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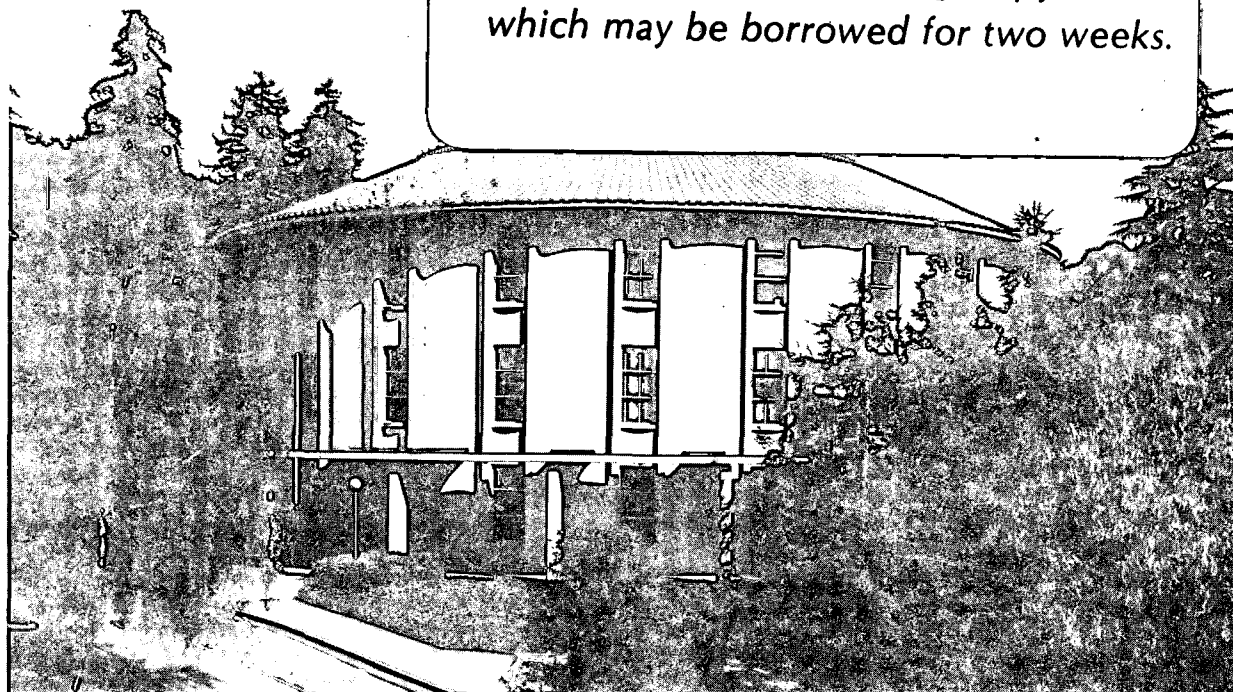
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THE OLD AND THE NEW: STUDIES OF METAL-CATALYSED EXCHANGE BY ^3H NMR SPECTROSCOPY.

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SUMMARY

Studies of the use of platinum, palladium and Raney nickel catalysts for exchange into organic substrates under mild conditions have been undertaken. Encouraging results were obtained with Raney nickel as catalyst, with high activity and specificity of label, with a number of pilot experiments yielding tritiated hydrocarbons with specific activities in the region of 30-400 GBq/mmole. NMR analyses of products and have shown that the mechanism of the exchange process is accessible, that aromatic vs aliphatic effects may be quantified, and that the resolution of modern day NMR instruments allows simple resolution of multiply labelled species. With extension of these experiments to more diverse substrates, and with careful radio-GLC and ^3H NMR analyses, we have gained insight into the range of application and the exchange mechanisms of these procedures.

