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# Potential kinetic control of ultrasonic $^1H \rightarrow ^2H$ isotopic exchange by transition metal doping of Raney–nickel® catalysts

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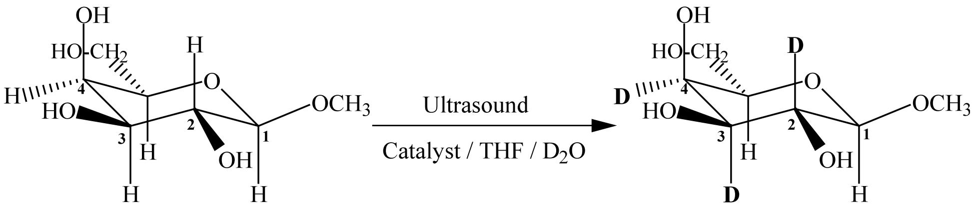
**Abstract**—Raney-nickel®-catalyzed $^1H \rightarrow ^2H$ isotopic exchange in non-reducing carbohydrates is conducted under mild conditions using ultrasonic irradiation. The initial and overall rates of isotopic exchange are modulated by the presence of transition metals, either in the initial alloy melt or subsequently plated onto the digested catalyst. Only the Raney-nickel® type alloys afforded stereospecific $C–^1H \rightarrow C–^2H$ isotopic exchange in an ultrasonic field. Typical supported precious metal catalysts, supported Ni catalysts, singular metal catalysts, or multi-phasic catalysts were either totally ineffective or caused substrate decomposition.

Deuterium and tritium labeling of carbohydrates and glycoconjugates have wide applicability in the biochemical and biophysical fields.[1] Carbohydrates function as receptors for a variety of hormones, and play critical roles in cell recognition and differentiation.[2] Labeled carbohydrates may serve as convenient probes into the molecular organization and structural dynamics of micelles and membranes,[3] or as metabolic and biosynthetic probes of cellular activity.[4] Further, deuterium labeled compounds are frequently utilized in the conformational analysis of oligo- and polysaccharides, as well as for glycoproteins, glycolipids, and cardioglycosides, to help alleviate resonance overcrowding in $^1H$ NMR spectroscopy.[5]

We are continuing to explore the empirical parameters attendant to the ultrasonically mediated, stereospecific $^1H \rightarrow ^2[C1]H$ catalytic exchange technique using Raney-nickel® catalysts that we have developed.[6–10] This facile technique is mild, tolerant of thermally-sensitive moieties, and since substrate epimerization, racemization, and degradation are absent, product isolation is generally quantitative. One of the limitations of this technique is the control of regioselectivity, which has been successfully addressed in part by the use of mixed co-solvent systems.[9]

Based upon the observed differences in both the initial and overall rates of isotopic exchange seen in an earlier morphological study of transition-metal doped Raney nickel® catalysts, we decided to examine a variety of heterogeneous catalysts. Many of these catalysts were typical hydrogenation catalysts, and included supported precious metal catalysts (e.g. Pd on carbon), supported Ni catalysts (e.g. Ni on kieselguhr), single metal catalysts (e.g. Ni), biphasic and triphasic mixed metal catalysts (e.g. Ni coated Al), and non-nickel containing Raney-type® catalysts (e.g. Raney-Co®). In addition, we examined non-digested Raney-nickel® catalysts, and a variety of transition metal modified Raney-nickel® catalysts, which either had the dopant metal as part of the initial alloy melt or was subsequently plated upon



**Scheme 1.** Stereospecific isotopic $^1H \rightarrow ^2H$ exchange using ultrasound and various catalysts.

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the digested catalyst. The model carbohydrate used to evaluate the extent of C–H→C–D exchange promoted by ultrasonic irradiation was 1-*O*-methyl-β-D-galactopyranoside (Scheme 1).

All ultrasonically-promoted exchange experiments were conducted at 40°C in a mixed THF–D$_2$O solvent system as outlined earlier,[6] and the percentage incorporation of $^2$H into each of the exchangeable vicinal C–H positions was assessed using high-field $^1$H NMR spectroscopy. The results of the labeling experiments conducted using the non-Raney-type® catalysts are shown in Table 1; the results of the labeling experiments using the Raney-type® catalysts are shown in Table 2.

Of all of the catalysts examined, *only* the Raney-nickel type® catalysts afford facile $^1$H→$^2$H isotopic exchange in an ultrasonic field. Non-Raney-type® catalysts, digested or not, gave either no reaction or promoted a slow decomposition of the model substrate. Of the Raney-type® catalysts, it appears that metallic Ni must be incorporated into the initial alloy melt in order to

