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Nickel-catalyzed hydrogen isotope exchange

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Nickel metal in various forms is useful for the catalytic exchange labeling of a wide range of compounds from isotopic water or isotopic hydrogen gas sources. Substantial investigative work has been done on the metal's activities in simple test compounds, providing information useful for selecting or developing conditions for labeling of more complex substances. In addition, Raney nickel has been shown to be particularly useful for labeling of carbohydrates, for which the assembled empirical data are sufficient for limited predictive purposes in new glycosides.

Keywords: nickel; Raney nickel; heterogeneous; catalytic exchange; deuterium labeling; tritium labeling

Introduction

Nickel-catalyzed hydrogen isotope exchange labeling has been used far less often than that with platinum or palladium, but like rhodium and ruthenium, nickel has characteristic properties that make it useful, and in some cases uniquely so. Most practical exchange labeling with nickel has utilized Raney-type nickel preparations, and most labeling has been done using deuterium sources rather than tritium. Thus, there is a relatively large body of data about the characteristics and capabilities of nickel for catalysis of hydrogen isotope exchange that has yet to be exploited for tritium. The report in this issue, *Tritium labeling of pharmaceuticals by metal catalysed exchange methods* by Hesk, Lavey and McNamara is recommended for readers interested in nickel's recent use in the tritium labeling of complex compounds. The present review covers all other aspects of the subject.

One reason perhaps for the more limited use of nickel, compared with palladium and platinum, for exchange labeling is its ability to modify a range of functional groups, even in the absence of (isotopic) hydrogen gas, depending on the form and method of preparation of the metal. This includes the reductive dehalogenation of halobenzenes, deoxygenation of aldehydes and ketones, and reduction of double bonds, nitro and nitrile groups.[1] The last has been exploited to prepare phen[1,1,2,2-D_4] ethylamines from phenylacetonitriles.[2]

Much of the literature of nickel-catalyzed hydrogen isotope exchange is concerned with the use of simple model compounds to explore various conditions for exchange and the patterns of substitution associated with them, often in comparison with other metal catalysts. As such, the information can be useful in the design and application to more complex substrates of practical value.

Labeling of hydrocarbons and silanes

A comparison was made[3] of the activity of various nickel catalysts with Pt black and Pd black for the deuterium exchange labeling of *p*-xylene from D_2O (Pt black: 80°C, 300 h; all others: 100°C, 150 h). All resulted in the incorporation of 3–4 mol D per mol substrate; however, the intramolecular distribution of isotope differed. Whereas, on a per-atom basis, ring hydrogens were replaced with deuterium 65% as efficiently as methyl hydrogens by Pt black and 30% as well by Pd black, practically all deuterium exchange catalyzed by Ni powder, Ni-kieselguhr and Raney Nickel (W2) occurred in the methyl groups. In contrast, various preparations of Ni/Al_2O_3 resulted in aryl labeling to some degree along with methyl labeling.

Studies using nickel–kieselguhr under similar reaction conditions[4,5] of the labeling of toluene, each isomeric xylene and two isomeric dimethylnaphthalenes also resulted in near exclusive labeling in the methyl groups. Exclusive alkyl labeling also was found for most other phenylalkanes tested, and the label distribution shown in Figure 1 is indicative of the general patterns. These are (a) barring steric encumbrance, the benzylic methylene (or methine) is labeled preferentially and (b) terminal methyl groups are favored over individual intervening methylene groups until they become structurally remote from the ring. Only in 4-*tert*-butylbenzene and in 2-methylphenanthrene was significant ring labeling observed.

At lower reaction temperature the selectivity is more distinct, as observed in the tritium labeling[4,6] of substrates by Raney nickel in THO at room temperature (Figure 2).

In separate investigations, when isotopic hydrogen gas was used as the source instead of water, qualitatively similar results were obtained. For example,[7] in the room temperature labeling of toluene, *m*-xylene, *n*-pentylbenzene and *s*-butylbenzene with vacuum-degassed Raney nickel and hydrogen–tritium gas mixtures, the label in each substrate resided on the benzylic carbon atom. With deuterium gas and nickel catalyst in the form of metal films and at temperatures of −10 to 0°C, the distribution of isotope in toluene, ethylbenzene, *n*-propylbenzene and the isomeric xylenes was similar to those in Figures 1 and 2, except that minor but significant amounts of labeling occurred in the aromatic rings.[4,8] Although optimization of tritium incorporation was not the objective of these experiments,

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Substrate	% D in α-CH_2/-CH	% D in other -CH_2	% D in –CH_3
Ethylbenzene	42	--	56
n-Propylbenzene	69	10	17
n-Butylbenzene	81	11	8
n-Hexylbenzene	44	49	7
i-Propylbenzene	14	--	83
Cyclohexylbenzene	57	41	--

Figure 1. Distribution of label incorporated by nickel–kieselguhr and D_2O.

