

Platinum-Catalyzed Exchange Labelling of Representative Organic Compounds with Tritium Gas or Tritiated Water.

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SUMMARY

A wide range of simple organic substrates has been successfully tritium labelled using reduced platinum oxide as catalyst. Exchange conditions involved reaction temperatures in the range 60–150°C, and reaction times of 3–7 days. The isotope sources for the reactions were tritium gas and tritiated water. Analysis of the labelled products was accomplished by radio-glc and by ³H NMR spectroscopy. The specific activities ranged up to 1100 mCi/mL, and most of the labelled products showed high radiochemical purity. The regioselectivity of tritium incorporation, as obtained from ³H NMR studies, supports currently accepted theories for mechanisms of platinum-catalyzed hydrogen isotope exchange. The results also show remarkable consistency for a heterogeneous system under widely varying reaction conditions.

KEYWORDS: Heterogeneous platinum, tritium gas, tritiated water, tritium NMR, radio-glc.

Introduction

Heterogeneous platinum-catalyzed hydrogen isotope exchange is a widely used technique for labelling molecules with deuterium or tritium.¹ Despite wide usage of the method and

documentation of the proposed reaction mechanism, the published evidence of patterns of isotope incorporation is scant since most of the work was performed before ^3H NMR spectroscopy was a readily available technique. More recently, ^3H NMR spectroscopy has been used to confirm regioselectivity in many catalytic exchange reactions,² but its application to platinum-catalyzed exchange has not been extensive.

Although early experiments using tritium gas^{3,4} and deuterium gas⁵ as isotope sources seemed promising as labelling methods, much work over the past twenty years has centred around the use of HTO or D_2O as isotope sources.⁶ The main advantage of using a labelled solvent as the isotope source is the elimination of hydrogenation reactions, but in the case of HTO this may place a practical limit on the level of incorporation of tritium into the substrate due to the difficulty of working with water of very high specific activity.

Heterogeneous metal-catalyzed exchange reactions have been conducted in many laboratories, but comparison of rates and position of incorporation between different compounds and between water and gas as isotope source is often difficult due to the variation in conditions employed. In particular, the catalysts have ranged from evaporated metal films to unreduced metal oxides, reaction temperatures have varied from -60 to 150°C ,⁷ and reaction times have covered the range from 0.5–200 hours.

We now present a comparison of platinum-catalyzed exchange reactions with tritium gas and tritiated water as the isotope sources. This work is unique because the extensive use of ^3H NMR spectroscopy offered the opportunity to compare detailed incorporation patterns for reactions performed in the same laboratory - where most experimental factors, such as catalyst variability, are held constant.

Experimental

Preparation of Tritiated Water. — Tritiated water was prepared by Raney nickel catalyzed exchange of distilled water with T_2 , at 100°C for 168 hours. Calibration of the specific activity of the water was performed by liquid scintillation counting after appropriate dilution.

Catalyst Preparation. — Platinum catalyst was prepared by reduction of the oxide with sodium borohydride. In a typical exchange experiment, platinum (IV) oxide (*ca.* 50mg, Johnson Matthey) was suspended in distilled water (5mL), and a few crystals of sodium borohydride added. When the reaction subsided, more borohydride was added until the supernatant liquid was colourless. The liquid was then decanted and the remaining finely divided metal washed several times with distilled water. The final suspension was heated to 70°C for 15 minutes to ensure complete hydrolysis of the borohydride.

Exchange Methodology. — For reactions with tritiated water, the suspension was washed again and transferred to a reaction ampoule having a constricted neck. After removal of as much residual water as possible, the organic substrate (typically 0.1mL) was added to the ampoule. Tritiated water (100 μL , 148GBq/mL (40Ci/mL)) was then added from a microsyringe, and the sample frozen in liquid nitrogen. The sample was outgassed, and the ampoule evacuated to approximately 2×10^{-3} torr before being flame-sealed.

In the case of reactions with tritium gas, the finely divided metal was prepared according to the reduction procedure outlined above. The metal was washed with absolute ethanol (10mL, 3x) to prepare it for transfer by pipette in minimum ethanol to section A of the reaction vessel, shown in Figure 1. Ethanol was chosen for final suspension of the catalyst in preference to distilled water for ease of evaporation to dryness in the vacuum system. The organic substrate (0.2mL) was outgassed in the side-arm tube (with breakseal, section B, Figure 1), which was then attached to the main apparatus (with glass breaker in place). Catalyst was pipetted into the bottom of section A, the ethanol removed under vacuum, tritium gas added, and the tube flame-sealed. The glass breaker was used to smash the breakseal and allow the mixing of the substrate with the catalyst and tritium gas.

All samples were held in thermostatically controlled ovens under the conditions given in Tables 1 and 2.