INTRODUCTION

Most methods yielding high specific activity tritiated organic substrates (370-3700GBq per mmole, or 10-100Ci/mmole) require the synthesis of unsaturated or halogenated precursors (ref. 1). Catalysed hydrogen isotope exchange procedures (ref. 2) are effective for labeling to lower levels (in the range 0-37GBq/mmole), and may be very specific in some cases (ref. 3). The practical maximum specific activity obtainable by the use of metal catalysts and labelled solvents is limited by difficulty in handling the solvents. Tritium gas is much easier to manipulate and catalysed exchange with tritium gas has been used with some success (ref. 3, 4 and refs therein).

Raney nickel has been employed as a catalyst for hydrogen isotope exchange under many conditions, including the labelling of alkanes with T_2 at room temperature or 60°C (ref. 5, 6 and refs therein), tritiation of several substrates with HTO at room temperature (ref. 7), tritium labelling of silanes with T_2 at 100°C (ref. 8), and labelling of various substrates with T_2 at 100°C (ref. 9). In addition Raney nickel is well-known as a hydrogenation catalyst, and has been used to reduce functional groups to give highly labelled products (ref. 10).

We have investigated the exchange of a series of simple organic substrates with tritium gas at room temperature, and analysed the products by the combined techniques of radio-GLC (ref. 11) and ^3H NMR spectroscopy (ref. 7).

METHODS

Materials:

Substrates were of spectroscopic grade, from various suppliers, and were used without further purification. Tritium gas was purchased from Oak Ridge National Laboratory, and contained 97.9% T_2 , with the largest contaminant being DT (1.76%). A 10:90 T:H source mixture was made by expanding 25kPa of T_2 into a stainless steel container, and addition of H_2 to a final

pressure of 250kPa. A 5:95 T:H mixture was made in a similar fashion.

Preparation of Catalysts:

Raney Nickel was prepared according to the method of Dominguez *et al* (ref. 12), stored at 4°C under ethanol, and was tested for pyrophoric and magnetic properties before use. Platinum and palladium catalysts were prepared by suspension of the oxide (100mg) in H₂O (approx 10mL) and slow addition of NaBH₄, after which the catalyst and supernatant were held at a temperature of 70°C for 30 minutes. The H₂O was decanted from the reduced catalyst and the catalyst washed with absolute ethanol (10mL, 3x).

Reaction Procedure:

Substrate (1mL) was outgassed by the application of several freeze-pump-thaw cycles in the side-arm tube shown in Figure 1 (part A). The sealed (teflon plunger) tube was then added to the reaction vessel (B), and catalyst (approx. 50mg) was added as a slurry. As much ethanol solvent was then removed as was possible (pipette) - for Raney nickel this was simple since the catalyst gathered around the stirrer bar. The apparatus was then attached via the "cut-off" tap (C) to the tritiation line. The catalyst was heated (heat-gun) and the vessel evacuated. After some heating, there was a rapid pressure increase to ~30kPa, and the apparatus then quickly pumped down to the reaction pressure. The apparatus was pumped by turbomolecular pump to a reaction pressure of ~2-3kPa, with a leak-rate of < 0.4kPa/min. Hydrogen gas was then admitted to a pressure of 100kPa, and the tritiation line isolated. The side-arm tube (A) was opened (pressure dropped to 85kPa), the reaction mixture was stirred at R.T., and the uptake of gas was monitored. After the reaction the substrate was frozen (liquid N₂) and the residual T₂ pumped away, with any residual dissolved T₂ being removed by repeated N₂ flushing and several freeze-pump-thaw cycles. The catalyst was then removed by filtering the mixture through a shortened Pasteur pipette containing glass wool, and an aliquot of the filtrate was dissolved in C₆D₆ for NMR study.