Substrate	% T in α-CH_2	% T in other -CH_2	% T in –CH_3
Ethylbenzene	75	--	25
n-Propylbenzene	>99	<1	<1
n-Butylbenzene	>99	<1	<1

Figure 2. Distribution of label incorporated by Raney nickel and THO.

the procedure used to conduct them illustrates a practical way to remove water and imbedded hydrogen from Raney nickel in order to minimize isotopic dilution of tritium.

Procedure for Raney nickel-catalyzed exchange of substrates from a tritium gas source (adapted from reference)[7]

To a flask with a septum sidearm, suitable for attachment to a tritium manifold, is added a suspension of Raney nickel. The flask is attached to the manifold, and with care the flask is opened to the vacuum. All water is removed at low pressure, with mild warming as necessary, until all visible water is removed. Thereafter, under full vacuum, the catalyst is heated gently (heat gun) until off-gassing is complete. The vacuum is replaced by one atmosphere of helium, then a solution of the substrate in the desired solvent is injected through the septum. The resulting suspension is subjected to freeze–pump–thaw cycles, tritium gas is introduced and the reaction run for the desired time. A suitable workup procedure for tritium manifold work is then conducted, and the product isolated and purified as appropriate.

Refluxing of a THF solution of diphenylmethane with 'deuterated' Raney nickel gave diphenyl[D_2]methane.[9] 'Deuterated' Raney nickel is prepared[10] by extensive washing of standard Raney nickel (prepared with non-isotopic water and base) with deuterium oxide. It is distinguished from 'deuterated Raney nickel' whose preparation, detailed below, involves isotopic reagents for its preparation. Although most studies use one of these two preparations, no study has been published exploring whether and to what degree they give different results.

The consistently observed preference for exchange at the benzylic positions of alkylaromatics supports the hypothesis that preferential labeling occurs via a π-allyl mechanism.[11]

Alkylsilanes have been tritiated by Raney nickel-catalyzed exchange with tritium gas.[12] At a reaction temperature of 100°C and reaction times of 64–160 h, triethylsilane, tetramethylsilane, hexamethyldisiloxane and chlorodimethylsilane were labeled to specific activities of 200–1700 mCi/mL. Significant exchange of all hydrogens – Si-H, methyl and methylene – was observed.

Labeling of heterocycles

A general trend, for both aromatic and aliphatic *N*-heterocycles, is isotopic exchange adjacent to nitrogen. In the case of pyridine as substrate, this holds for nickel–kieselguhr and D_2O[4,13] at 99°C, nickel metal film and D_2 gas at 42°C[4,14] and vacuum-treated Raney nickel and a tritium–hydrogen mixture at room temperature,[7] where at least 96% of label was incorporated into C2 and C6; and borohydride-reduced $NiCl_2$ and D_2O at 130°C, where 74% of label was found to be in C2/C6, 24% in C3/5 and 4% in C4.[4,15] Curiously, pyridine was not labeled by microwave treatment in D_2O in the presence of Raney nickel.[16]

Similarly to pyridine, in quinoline 70% of deuterium incorporated under the influence of nickel–keiselguhr/D_2O at 99°C was divided equally between C2 and C8, with little incorporation at other sites, and with isoquinoline, nearly all incorporated at C1 and C3.[13] Analogously, quinuclidine was converted to [2,2,6,6,7,7-D_6]quinuclidine of high isotopic purity by treatment with Raney nickel/D_2O at 100°C for 40 h.[17]

These high regioselectivities have been interpreted as indicative of the strong adsorption of the heteroatom to the catalyst metal surface during the exchange process;[11] the selectivity of palladium and platinum catalysts under similar conditions is less strongly expressed.[2]

Nickel's strong propensity for labeling alkyl groups attached to aromatic rings, as described in the previous section, therefore anticipates the competitive regioselectivity of labeling in alkyl-substituted aromatic *N*-heterocycles.