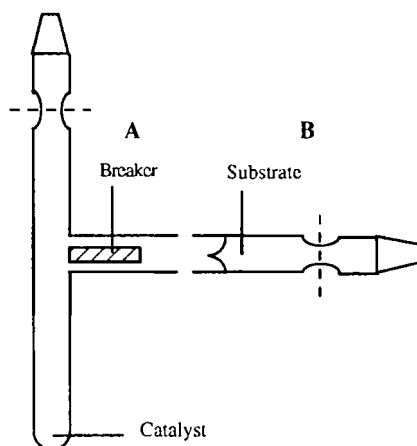


Figure 1: Apparatus for tritium gas reactions.

Isolation of Substrates. — For samples containing tritiated water, the organic substrates were removed by simply opening the ampoule, adding a small amount (*ca.* 0.5mL) of distilled water and removing the substrate with a Pasteur pipette or a microlitre syringe. In the case of the amines, which are miscible with water, the ampoule was opened and anhydrous sodium carbonate was

added, thereby reducing the solubility of the organic. The organic layer was subsequently removed as above and the isolated substrates were dried over anhydrous sodium sulphate prior to further treatment.

For reactions with tritium gas, the organic substrate was generally isolated by distillation back through the breakseal into the side-arm, which was then cut off the reaction ampoule.

Analytical Procedures. —

Radio-Gas Chromatography. — Volatile compounds were analysed by radio-gas chromatography.⁸ A flame ionisation detector (HP5750 Research Chromatograph, HP3373B Integrator) and an ionisation chamber permitted simultaneous analysis of chemical composition and radioactivity of each sample. A 12' x 1/8" I.D., 5% silicone oil on Chromosorb G column was used for all analyses, and dry nitrogen was the carrier gas.

Tritium NMR Spectroscopy. — Two instruments were used for ³H NMR studies;² a Bruker WP-60 (³H at 64MHz), and a Bruker CXP-300 (³H at 320MHz). All tritium spectra were obtained with broadband proton decoupling.

For the WP-60 the following parameters were used: an excitation pulse of 1.5 μ s, data acquisition time 1.7s (2K data points). Some experiments employing a 3.4s acquisition time (4K data points) were carried out where higher resolution was required. The samples (at least 50 μ L of liquid) were placed in 3mm micro-NMR tubes (Wilmad), and a small quantity of tritiated hexamethyldisiloxane (HMDSO) reference material added. The tubes were then flame-sealed and placed inside a 5mm NMR tube with D₂O or C₆D₆ in the annulus to provide the field-locking signal.

The same double encapsulation system was used for the CXP-300, where the inner tube was a 5mm O.D. NMR tube, and the ideal volume of sample 0.5mL. The reaction samples (0.05-0.2mL) were made up to 0.5mL with starting material or a solvent such as carbon tetrachloride, protiated TMS (10 μ L) was added as reference material, and chemical shifts were thereby referenced to a ghost TMS signal generated in the tritium spectrum.⁹ ³H spectra were usually acquired with a 30 μ s pulse, 8K data points, 3sec recycle time, sweep width 3000Hz, and 1-10,000 repetitions.

Results

Tritium gas exchange. —

A wide range of simple organic substrates was exchange labelled at 60, 80 or 100°C over a period of 72 hours, catalyzed by sodium borohydride-reduced platinum (IV) oxide. The results derived from radio-GLC and ³H NMR analyses are shown in Table 1. The %approach to

equilibrium for all samples was calculated on the assumption that the substrate would contain 100% of the available tritium at equilibrium, since the mole fraction of the tritium gas was negligible. The distribution of tritium in the compounds in Table 1 is expressed as the % tritium in each magnetically distinct position. The levels of impurities are recorded as a percentage of the total observed organic tritium content of the sample.

The extent of the labelling of the substrates varied considerably, from <1% incorporation in thiophene to 67.5% in toluene. The specific activities obtained were from 0-1012mCi/mL of substrate (*ca.* 0-100mCi/mmol). The maximum attainable specific activity was limited to *ca.* 250mCi/mmol by the small quantity of tritium gas used in the reactions.

Radiochemical impurities were detected in many of the samples, ranging from 1.8-56% of the total sample activity. In toluene only 1.8% of the radioactivity was present as impurities, whilst in chlorobenzene *ca.* 56% of the product activity was in components other than the starting material. Generally, the nature of the impurities was not pursued, but in some cases they were easily identified by ³H NMR analyses. For example, in the case of chlorobenzene one of the impurities was the dehalogenation product, benzene. Generally, the byproducts were easily detected by virtue of their radioactivity, even though they were present in very low chemical concentration in the reaction product mix. It is to be expected that hydrogenation and possibly rearrangement products would result from reaction with platinum under the conditions used, as platinum is well-established as a catalyst for these types of reactions.¹¹ However, it has also been shown that as the pressure of hydrogen over a palladium catalyst is decreased, hydrogenation of unsaturated compounds becomes a much less dominant reaction than exchange,¹² and a similar behaviour might be expected of platinum.