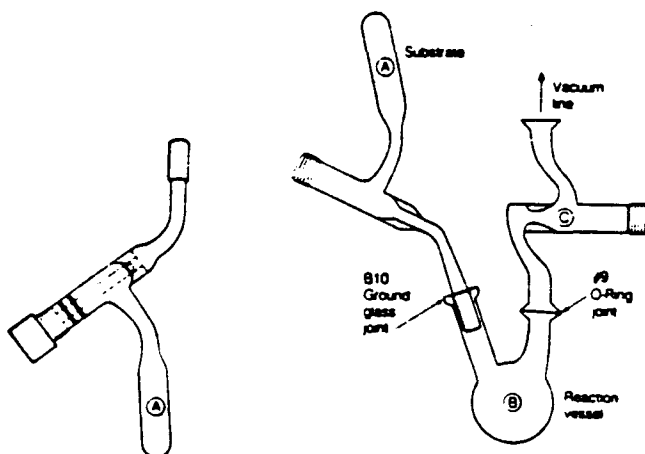


Figure 1. Reaction Apparatus for Tritiation Experiments.

Radio-Gas Chromatography:

Reaction products were first analysed for total radioactivity by liquid scintillation counting. A small aliquot (1-10 μ L) was added to n-hexane (1-5mL) and 1 μ l of this solution counted in Opti-

Fluor™ (Packard) scintillant on a Packard 1500 Tri-Carb liquid scintillation analyzer. The diluted samples were then analyzed by radio-GLC on a Varian 3700 GC, with a Carbowax column. The diluted sample (0.5-5 μ L, containing 100-200kBq) was co-injected into the chromatograph with cold standard. A radioactivity peak of 100Bq was considered significant, with a background of 50Bq, and injected radioactivity was detected with an overall efficiency of 8%.

NMR Spectroscopy:

Reaction product (50-150 μ L, 37-2,500MBq) was diluted with C₆D₆ to a final volume of 200 μ L in teflon tubes (Wilmad, #6005), which were then placed inside 5mm glass NMR tubes having a screw-cap (Wilmad, 507-TR-8"). NMR spectroscopy was carried out on an IBM Instruments Inc. AF-300 spectrometer (³H at 320 MHz, ¹H at 300 MHz), using a ³H/¹H 5mm dual probe. Tritium spectra were acquired over a spectral width of 3400Hz, with 8K data points, an excitation pulse of 3.6 μ sec, recycle time of 5 sec., and all spectra were acquired at 297K with the sample spinning. Similar parameters were used for proton NMR spectroscopy. Referencing of chemical shifts was achieved as previously described (ref. 7).

RESULTS and DISCUSSION

The results of the exchange reactions with tritium gas at R.T. over either Raney nickel, heterogeneous platinum or palladium catalysts are given in Table 1. Products had specific activities in the 3.7-555GBq/mmole range, and many had >95% radiochemical purity.

In aromatic hydrocarbons highly specific labelling was observed, with toluene, *m*-xylene, *n*-pentylbenzene and *s*-butylbenzene labelled almost exclusively in the α -CH positions. This is in agreement with results already in the literature, and is thought to occur by way of a π -allyl mechanism (ref. 13). Close scrutiny of the ³H NMR spectra for the toluene samples labelled with 100% T₂ (Figure 2a) shows that hydrogenation (to give methyl cyclohexane) is a significant reaction over platinum. In addition, inspection of the expanded methyl pattern (Figure 2b) shows a large proportion of CT₃ species over the platinum catalyst. This suggests that the substrate is very strongly adsorbed on platinum, allowing multiple exchange reactions to predominate. On nickel and palladium catalysts the exchange patterns reflect a much higher predominance of one hydrogen replacement per visit to the catalyst. Over nickel and platinum the aromatic centres are labelled predominantly in the *meta* and *para* positions. The likely mechanism for aromatic exchange is the dissociative π -complex mechanism due to Garnett (ref. 13). Over palladium catalyst the aromatic centre of toluene was more heavily labelled in the *ortho* position than either *meta* or *para*. This orientation was not observed at higher temperatures for a similar reaction (ref. 9), and this anomaly could explain the proposal of conflicting exchange mechanisms in the literature in the 1960's, where the associative mechanism was favoured by workers studying exchange over metal films at low temperature.