Thus, the labeling of 2-methylpyridine resulted in the highest incorporation at C6 followed closely by the methyl group, with low levels at the other positions, in independent studies utilizing D_2 and nickel film at 42°C[4,14] and utilizing borohydride-reduced $NiCl_2$ in D_2O at 130°C.[4,15] The corresponding results with 3-methylpyridine differed slightly, with the high-temperature exchange reaction giving incorporation levels (C2+C6) ≈ Me > C5 > C4, while the relative labeling efficiency under the lower-temperature process was in the order C6 > C2 > Me ≈ C4 ≈ C5. In the case of 4-methylpyridine, the label incorporation was Me > (C2+C6) > (C3+C5) (reduced $NiCl_2$, D_2O, 130°C) or essentially all label in Me (deuterated Raney nickel, D_2O, microwaves.[16] The labeling patterns in 2,4- and 2,5-dimethylpyridine (reduced $NiCl_2$, D_2O, 130°C) were unsurprising given the above, with the order of incorporation being C2-methyl > C6 > C4/5-methyl > other positions.[4,17]

Preparation of deuterated Raney nickel[18]

The catalyst is prepared by slowly adding Raney nickel alloy (2 g) in D_2O (4 mL) to ice-cold NaOD (40% w/v in D_2O, 4 mL), then heating the mixture at 100°C until the evolution of gas has ceased. The resulting solid is washed with portions of D_2O to pH 7.5 and stored until use in D_2O.

In aminopyridines, the amino group, even if alkylated, appears to be much more influential than the ring nitrogen in guiding the regioselectivity of deuterium exchange, delivering deuterium into positions *ortho* and *para* to itself, thereby suggesting an electrophilic influence on the mechanism of exchange.[16]

The deuterated Raney nickel-catalyzed exchange labeling of indole and *N*-methylindole from various deuterium sources has been explored.[16,19] Under 'thermal' conditions (deuterated Raney nickel, deuterated solvent, r.t. or 40°C, 1 week),[19] the rank order

of the effectiveness of the perdeuterated solvents was water ~ methanol > ethanol ~ propanol > acetone ~ acetonitrile > chloroform. The extent of deuterium labeling of indole ranged from a few percent ($CDCl_3$) to around 80% of theoretical (D_2O and CD_3OD), and the facility with which individual sites were labeled were greatest at C2 and C7 (adjacent to NH), followed by C3 and then the remaining sites (C4–C6) in the benzo ring. This pattern is consistent with the model that envisions heteroatom binding to the catalyst surface as the key facilitator of exchange. In contrast, the labeling of *N*-methylindole, which ranged from a few percent in $CDCl_3$ to 58% of theoretical in D_2O and CD_3OD, occurred in the order: C3 > C2 > Me, C4, C5, C6 > C7. Here, with heteroatom binding to the catalyst retarded by the methyl group, the labeling is slowest in the most hindered site, C7, and most rapid in the pyrrolo moiety.

More recently, a similar study[16] was conducted in some of the same solvents, but using the hydrochloride salts of the test compounds and employing microwave irradiation with reaction times of just a few minutes. Under these conditions, the overall labeling of both test compounds in D_2O, CD_3OD and [D_6]acetone was nearly as great as in the earlier study. Some differences were apparent between the two studies in the labeling of certain sites in one or another of the solvents, but the data are too preliminary to support any conclusions regarding any changes in exchange regioselectivity.

The ionic liquids *N*-butyl-*N*′-methyl[D_3]imidazolium chloride and tetrafluoroborate have been prepared by microwave irradiation of solutions of the unlabeled compounds in D_2O in the presence of 'deuterated' Raney nickel.[20]

Furan and thiophene have been subjected[21] to exchange conditions (reduced $NiCl_2$, D_2O, 130°C) which resulted in moderate deuterium incorporation into the former and low incorporation into the latter, in both cases nearly exclusively at C2 and C5, adjacent to the heteroatom.

Labeling of anilines

As the amino function is a strong director of heterogeneous nickel-catalyzed exchange, it is not surprising that in aniline itself, most of the label incorporated under any conditions is at C2 and C6. Where lower temperatures are used (nickel–kieselguhr, D_2O, 99°C[13] and deuterated Raney nickel D_2O, microwaves[16]) essentially all the label was found in those positions. At higher temperatures (either Raney nickel or reduced $NiCl_2$, 130°[15]), 65–75% of the label resided at C2 and C6, and the rest was distributed in the *meta*- and *para*-positions. Although the hydrochloride salts of anilines were used in reference 16 rather than the free bases, the labeling outcomes do not appear to have been altered thereby.