Consideration of the ³H NMR data in Table 1 suggests that exchange of organic compounds with tritium gas over unsupported heterogeneous platinum catalyst has the following general characteristics:

- predominantly meta/para exchange in the benzene rings of substituted benzenoid compounds,
 - strong α -CH exchange, and decreasing exchange in alkyl protons more remote from the aromatic centre,
 - predominantly 2,6 exchange in pyridine,
 - α exchange in 5-membered ring heterocycles,
 - β exchange in naphthalene,
- and
- facile exchange in alkanes.

Table 1 - Heterogeneous Platinum-catalyzed Exchange with T₂ Gas

Compound	Activity (mCi/mL)	% Approach to Eq ^a	Impurities #, %	<i>o</i>	<i>m</i>	% Incorporation per Position <i>p</i>	Other Positions
Toluene (ref. 10)	1012	67.5	1, 1.8	<1	10.2	4.3	CH ₃ -85.5
Hexylbenzene [10]	785	52.4	1, 8.6	<1	20.6	10.1	α-CH ₂ -48.6; β-CH ₂ -15.0; γ-CH ₂ -3.2; δ,ε-CH ₂ -2.8; CH ₃ <1
Heptylbenzene ^b	634	30.6	1, 14.2	<1	9.5	3.8	α-CH ₂ -73.1; β-CH ₂ -9.1; γ-CH ₂ -2.3; other-CH ₂ <1; CH ₃ <1
Nonylbenzene	132	5.3	1, 51.0	<1	12.8	8.0	α-CH ₂ -57.4; β-CH ₂ -9.6; γ,δ-CH ₂ -6.4; ε,φ-CH ₂ -6.0; (ω-1)-CH ₂ <1; ω-CH ₂ <1; CH ₃ <1
<i>i</i> -Propylbenzene [10]	358	23.8	1, 26.1	<1	39.2	19.1	CH-21.1; CH ₃ -20.4
<i>t</i> -Butylbenzene	887	35.5	4, 8.8	<1	62.8	34.5	CH ₃ -2.6
4- <i>t</i> -Butyltoluene	724	29.0	—				2-37.0; 3<1; CH ₃ -33.6; <i>t</i> -Bu-CH ₃ -29.4
<i>m</i> -Xylene	821	32.8	1, 18.1				2<1; 4,6<1; 5-22.4; CH ₃ -77.4
Chlorobenzene	58	3.9	2, 56.1	5.8	53.0	41.1	CH ₃ -0.5
Anisole	573	23.0	—	<1	48.1	51.4	CH ₃ -25.2
Acetophenone	807	32.3	4, 2.5	<1	49.7	25.1	
Nitrobenzene	339	13.6	3, 2.4	<1	63.4	36.6	
Benzaldehyde	266	10.7	5, 27.1	5.9	3.5	<1	α-CH-90.6
Trifluorotoluene	960	38.4	1, 7.1	<1	59.6	40.4	
Benzoic acid		Activity and purity not determined		<1	40.2	26.1	Acid-33.7
Trimethylphenylsilane	495	19.8	5, 37.1	5.5	49.7	44.8	CH ₃ <1
Pyridine ^c	508	20.3	5, 19.5				2/6-92.0; 3/5-8.0; 4<1
Pyridine	758	30.3	2, 7.6				2/6-91.6; 3/5-8.4; 4<1
Furan ^b	288	11.5	1, 23.3				α-91.4; β-8.6
Pyrrrole ^b	758	30.3	1, 5.8				α-72.1; β-27.9; NH<1
Thiophene	—	<1%	many ^d				α-100.00; β<1
Naphthalene	525	21.0	2, 17.9				α-9.2; β-90.8
<i>n</i> -Hexane	187	7.5	1, 21.8				CH ₃ -38.4; 2&5-CH ₂ -30.8; 3&4-CH ₂ -30.8
2,3-Dimethylbutane	474	19.0	1, 24.9				CH-19.0; CH ₃ -81.6
Methylcyclohexane ^b	534	21.4	1, 4.4				CH ₃ -11.5; 1-axial-5.1; 2-axial-10.2; 2-eq ^l -19.9; 3-axial-13.8; 3-eq ^l -23.1; 4-axial-4.8; 4-eq ^l -11.7
<i>t</i> -Butylcyclohexane ^b	485	19.4	many, 13.8				CH ₃ -20.8; 1-axial-4.4; 2-axial-6.2; 2-eq ^l -18.5; 3-axial-12.9; 3-eq ^l -18.3; 4-axial-10.6; 4-eq ^l -8.2

Reaction time 72 hours for all samples. Reaction temperature 100°C unless otherwise noted.

a - See text for definition. b - Reaction temperature 80°C. c - Reaction temperature 60°C. d - Total activity = 292 mCi/mL.