**Table 1.** Non-Raney® type catalysts examined for C–$^1$H→C–$^2$H exchange in 1-*O*-methyl-β-D-galactopyranoside

| Catalyst, non-Raney®-type | Sonication time (min) | % $^1$H→$^2$H exchange* | | |
|---|---|---|---|---|
| | | C$_2$ | C$_3$ | C$_4$ |
| Aluminum | 180 | NR | NR | NR |
| Aluminum zirconide (ZrAl$_3$) | 180 | NR | NR | NR |
| Chromium-Al (85/15 w/w%) | 180 | NR | NR | NR |
| Nickel | 180 | NR | NR | NR |
| Nickel-coated Al (80/20 w/w%) | 180 | NR | NR | NR |
| Nickel-coated Al (digested†) | 180 | NR | NR | NR |
| Ni–Al (undigested 50/50 w/w%) | 180 | NR | NR | NR |
| Ni–Al (undigested NiAl) | 180 | NR | NR | NR |
| Ni–Al (digested† NiAl) | 180 | NR | NR | NR |
| Ni–Al (undigested Ni$_3$Al) | 180 | NR | NR | NR |
| Ni–Al (digested† Ni$_3$Al) | 180 | NR | NR | NR |
| Nickel on silica-alumina | 180 | NR | NR | NR |
| Nickel on Kieselguhr | 180 | NR | NR | NR |
| Nickel phosphide (Ni$_2$P) | 180 | NR | NR | NR |
| Nickel boride (NiB) | 180 | NR | NR | NR |
| Magnesium | 180 | NR | NR | NR |
| Magnesium–Ni (98/2 w/w%) | 180 | NR | NR | NR |
| Niobium aluminide (Nb$_3$Al) | 180 | NR | NR | NR |
| Palladium on carbon, 10% | 180 | sl. decomposition; no$^2$H incorporation | | |
| Platinum on carbon, 10% | 180 | NR | NR | NR |
| Silver oxide (AgO) | 180 | sl. decomposition; no$^2$H incorporation | | |
| Titanium–Al (65/35 w/w%) | 180 | NR | NR | NR |

* NR = no reaction, sl. = slight.

† Prepared using the W-2 Raney-nickel digestion protocol.[12]

**Table 2.** Raney®-type catalysts examined for C–$^1$H→C–$^2$H exchange in 1-*O*-methyl-β-D-galactopyranoside

| Catalyst, Raney-type (W-2 digested) | Sonication time (min) | % $^1$H→$^2$H exchange* | | |
|---|---|---|---|---|
| | | C$_2$ | C$_3$ | C$_4$ |
| Raney-cobalt | 180 | NR | NR | NR |
| Raney-copper | 180 | NR | NR | NR |
| Raney-nickel | 1 | 13 | 70 | 69 |
| Raney-nickel | 180 | 40 | 72 | 88 |
| Raney-nickel, deactivated‡ | 120 | 3 | 11 | 11 |
| Raney-nickel, Cu plated | 30 | 6 | 6 | 10 |
| Raney-nickel, Cu plated | 120 | 9 | 51 | 53 |
| Raney-nickel, Cr$^{+3}$-doped | 1 | 50 | 67 | 62 |
| Raney-nickel, Cr$^{+3}$-doped | 180 | 21 | 97 | 98 |
| Raney-nickel, Mo$^{+6}$-doped | 1 | 5 | 25 | 14 |
| Raney-nickel, Mo$^{+6}$-doped | 180 | 11 | 91 | 70 |
| Raney-nickel, Pt plated | 60 | 15 | 22 | 25 |
| Raney-nickel, Pt plated | 120 | 19 | 59 | 64 |
| Raney-nickel, Pt plated | 180 | 20 | 80 | 83 |

* NR = no reaction.

‡ Deactivation by refluxing catalyst in (CH$_3$)$_2$CO and drying prior to ultrasound reaction.

afford a viable exchange catalyst (R–Ni). The differences in the initial or overall exchange rates in doped or plated catalysts at individual sites (i.e. equatorial C–H's versus axial C–H's) effect kinetic control of regioselectivity, especially if only low-levels of isotopic enrichment are desired (e.g. R–Ni versus $Cr^{+3}$-doped R–Ni). In general, the relative rates of stereospecific exchange are equatorial-H>axial-H≫*syn*-axial-H. Furthermore, the overall reaction sequence is reversible ($^2H \rightarrow {}^1H$; if $H_2O$ is used as the isotope source starting with pre-labeled $^2H$ substrates). This reversibility of exchange may be exploited for isotopic exchange at a singular site by a judicious sequential use of differently doped alloys and different solvent mixtures.[9,11]

We have continued our development of an ultrasonically mediated, stereospecific $^1H \rightarrow {}^2H$ catalytic exchange technique in a heterogeneous reaction scheme. A total of nineteen non-Raney-type® catalysts were examined as potential candidates; these catalysts afforded either no $^2H$ incorporation or slowly decomposed the substrates. Of all of the digested Raney-type® catalysts examined, only the nickel-containing Raney-type® alloys afforded facile $^2H$ incorporation. The initial and overall rates of incorporation were modulated by transition metals, either as initial dopants in the alloy melt or in the penultimate digested catalyst, thus providing potential kinetic control of the $^1H \rightarrow {}^2H$-exchange regioselectivity. Further modifications of Raney-nickel-type® catalysts are currently underway.

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