Again, alkyl substituents are subject to labeling in competition with ring *ortho*-positions, as summarized in Figure 3.[13]

Labeling of benzoic acids and related compounds

Although ethyl 4-methylbenzoate underwent exchange nearly exclusively in the methyl group (nickel–kieselguhr, D_2O, 99°C),[4,5] the free acid underwent much more extensive labeling under milder conditions (deuterated Raney nickel, D_2O, 17–20°, 2 weeks),[18] giving a net incorporation of 6.2 mol D/mol substrate. Other alkyl-substituted benzoic acids behaved similarly.

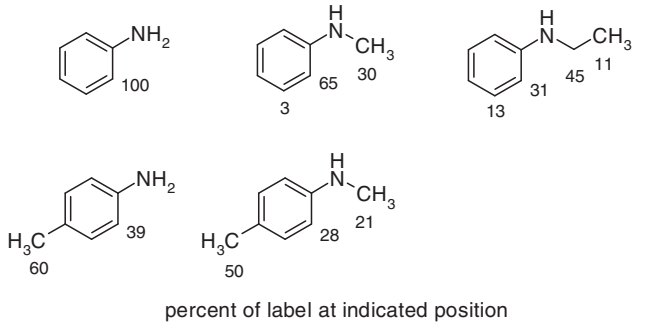

Figure 3. Regioselectivity of deuteration of anilines (nickel–kieselguhr, D_2O).

Benzoic acid itself, treated with 'deuterated' Raney nickel in D_2O at 70–80°C for 18 h, is perdeuterated, while under refluxing conditions it is reduced to [D_{11}]cyclohexanecarboxylic acid.[9] When benzoic acid is partially deuterated under milder conditions (Raney nickel alloy, NaOD/D_2O, 40°C, 30 min),[22] the resulting product, a mixture of [D_1]- to [D_5]-isotopologs, was deuterated most heavily in the *meta* and *para* positions; conversely when perdeuterobenzoic acid was treated in the same way with non-isotopic reagents, the unexchanged deuterium remaining in the product resided predominantly in the *ortho* positions. Thus, the heterogeneous catalytic exchange of benzoic acid is subject to steric hindrance by the carboxyl/carboxylate group, *despite* the strong likelihood that this polar function facilitates exchange in the ring by binding to the surface of the metal catalyst. A substrate–metal interaction model has been proposed to rationalize these findings.[22] Direct connection between the carboxyl group and the ring is evidently necessary for the facilitation of aromatic hydrogen exchange, as phenylacetic acid and 3-phenylpropanoic acid undergo little or no ring labeling under the low temperature-long duration conditions.[18] In curious contrast, cinnamic acid undergoes concomitant reduction and perdeuteration under both the conditions of References 9 and 19.

In the deuterium exchange of substituted benzoates,[18] steric inhibition of labeling is evident in positions *ortho* to the substituent (OMe > Me) as well as the carboxyl group, leading to little or no exchange at C2 of 3-functionalized benzoates.

Labeling of phenols and anisoles

The isomers 2-, 3- and 4-methylanisole were exposed to deuterium exchange conditions (nickel–kieselguhr, D_2O, 99°C),[23] and in each case at least 98% of the incorporated isotope resided in the *C*-methyl group and little or none in the *O*-methyl. This behavior is analogous to the labeling of hydrocarbons such as methyl-substituted benzenes, as described above.

In contrast, alkyl-substituted phenols exposed to the same conditions[13,23] behaved more like anilines, in that labeling was directed to the positions *ortho* to the hydroxyl group as well as into the alkyl substituents. The results are depicted in Figure 4. One notable difference between *N*-methylanilines and anisoles is that *O*-methylation abolishes the directing ability of the phenol hydroxyl group and the labeling of the methyl attached to oxygen, the same modification of anilines does neither. However, it would be anticipated that *N*,*N*-dialkylation of an aniline would abrogate the ability of its amino group to direct labeling, analogous to the case of *N*-methylindole discussed above. The lack of labeling in the methyl groups of

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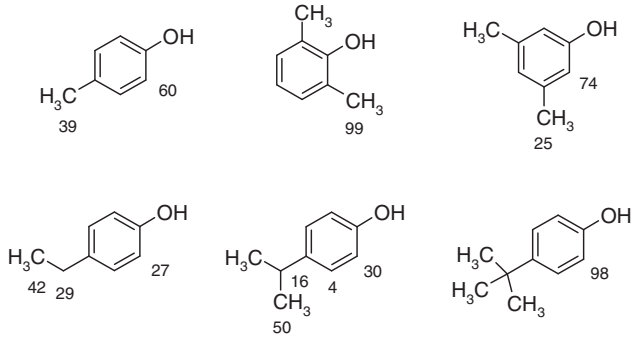

Figure 4. Labeling of alkyl-substituted phenols (nickel–kieselguhr, D_2O).

tert-butylphenol suggests the intermediacy of metal π-allyl intermediates in the labeling of homobenzylic C–H bonds.