Tritiated Water Exchange.—

More than 20 simple organic substrates were exchange labelled by sodium borohydride-reduced platinum (IV) oxide catalyst, using HTO as the isotope source. The reaction temperatures ranged from 60-150°C, with reaction times from six hours to 35 days. Results derived from radio-GLC and ^3H NMR analyses are shown in Table 2. The % approach to equilibrium for all samples was calculated on the assumption that all substrate and isotope source hydrogens were exchangeable. The distribution of tritium in the compounds in Table 2 is expressed as the % tritium in each magnetically distinct position.

The extent of the labelling of the substrates varied considerably, from 1% incorporation in the case of cyclohexylbenzene to 65.2% for aniline. Typical specific activities obtained were in the 100-300mCi/mL range (*ca.* 10-30mCi/mmol).

The results in Table 2 show the following characteristics for products of platinum-catalyzed exchange of organic substrates with HTO:

- very high chemical and radiochemical purity,
 - predominantly meta/para aromatic exchange in alkylbenzenes and halobenzenes,
 - α -CH exchange in alkylbenzenes, diminishing along the alkyl chain,
- and
- rapid exchange next to a group capable of binding to the catalyst surface (*e.g.* *N*-methylaniline).

Discussion

Tritium Gas Exchange.—

The results in Table 1 compare remarkably well with the previously published regioselectivity studies, especially considering the range of catalyst preparation and reaction conditions in the literature. Previous isotope orientation results for platinum-catalyzed hydrogen (D_2 or T_2) exchange have been deduced from mass spectral patterns, IR measurements, occasionally from ^1H NMR analyses, and most recently from ^2H NMR studies of reaction products. These past results will be discussed with reference to the current studies.

The high level of methyl labelling in toluene compares very well with previous reports. Deuteration studies at low (*ca.* 1-2 torr) pressures of D_2 gave mostly methyl labelling, with slower meta/para exchange, and some hydrogenation.¹⁴ Toluene exchange at room temperature in the presence of T_2 at one atmosphere of pressure¹⁵ also gave extensive methyl labelling, with multiply tritiated methyl groups detected. In that case, however, the majority of the tritiated product (74%) was the fully reduced compound, methyl cyclohexane. These results support the report¹² that

