*-



9 10 11 12

$[Pt(NH_3)_2(Th)_2]Cl_2$ **12**, thereby greatly simplifying the fully characterization of such species. Metal ions typically increase the isotopic exchange rates of azoles by a factor of 10^3–10^4 when compared to the neutral uncomplexed substrates, but are less effective in this respect than protons (which increase exchange rates by a factor of 10^4–10^6). Complex **9** represents the first example of metal catalysis which is more active by a factor of *ca*. 20 in catalysing C(2)–H exchange than H^+, with an observed rate constant $k = 6.0 \times 10^3$ dm^3 mol^{-1} s^{-1} at 35 °C. It should be noted that the relatively inert C(4,5) positions were also significantly activated and exchange under the mild conditions of these experiments. As for the complexes **10**–**12**, Pt^{II} enhanced C(2)–H exchange by a factor of *ca*. 10^6, and C(5)–H exchange by 6×10^3, compared to the neutral heterocycles. There can be little doubt that the isotopic exchange reactions of the transition metal heterocyclic complexes will be the focus of extensive future work, both as mechanistic probes and for preparative applications.

Table 2 Labelling results with 'deuterated' montmorillonite clay

Substrate	Exchange position(s)	Exchange (%)
Indole	C–3; N–H	88
2-Methylindole	C–3; N–H	95
Pyrrole	C–2,3,4,5; N–H	88
Indene	$-CH_2-$	15
Fluorene	$-CH_2-$	35
Phenylacetylene	≡C–H	90
Ethyl 3,5-dimethylpyrrole-2-carboxylate	$C_{Pyrrole}$–4; N–H	95

8 Other approaches

While several examples have been reported for the enzymatic syntheses of isotopically labelled compounds, the application of enzymatic H → D exchange catalysts is still in its infancy. Faleev *et al.*[30] reported the convenient preparation of α-deuterated L amino acids by tryptophanase-catalysed H → D exchange. It is not necessary to isolate the enzyme before its use. Thus, lyophilized *Escherichia coli B*/It7-A cells produced labelled valine, leucine, norvaline, methionine, phenylalanine, histidine, arginine and various non-natural amino acids in good to excellent yields, without losses in chiral purity.

In an extension to zeolite catalysed exchange procedures,[4] exceptionally mild conditions were realized in the deuteration of various organic substrates with 'deuterated' montmorillonite clay, prepared by saturating the acid-washed clay with deuterium oxide.[31] Surface-adsorbed and interlamellar water contained in the layered aluminosilicate structure of this material can be driven off at high temperature, and subsequently be replaced by deuterium oxide. The product constitutes an active deuteration catalyst. In addition to carbonyl compounds containing acidic protons, a series of aromatic and unsaturated substrates was successfully deuterated at ambient temperature (Table 2). This approach offers the advantages of convenience and excellent regioselectivity, but its scope remains largely unknown.

Isotope exchange reactions in alkenes are frequently accompanied by undesired side reactions which result in addition reactions. Recently, it was found that the alkali metal fullerides $C_{60}M_6$ and $C_{70}M_6$ (M = Cs, K, Na) exhibit remarkable properties as H_2–D_2 exchange catalysts under mild conditions, with specific activities reported to be similar to those of the noble metals Pt and Rh.[32] Some fullerides, notably $C_{70}Cs_6$, were also found to catalyse the hydrogenation (deuteration) of ethylene to ethane. It remains to be determined whether alkali metal fullerides can serve as noble metal analogues for H → D exchange reactions in organic substrates.

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Received, 18th April 1997
Accepted, 17th June 1997