Labeling of carbohydrates

Apparently no instance of nickel-catalyzed exchange labeling of carbohydrates with tritium has been published. However, extensive work with deuterium has been reported.

In their synthesis of perdeutero D-glucose, Koch and Stuart[10] used Raney nickel-catalyzed deuteration ('deuterated' Raney nickel, D_2O, reflux, 15 h) at two stages to install most of the labels. As illustrated in Figure 5, 1,2-*O*-isopropylidene-α-D-[1-D]glucofuranose (**I**) so treated gave the corresponding [1,5,6,6-D_4]-isotopolog (along with its C5-epimer), and methyl α-D-[1,5,6,6-D_4]glucopyranoside (**II**) its perdeuterated isotopolog. In both exchange labeling procedures, it was the vicinal dihydroxy moieties in the structures that underwent exchange.

Raney nickel has long been known to catalyze hydrogen transfer between alcohols and carbonyl compounds,[24] and to isomerize cyclohexanols[25] and 1-deoxyalditols (acyclic polyols).[26] Such activity is explained by dehydrogenation–hydrogenation mechanisms. Thus, the use of a large pool of isotopic hydrogen in the form of water, which readily exchanges with the hydrogen on the metal, provides the opportunity for catalytic replacement of geminal hydrogens in alcohols with deuterium or tritium.

The key finding in the Koch and Stuart study, however, was that the configuration of the C2, C3 and C4 hydroxy groups of **II** was retained through the labeling, indicating that exchange is faster than isomerization. This phenomenon may be the result of the reduced conformational degrees of freedom imposed by the cyclic structure, and/or the strong adsorption of the molecule to the metal surface, compared with similar acyclic structures.

Upon further investigation[27] it was found that other methyl glycosides – methyl α-D- and β-D-galactopyranoside, methyl α-D-mannopyranoside and methyl α-D- and β-D-glucopyranoside – could similarly be labeled at their hydroxylated ring carbons, without significant isomerization over a 10-hour period of reflux. However, longer periods of reflux (2.5 d) resulted in mixtures of carbohydrates resulting from isomerization at one or more of the labeled carbons. The carbocycle *myo*-inositol was perdeuterated using the 10-hour reflux procedure. Clearly, carbohydrates not derivatized at their C1 hydroxy groups (aldoses) would not be suitable substrates for Raney nickel-catalyzed deuterium exchange labeling, because they would be rapidly reduced, forming acyclic alditols which then would undergo multiple isomerizations.

Studies[28] of the time course of exchange of different hydrogens in 11 methylglycosides ('deuterated' Raney nickel, D_2O, reflux) established the rank order of exchange rates at various sites of different sugars; for instance, in methyl α-D-glucopyranoside the relative rates were C2 ≈ C4 > C6$_S$ > C3 > 6$_R$. The data revealed that in general axial H are exchanged faster than equatorial H, and permitted the authors to propose substrate–metal binding modes (Figure 6) to rationalize their findings and provide a predictive model for new glycosides. Included in these studies were measures of glycoside isomerization rates, which were invariably found to be slower than deuterium exchange.

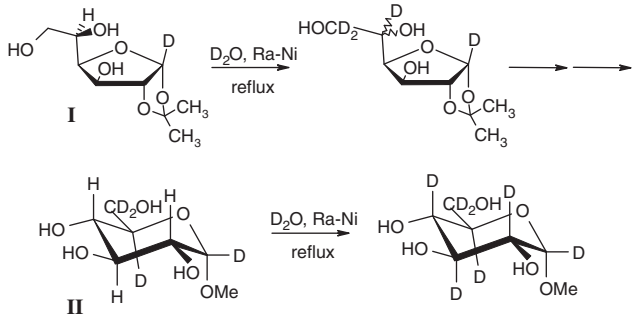

Figure 5. Catalytic exchange labeling steps in the synthesis of a perdeuteroglycoside.