Table 2 - Heterogeneous Platinum-catalyzed Exchange with HTO

Compound	Time (hours)	Temp. (°C)	% Approach to Eqm	% Incorporation per Position				
				<i>o</i>	<i>m</i>	<i>p</i>	Other Positions	
Fluorobenzene	6	125	15.0	24.8	51.2	24.1		
	12	125	37.3	24.0	56.4	19.6		
	49	125	58.8	29.2	47.6	23.3		
Chlorobenzene	49	125	15.8	<1	55.8	44.1		
	41	130	3.3	6.0	44.4	49.6		
	35d	125	6.4	3.8	65.2	31.1		
Toluene	16	100	6.6	14.8	44.0	25.7		CH ₃ -15.6
	11	125	32.8	25.8	25.6	13.7		CH ₃ -35.1
Ethylbenzene	10	130	32.7	<i>o&p</i> -25.5	38.0			CH ₂ -20.6; CH ₃ -15.9
Propylbenzene	16	100	1.3	<i>o&p</i> -28.5	29.8			α -CH ₂ -14.8; β -CH ₂ -13.6; CH ₃ -13.2
Butylbenzene	10	130	29.6	<i>o&p</i> -27.0	19.0			α -CH ₂ -22.0; β -CH ₂ -17.2; γ -CH ₂ -9.0; CH ₃ -6.0
	25	150	22.7	<i>o&p</i> -16.5	13.0			α -CH ₂ -26.6; β -CH ₂ -16.6; γ -CH ₂ -13.2; CH ₃ -14.1
Pentylbenzene	10	130	13.5	<i>o&p</i> -13.8	28.0			α -CH ₂ -31.6; β -CH ₂ -13.2; γ - δ -CH ₂ -9.6; CH ₃ -3.9
Heptylbenzene	99	125	7.9	<1	26.6	12.5		α -CH ₂ -37.8; β -CH ₂ -13.6; γ -CH ₂ -3.8; other-CH ₂ -3.6; CH ₃ -2.4
<i>i</i> -Propylbenzene	8	130	54.0	13.6	31.2	16.2		CH-11.90; CH ₃ -27.0
<i>i</i> -Butylbenzene	64	130	20.2	8.0	15.6	16.8		CH ₂ -21.0; CH-11.8; CH ₃ -27.0
<i>s</i> -Butylbenzene	25	150	38.4	14.8	35.4	22.3		CH-3.9; CH ₂ -5.6; α -CH ₃ -9.9; CH ₃ -8.1
<i>t</i> -Butylbenzene	24	120	7.9	<1	33.6	13.5		CH ₃ -53.1
	48	125	14.9	<1	30.6	10.9		CH ₃ -58.4
<i>c</i> -Hexylbenzene [13]	16	100	1.0	8.2	38.4	21.3		CH-25.3; CH ₂ -7.0
<i>o</i> -Xylene	24	130	38.7					4,5-19.6; 3,6-18.4; CH ₃ -61.8
<i>m</i> -Xylene	24	130	30.1					2<1; 4,6-28.0; 5-14.8; CH ₃ -57.6
<i>p</i> -Xylene	24	130	17.4					2,3,5,6-32.0; CH ₃ -67.8
<i>m</i> -Diethylbenzene	24	130	39.3					2-1.3; 4,6-12.8; 5-7.3; CH ₂ -36.8; CH ₃ -41.4
Diphenylmethane	16	100	6.1	<i>o&p</i> -54.0	33.2			CH ₂ -13.2
Triphenylmethane [13]	16	100	2.8	13.8	57.0	29.4		CH<1
Aniline	24	60	59.3	31.0	32.8	15.9		amino-20.2
	6	120	65.2	29.0	31.4	14.5		amino-25.2
<i>N</i> -Methylaniline	24	60	23.3	67.4	17.6	11.6		amino-2.8; CH ₃ -0.6
	6	120	8.1	65.6	8.2	7.0		amino-11.6; CH ₃ -7.5
<i>N,N</i> -Dimethylaniline	10d	60	9.3	8.4	32.4	52.4		CH ₃ -7.2
	10d	120	5.9	19.4	33.2	37.0		CH ₃ -10.2
<i>n</i> -Hexane	170	150	17.0					CH ₃ -39.6; 2&5-CH ₂ -29.6; 3&4-CH ₂ -31.2

hydrogenation is favoured at high tritium pressures over heterogeneous catalysts, but appreciable and useful exchange may be observed at low T_2 pressures. The regioselectivity of the tritium incorporation into the aromatic ring of toluene (Table 1) showed no detectable exchange at the ortho positions, with similar rates in the meta and para positions. Aromatic exchange is thought to occur by way of a π -complex mechanism,¹⁶ and the reaction intermediates for the proposed dissociative and associative schemes are shown in Figures 2A and 2B, respectively. The observed lack of reactivity of the hindered ortho hydrogens is taken as support for the dissociative scheme, since absorption of the dissociated species, and hence the exchange position, will be favoured at unhindered sites in the molecule. In contrast, the attacking T species envisaged in the associative process would not be expected to show any sensitivity to steric constraints.

There is very little literature on the exchange patterns of branched- or straight-chain alkylbenzenes under similar conditions to those reported here. *t*-Butylbenzene has been deuterated over an evaporated platinum film¹⁷ and three hydrogens were rapidly exchanged before the substrate was extensively deuterated to *t*-butylcyclohexane. The three most exchangeable protons were proposed to be the meta and para positions in the aromatic ring, and this conclusion is confirmed by the result for *t*-butylbenzene in Table 1, where there is no detectable exchange in the ortho positions, but the meta and para protons are much more rapidly exchanged than the methyl hydrogens. The three straight-chain alkylbenzenes labelled (Table 1) showed large amounts of exchange (*ca.* 50%) at the α -CH position, with much less tritium in methylene positions more remote from the aromatic ring. The distinctive α -CH exchange pattern observed for these substrates is thought to occur *via* a π -allylic mechanism involving the intermediate shown in Figure 2C, as previously proposed for nickel catalysts.¹⁸

The di-substituted alkyl aromatics, 4-*t*-butyltoluene and *m*-xylene, showed no exchange in the most hindered aromatic positions, but gave facile methyl labelling, especially in the CH_3 groups attached to the aromatic ring. Previous studies of exchange of *p*-xylene with D_2 over platinum catalysts have shown that the ratio of methyl to aromatic exchange depends on the physical form of the catalyst. Evaporated films of platinum gave the methyl rate as approximately three times that of the aromatic positions,¹⁹ whilst alumina supported catalysts gave faster aromatic than methyl exchange.²⁰ In addition to the comparison of methyl *vs* aromatic labelling, we are currently also able to distinguish aromatic rates, and the lack of exchange in doubly hindered positions is additional evidence in support of the dissociative π -complex exchange mechanism (Figure 2A).¹⁶

Previous exchange studies of fluoro-, chloro- and bromobenzene with D_2 over platinum films have shown that their exchange rates are all less than that of benzene, and that the rate decreases with increasing size of the halogen substituent.²¹ There was no detectable regioselectivity for fluorobenzene exchange, but slight ortho deactivation for chloro- and bromobenzene. In the present work, chlorobenzene shows marked ortho deactivation from the reasonably bulky chlorine atom, and considerably faster exchange at the para position than at the meta. Decomposition to benzene and hydrogenation to halo-cyclohexane derivatives greatly complicated the earlier studies,²¹ and these processes were also observed in the current experiments.