Hydrocarbons containing functional groups (anisole, nitrobenzene, fluorobenzene) and naphthalene were not cleanly labelled, and a major competing reaction appeared to be ring saturation or reduction of the functional group. This preparation of Raney nickel is known to give saturation and reduction products in good yield under only slightly more stringent conditions (ref. 10). In particular, at 40-50°C and 280-410kPa of hydrogen gas, β -naphthol gave 5,6,7,8-

tetrahydronaphthol in 83% chemical yield, phenol gave cyclohexanol (92%), and heptaldehyde gave 1-heptanol (90%).

Alkanes (*n*-heptane, methyl cyclohexane) were labelled only slightly, and did not give high radiochemical purity. The specific activities obtained were comparable to other reported results, and mechanisms for isomerisation have been proposed (ref. 5, 6).

In general much higher specific activities have been reported here than are generally obtained through many exchange labelling processes. One advantage of the technique discussed here is the mild experimental conditions. An apparent problem is the destruction of functional groups on several of the substrates under study. These experiments show the power of using combined analytical techniques such as radio-GLC and ³H NMR spectroscopy for the characterization of labelling methods.

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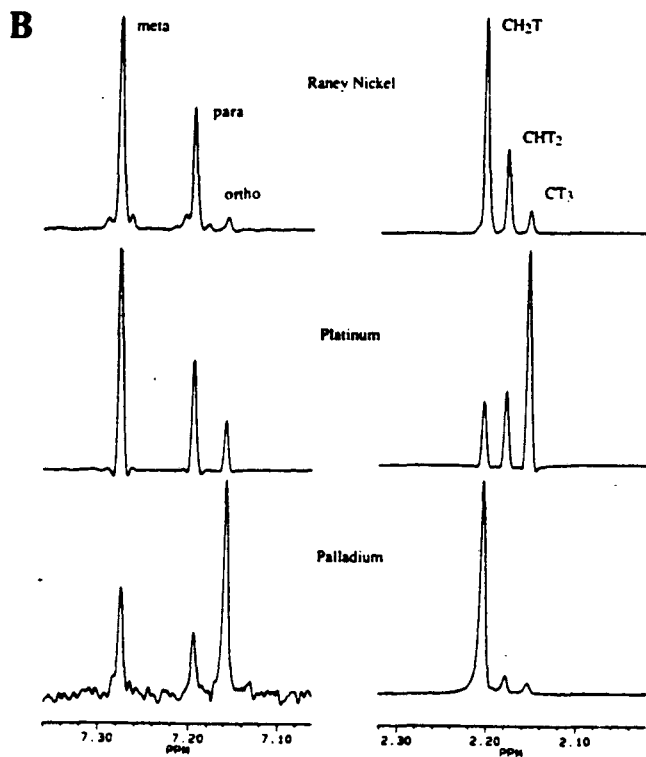
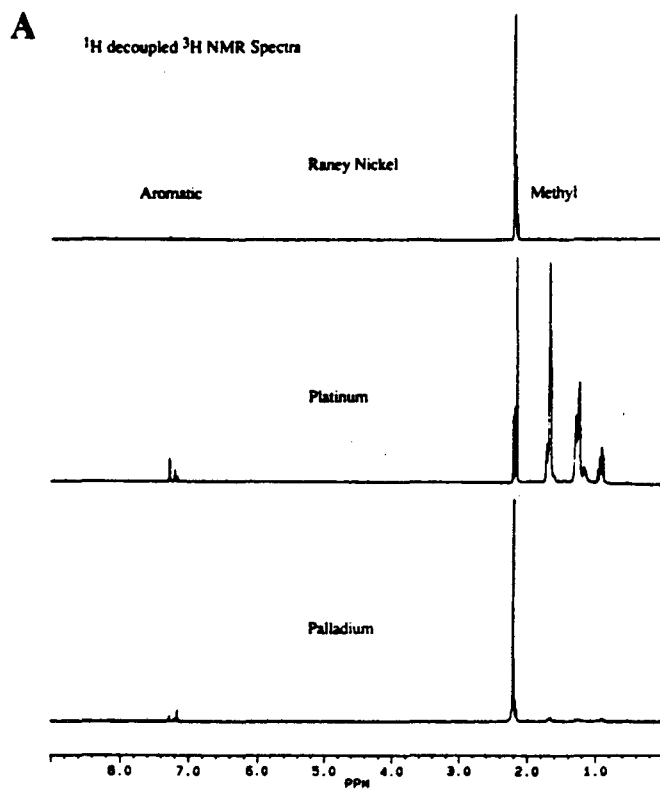
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Table 1 - Exchange Reactions