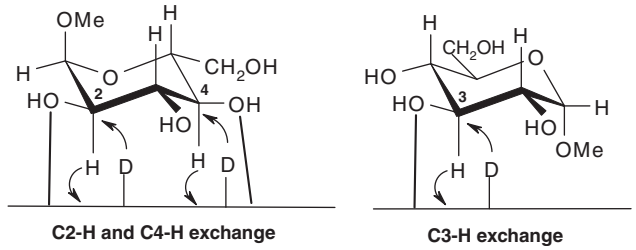

Figure 6. Proposed glycoside–nickel binding modes.

Further studies[29] of the exchange of 13 methyl glycopyranosides and 12 methyl glycofuranosides, utilizing the same catalyst type and D_2O at temperatures of 60–100°C and reaction times of 8–95 min, extended the data set on the relation between exchange rate and conformation to axial H > equatorial H > *syn*-axial H. They also identified conditions for highly selective exchange (> 10:1) in several sugars, such as C5 of methyl β-D-fructopyranoside, C3 of methyl β-D-fructofuranoside and C3 and C4 of methyl β-D-galactopyranoside.

Subsequently 'deuterated' Raney nickel was used with ultrasound stimulation in lieu of temperature/time control to prepare deuterated versions of 1-*O*-methyl-β-D-galactosyl ceramide (**III**)[30] and (*N*-dodecyl)-4-*O*-β-D-galactopyranosyl-D-gluconylamide (**IV**)[31] (D_2O/THF, 40°C, 30 min irradiation), and of 1-*O*-methyl-*N*-acetylneuraminic acid (**V**)[32] (D_2O, 65°C, 60 min, repeated once with refreshed catalyst) (Figure 7). The objective of these labeling procedures was to provide deuterated materials for NMR conformational assessments, not to maximize the extent or selectivity of labeling. Nevertheless, the deuterium incorporation into sugar C3 and C4 of **III** was reported to be high (the side chain double bond was also reduced), and similarly high was the incorporation into C8 and C9 of **V**. The percentage of deuterium at various sites in **IV** is indicated by the numbers adjacent. One clear difference between the labeling patterns of ultrasound-treated **III** and **IV** compared with those of the carbohydrates earlier studied (labeled under thermal

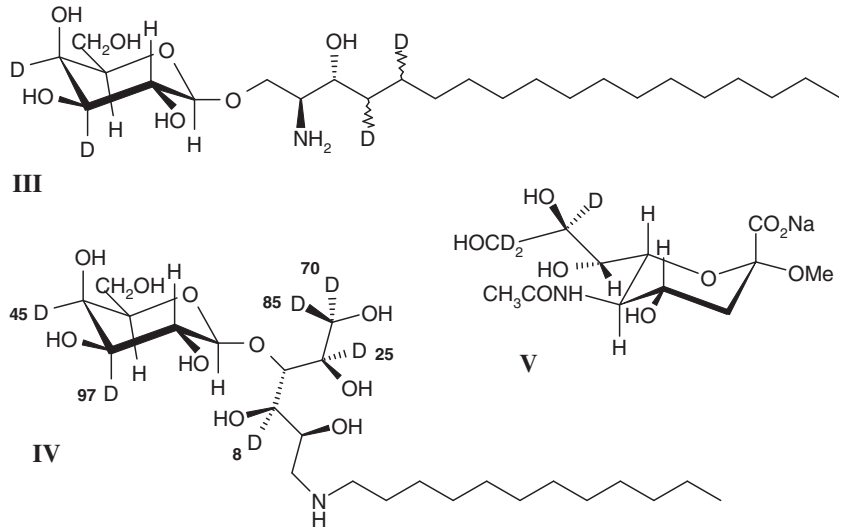

Figure 7. Compounds labeled by ultrasound-enhanced Raney nickel-catalyzed exchange.

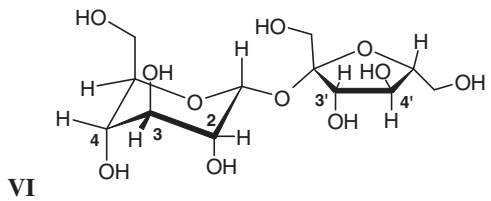

Figure 8. Sites in sucrose labeled by microwave-enhanced Raney nickel-catalyzed exchange.

conditions) is the lack of isotope incorporation into the C6 position of the pyranosides. In the case of **III**, a parallel ultrasound labeling experiment was conducted with the previously studied 1-*O*-methyl-β-D-galactopyranoside (the head group of **III**), and it also was not labeled at C6, thus supporting the likelihood of a real difference in outcome between thermal and ultrasound-enhanced labeling procedures.