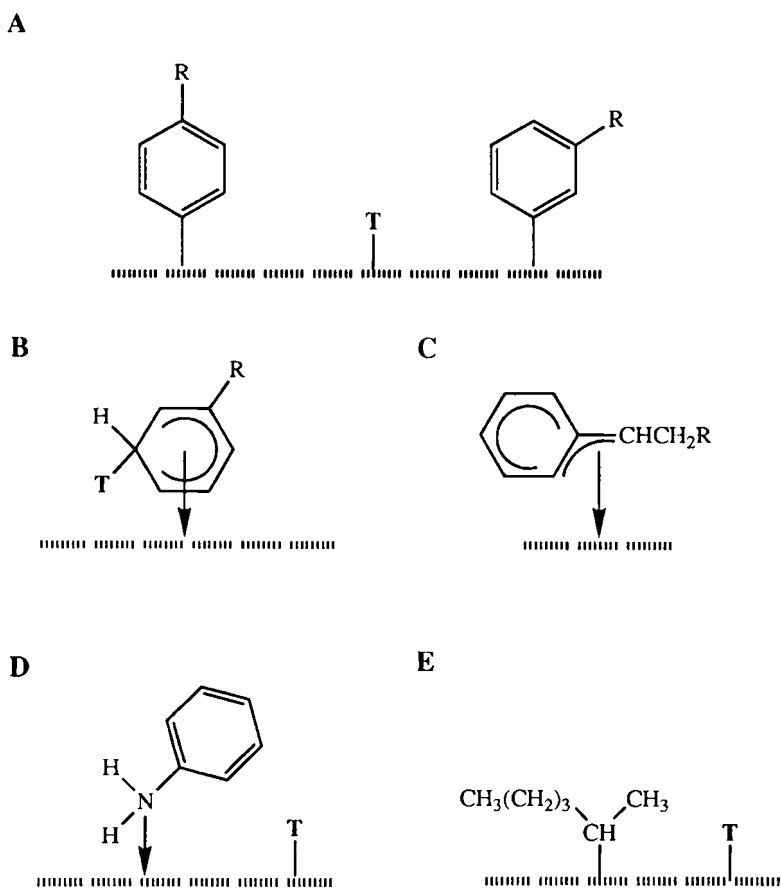


Figure 2: Possible reaction intermediates in heterogeneous metal catalyzed exchange. (A). Dissociative π -complex intermediates, (B). associative π -complex intermediate, (C). π -allylic intermediate, (D). initial adsorption in exchange of strongly adsorbing molecules, and (E). alkane exchange intermediate.

A number of other singly substituted aromatic compounds were effectively labelled, including several which are poorly labelled by acid-catalysis techniques (α,α,α -trifluorotoluene, benzoic acid, benzaldehyde, nitrobenzene) or by heterogeneous metal catalyzed exchange with HTO (acetophenone,²² nitrobenzene²³). The incorporation patterns observed for exchange of these substrates are clearly meta/para in every case except benzaldehyde, where it seems that initial adsorption to the catalyst is similar to that shown in Figure 2D for aniline, and the ortho positions are held in close proximity to the catalyst surface where they are readily exchanged. A similar ortho orientation has been demonstrated in the homogeneous metal catalyzed labelling of aromatic acids, amides and amines,²⁴ and in heterogeneous exchange reactions of heterocyclic compounds with HTO.²⁵ We have also recently reported strong ortho labelling of aniline by exchange with T₂ under similar conditions to those described here.²³

The result for anisole (Table 1) is in strong contrast to a previous report for D₂ exchange over evaporated platinum film,²⁶ which compared calculated and observed mass spectrometric distributions and thereby proposed similar rates of exchange for all aromatic positions. However, the equal total incorporation at meta and para positions is very similar to the pattern reported for the platinum-catalyzed exchange of deuterated anisole with H₂O.²²

The tritiation of pyridine was predominantly in the positions adjacent to the hetero-atom, and a similar pattern of exchange has previously been observed with D₂ over a powdered platinum catalyst at 100°C.²⁷ H-D exchange in pyridine has recently been investigated by high resolution electron energy loss spectroscopy (HREELS) over a Pt{110} single crystal surface, and at high pyridine coverages exclusively 2,6 exchange was observed.²⁸ These results suggest preferential adsorption at the hetero-atom (*c.f.* Figure 2D), and this exchange mechanism has been extensively discussed.²⁵ A similar mechanism has been reported for exchange into the five-membered ring heterocycles,²⁹ where predominant α labelling was also observed (Table 1). Even though the great majority of the product from the thiophene reaction seemed to be the hydrogenated compound, there was sufficient exchanged material for observation of the labelling pattern in the ³H NMR spectrum.