Substrate	R _x Time	%T	Specific Activity* GBq/mL GBq/mM		GLC	Comments
NICKEL:						
Toluene	6h 52'	5%	28.2	3.00	-	Almost exclusively methyl exchange. Some methyl cyclohexane.
Methyl Cyclohexane	7h 16'	5%	3.7	0.47	-	
Toluene	6h 15'	100%	approx. 3700		-	Almost exclusively methyl exchange. Some methyl cyclohexane.
Methyl Cyclohexane	4h 45'	100%	-	-	-	
Toluene	4h 05'	10%	511.0	54.32	2.13, <u>97.87</u>	All methyl exchange. m/p in the ring. Oxygen in the System??
m-Xylene	4h 05'	10%	164.7	20.25	<u>100%</u>	
s-Butylbenzene	4h 10'	10%	34.1	5.31	1.26, 4.50, <u>80.20</u> , 1.30, 0.02, 12.72%	All tritium in the methyls! α-CH exchange only 67% in starting material, by NMR.
m-Xylene	4h 20'	10%	178.0	19.34	4.7, <u>95.3%</u>	
Anisole	4h 35'	10%	132.5	14.38	33.0, 30.7, 15.7, <u>16.8, 3.8%</u>	All methyl exchange. Anisole is 10.8% by NMR.
Pyridine	4h 05'	10%	108.0	8.71	<u>100%</u>	
Nitrobenzene	4h 05'	10%	52.2	5.34	84.3, 15.7, <u>0.0%</u>	Entirely 2,6 exchange. Aniline, other amine??
Fluorobenzene	4h 00'	10%	8.9	0.84	22.0, 76.1, <u>1.8%</u>	
Methyl Cyclohexane	4h 00'	10%	39.0	4.98	<u>3.9, 96.1%</u>	Some saturated products(?).
n-Heptane	4h 10'	10%	2.0	0.30	<u>38.17, 40.50,</u> <u>16.18, 5.14</u>	
n-Pentylbenzene	4h 15'	10%	75.8	13.06	3.6, <u>94.8, 1.6%</u>	Nearly all α-CH ₂ exchange. β > α Naphth. only 3.7% by NMR.
Naphthalene	4h 20'	10%	36.7	-	6.7, <u>86.8, 6.8</u>	
PLATINUM:						
n-Pentylbenzene	4h 00'	5%	48.5	8.36	-	Lots of T ₃ methyl species. Bulk methyl cyclohexane.
Toluene	5h 10'	100%	-	-	-	
Methyl Cyclohexane	3h 50'	100%	-	-	-	Impurities 74.5% by NMR. Mostly methyl cyclohexane.
Toluene	4h 05'	10%	37.9	4.03	73.7, 2.6, <u>23.7%</u>	
PALLADIUM:						
Toluene	3h 50'	100%	-	-	-	>95% methyl exchange. Ring o > m,p !!
Methyl Cyclohexane	5h 38'	100%	-	-	-	
Toluene	4h 20'	10%	18.2	1.94	1.1, <u>98.9</u>	Confirms 100% result.

* - Calculated assuming radiochemically pure product.



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Figure 2. 320 MHz ^3H NMR spectra of toluene.
 a). Comparison of the full spectrum for products of labelling by Ni, Pt and Pd catalysts.
 b). Comparison of the aromatic and methyl portions of the spectra.

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