Typical ultrasound-enhanced exchange procedure[30]

A 3-neck flask equipped with a central ground glass joint ca. 14 cm long was charged with 20 mg of substrate, 0.5 mL (settled volume) of 'deuterated' Raney nickel, 10 mL of THF and 2 mL of D_2O. The flask was immersed in a 40°C water bath, and the flask contents were gently swept with a stream of inert gas. Sonication was conducted via a titanium-tipped ultrasonic probe inserted directly through the central joint into the reaction mixture. Workup included centrifugation, decantation of the supernatant and passing of it through a bed of ion-exchange resin to remove any trace of paramagnetic impurities.

More recently, an exploration was made[33] of solvent effects on labeling of 1-*O*-methyl-β-D-galactopyranoside under the influence of ultrasound ('deuterated' Raney nickel, D_2O/THF, 40°C, sonicate 2 h). The extent of label incorporation generally followed trends (axial > equatorial > *syn*-axial) earlier recognized under thermal conditions; however, again C6 was not labeled. The only novel result was that obtained in dimethoxyethane solvent, where C3 was unlabeled but C2 and C4 were (but only to the extent of 15% and 29%, respectively).

A variety of modified Raney nickel and other catalysts were surveyed in the deuterium labeling of the same test substrate.[34] Only Raney nickel and some of its variants were active, Cr^{+3}-doped Raney nickel being marginally more so, but again the normal regioselectivity of exchange was not greatly influenced by change of catalyst.

Lastly, microwave enhancement was tried[35] in the deuterium exchange labeling of 1-*O*-methyl-β-D-galactopyranoside and of sucrose. Again C6 was not labeled, and in the monosaccharide some discrimination between the rate of labeling at C3 and C4 was evident under some protocols, although only at moderate labeling levels. The labeling in sucrose occurred at the numbered positions of the structure shown in Figure 8, and ranged among the five sites from 3 to 25% (2 × 15 s irradiation) to 17–91% (24 × 15 s).

Labeling of complex mixtures

Raney nickel was found to be the best catalyst for the practically uniform tritium labeling of the complex organic components of oil shale process water[36] and of engine oil basestocks.[37] Representative labeling of all the components of each mixture was desired in order to enable valid tracing of the fates of such materials in the environment or in engine performance assessments. Comparisons of the 1H- and 3H-NMR spectra of the mixtures labeled with Raney nickel (THO, 120°C, 20 h – 6 days) showed closer correlations in both chemical shift distributions and peak heights, compared with samples labeled by platinum catalysis.

References

[1] M. B. Smith, J. March, *Advanced Organic Chemistry*, 5th ed., Wiley-Interscience, New York, **2001**.
[2] T. Tsukinoki, H. Tsuzuki, K. Ishimoto, K. Nakayama, T. Kakinami, S. Mataka, M. Tashiro, *J. Label. Compd. Radiopharm.* **1994**, *34*, 839–844.
[3] K. Hirota, T. Ueda, *Bull. Chem. Soc. Jpn.* **1962**, *35*, 228–232.
[4] J. L. Garnett, M. A. Long, Catalytic exchange methods of hydrogen isotope labelling, in *Isotopes in the Physical and Biomedical Sciences* (Eds.: E. Buncel, J. R. Jones), Elsevier, Amsterdam, **1987**, pp. 86–121.
[5] C. G. Macdonald, J. S. Shannon, *Aust. J. Chem.* **1965**, *18*, 1009; C. G. Macdonald, J. S. Shannon, *Tetrahedron Lett.* **1963**, 1349.