Naphthalene is tritiated more readily in the β position than the α (90.8:9.2). A less pronounced selectivity previously observed (65:35)³⁰ may well have been a result of the higher exchange temperature (200°C). From a mechanistic standpoint, naphthalene may be viewed as a substituted benzene ring, and the lower labelling of the more hindered α positions is further support for the dissociative π -complex mechanism (Figure 2A).

The relative exchange rates of CH, CH₂ and CH₃ protons in alkanes have been the subject of extensive discussion, since they may hold the key to the primary mechanisms of hydrocarbon adsorption and exchange. Early reports of propane exchange over platinum gauze³¹ described preferential methylene labelling, deduced from comparisons of fragment ions in mass spectra. A later study³⁰ used the integration of residual signals in the ¹H NMR spectra of deuterated alkanes. This work confirmed the first report, and further showed that both CH and CH₂ hydrogens were more readily exchanged than CH₃, though the difference in rate between CH and CH₂ could not be reliably determined. Recent studies^{32,33} using ²H NMR spectroscopy as the analytical technique have not been consistent, with one supporting the prior reports,³² and the other claiming preferential CH₃ exchange.³³

³H NMR spectroscopy has the advantage over the ²H method of narrower lines (and seven-fold greater dispersion) and zero natural abundance of the nucleus, yielding readily interpretable spectra. The results for n-hexane, 2,3-dimethylbutane and two cyclohexane derivatives (Table 1) support the previous reports³⁰⁻³² that both CH and CH₂ exchange rates are greater than CH₃. Further, it appears that equatorial protons in methyl- and t-butylcyclohexane are more readily exchangeable than axial protons. The spectra of the tritiated cyclohexanes were assigned by comparison with published proton data,³⁴ and with products from other labelling reactions.³⁵

Alkane exchange occurs by direct dissociation,³⁶ so that the intermediate may appear as in Figure 2E. The relative importance and exact details of the mechanisms of multiple exchange at one carbon, and at adjacent or distant carbons in the same molecule (the αα, αβ or αγ processes, involving multiple points of attachment to the catalyst) have not been clearly determined. In the current work, the differences in exchange rates between alkane positions does not appear to be great, and no new information was gained as to the mechanisms of multiple exchange processes. However, a more detailed ³H NMR study may yield such mechanistic information as was sought in the previous ²H NMR reports,^{32,33} but with more facility due to the better NMR characteristics of the ³H nucleus.

Tritiated Water Exchange. --

While the exchange patterns in a significant number of biologically important compounds^{2,37} and simple monomers^{38,39} have been examined by ³H NMR techniques, there are few reports on the labelling of simple organic substrates such as those in Table 2 by exchange with tritiated water. A previous ³H NMR study of HTO exchanged alkylbenzenes⁴⁰ reported uniform

labelling, but this may have been because the samples were exchanged almost to equilibrium, and any regioselectivity information had been obscured.

The results (Table 2) for orientation of exchange with tritiated water are similar to those reported in Table 1 for heterogeneous platinum-catalyzed T₂ gas labelling - *i.e.* substituted benzene rings gave predominant exchange in less hindered positions (meta and para), and alkyl positions showed some exchange, the extent of labelling decreasing with greater distance from the aromatic ring. Some differences were obvious, however, between the two exchange systems. The deactivation of the ortho positions toward exchange in substituted benzenoid compounds is not nearly as complete when water is the isotope source as when deuterium or tritium gas is used under similar conditions. For example, in Table 1, there are only three substituted aromatic compounds showing detectable exchange with T₂ gas in the ortho position, with the full range of alkylbenzenes and m-xylene showing complete deactivation in any sterically hindered position. In contrast, almost all the HTO exchange results in Table 2 show between eight and 30% of the incorporated tritium in the ortho positions.