[6] J. M. A. Al-Rawi, J. A. Elvidge, J. R. Jones, R. B. Mane, M. Saieed, *J. Chem. Res. (S)* **1980**, 298.
[7] P. G. Williams, H. Morimoto, M. Saljoughian, in *Synthesis and Applications of Isotopically Labelled Compounds 1988* (Eds.: T. A. Baillie, J. R. Jones), Elsevier: Amsterdam, **1989**, pp. 55–60.
[8] E. Crawford, C. Kemball, *Trans. Faraday Soc.* **1962**, *58*, 2452.
[9] P. M. Pojer, *Tetrahedron Lett.* **1984**, *25*, 2507–2508.
[10] H. J. Koch, R. S. Stuart, *Carbohydrate Res.* **1978**, *64*, 127–134; H. J. Koch, R. S. Stuart, *Carbohydrate Res.* 1977, 59, C1–C6.
[11] J. L. Garnett, *Catal. Rev.* **1971**, *5*, 229–268.
[12] M. A. Long, J. L. Garnett, C. A. Lukey, P. G. Williams, *Aust. J. Chem.* **1980**, *33*, 1393–1395.
[13] C. G. Macdonald, J. S. Shannon, *Tetrahedron Lett.* **1964**, 3351.
[14] R. B. Moyes, P. B. Wells, *J. Catal.* **1971**, *21*, 86.
[15] G. E. Calf, J. L. Garnett, V. A. Pickles, *Aust. J. Chem.* **1968**, *21*, 961.
[16] S. Anto, G. S. Getvoldsen, J. R. Harding, J. R. Jones, S.-Yl Lu, J. C. Russell, *J. Chem. Soc. Perkin Trans.* **2000**, *2*, 2208–2211.
[17] J. P. Dinnocenzo, T. E. Banach, *J. Am. Chem. Soc.* **1988**, *110*, 971–973.
[18] W. J. S. Lockley, G. Kershaw, in *Synthesis and Applications of Isotopically Labelled Compounds 1991* (Eds.: E. Buncel, G. W. Kabalka), Elsevier: Amsterdam, **1992**, 604–607.
[19] W.-M. Yau, K. Gawrisch, *J. Label. Compd. Radiopharm.* **1999**, *42*, 709–713.
[20] R. N. Garman, G. S. Getvoldsen, J. R. Jones, K. W. M. Lawrie, S. Y. Lu, P. Marsden, J. C. Russell, K. R. Seddon, in *Synthesis and Applications of Isotopically Labelled Compounds*, Vol. 7 (Eds.: U. Pleiss, R. Voges), Wiley, Chichester, **2001**, pp. 97–100.
[21] G. E. Calf, J. L. Garnett, *Aust. J. Chem.* **1968**, *21*, 1221.
[22] M. Tashiro, K. Nakayama, G. Fukata, *J. Chem. Soc. Perkin Trans. I* **1983**, 2315–2318.
[23] C. G. Macdonald, J. S. Shannon, *Aust. J. Chem.* **1967**, *20*, 297.
[24] E. C. Kleiderer, P. C. Kornfeld, *J. Org. Chem.* **1948**, *13*, 455–458.
[25] R. J. Wicker, *J. Chem. Soc.* **1956**, 2165–2173.
[26] H. Harness, N. A. Hughes, J. Chem. Soc., *Perkin Trans. I* **1972**, 38–41.
[27] H. J. Koch, R. S. Stuart, *Carbohydrate Res.* **1978**, *67*, 341–348.
[28] F. Balza, A. S. Perlin, *Carbohydrate Res.* **1982**, *107*, 270–278; G. K. Hamer, F. Balza, N. Cyr, A. S. Perlin, *Can. J. Chem.*, **1978**, *56*, 3109–3116.
[29] S. J. Angyal, J. D. Stevens, L. Odier, *Carbohydrate Res.* **1986**, *157*, 83–94; S. J. Angyal, L. Odier, *Carbohydrate Res.*, **1983**, *123*, 13–22.
[30] E. A. Cioffi, J. H. Prestegard, *Tetrahedron Lett.* **1986**, *27*, 415–418.
[31] P. Ram, J. H. Prestegard, *J. Am. Chem. Soc.* **1988**, *110*, 2383–2388.
[32] D. S. Thomson, J. H. Prestegard, *Carbohydrate Res.* **1990**, *196*, 206–210.
[33] E. A. Cioffi, *Tetrahedron Lett.* **1996**, *37*, 6231–6234.
[34] E. A. Cioffi, K. E. Alston, A. M. Patel, *Tetrahedron Lett.* **2002**, *43*, 8985–8987.
[35] E. A. Cioffi, R. H. Bell, B. Le, *Tetrahedron: Asymmetry* **2005**, *16*, 471–475.
[36] D. S. Farrier, J. R. Jones, J. P. Bloxidge, L. Carroll, J. A. Elvidge, M. Saieed, *J. Label. Compd. Radiopharm.* **1982**, *19*, 213–227.
[37] L. Carroll, J. R. Jones, P. R. Shore, *J. Label. Compd. Radiopharm.* **1987**, *24*, 763–772.