The extent of alkyl exchange is generally less when water rather than tritium gas is the isotope source. A feature of the tritium gas results (Table 1) is the very high incorporation in alkyl groups, especially hydrogens on a carbon atom adjacent to an aromatic ring. For example, in toluene approximately 85% of the incorporated radioactivity is in the three methyl positions, leaving 15% in the five aromatic positions. Similarly iso-propylbenzene has 21% in the methine position, n-hexylbenzene has 50% in the α -methylene hydrogens, and m-xylene has almost 80% in the six methyl positions. In contrast, the total amount of tritium in the alkyl portion of straight-chain alkylbenzenes labelled by HTO exchange increases as the number of alkyl vs aromatic protons increases (*c.f.* toluene [3 alkyl H's (15.6%) vs 5 aromatic (84.4%)] with n-heptylbenzene [15 (60.9%) vs 5 (39.1%)], Table 2). Branching of the alkyl substituent or steric hindrance of the aromatic positions upsets this trend, but it is clear that the alkyl and aromatic tritiation rates are more nearly equal in the case of HTO exchange than with T₂ gas. This may be a reflection of a lower sensitivity of the HTO exchange process to the structure of the alkylbenzene substrate.

In HTO exchange reactions the incorporation at α -CH sites is a very significant portion of the total incorporation (Table 2), but is less than that obtained when T₂ is the isotope source. The observed aromatic vs aliphatic, and α -CH vs general alkyl labelling effects must be a reflection of the stability of many possible intermediates under the reaction conditions, but the incorporation pattern may also be influenced by the catalyst sites available to the substrate, and its strength of

adsorption relative to the strength of adsorption of the isotope source, as previously proposed.³⁰

Consideration of the data for aniline and its derivatives (Table 2) gives some interesting information. Aniline is rapidly labelled, and even under fairly mild conditions (60°C) the tritium is almost statistically distributed in the aromatic ring. In the case of *N*-methylaniline, the majority of labelling takes place at the ortho position, with much less in the meta and para positions. This pattern suggests adsorption to the catalyst *via* the nitrogen atom (Figure 2D), as previously proposed in the HTO labelling of a series of pyridine derivatives.^{25,41} The statistical distribution of tritium in aniline also supports this previous work, which showed that true regioselectivity information may only be derived from NMR study in the first 5-20% of the exchange cycle.²⁵ This is especially true for metal catalysts, where our experience is that the distribution of tritium at 50-60 % approach reflects the equilibrium situation. For example, the tritiation of naphthalene has been reported to yield a statistical distribution (α -49, β -51%),² but under conditions where the substrate was less than 50% exchanged the orientation was marked, *e.g.* the β proton peak was the dominant feature in the ¹H NMR spectrum of naphthalene-D₈ exchanged with H₂O.⁴² In contrast to the other anilines, *N,N*-dimethylaniline was preferentially labelled in the meta and para positions, which suggests that the methyl substitution on the nitrogen precludes strong binding of the molecule to the catalyst *via* this atom, and the usual meta/para aromatic labelling pattern results.

In contrast to alkane exchange with D₂ or T₂, the order of reactivity of protons in homogeneous platinum-catalyzed exchange of alkanes with water was reported^{43,44} to be CH₃ > CH₂ > CH. Subsequent work³⁰ with heterogeneous platinum and D₂O confirmed these findings, and showed that the labelling pattern obtained was a function of the quantity of water present in the exchange system. The influence of oxygen and OH (or OD) species adsorbed on the metal surface was considered possible through either steric or long-range electronic effects on the environment of an adsorbed substrate molecule.³⁰ The result shown in Table 2 is the only one obtained using ³H NMR spectroscopy and shows methylene labelling to be slightly faster than methyl exchange. Since the regioselectivity appears to depend on the method of preparation of the catalyst or the platinum to water ratio, a great deal more work will be required before the exchange mechanism is well characterized.

Conclusion

The features of platinum-catalyzed exchange of organic molecules with tritium gas or HTO are now well-established.^{1,6} The results presented here confirm the following principles:

1. Exchange in the aromatic centres of substituted benzenoid compounds takes place most readily in those positions distant from the substituent (*i.e.* less hindered).

2. Alkyl exchange in alkylbenzenes is greatest in the α -CH position and less for carbons more remote from the aromatic centre. Alkyl exchange seems generally more dominant over aromatic when T_2 is the isotope source than for HTO reactions.
3. Exchange in heterocyclic substrates occurs most readily adjacent to the heteroatom. Other substrates which are capable of binding to the catalyst surface, such as aniline or benzaldehyde, also show most exchange in the closest aromatic (ortho) positions.
4. Alkane exchange is facile, and the pattern of labelling seems to favour CH and CH_2 groups over CH_3 . However, the difference in rates is slight under the conditions reported here, and may vary with catalyst preparation, isotope source and reaction temperature.

In general, the present results compare very well with previous work, even though many of the experimental parameters are substantially different. Hydrogenation products from tritium gas reactions usually constituted less than 25% of the radioactivity yield, suggesting that this is a useful exchange technique at low pressures of T_2 (several torr). As expected, products of HTO exchange reactions were free of any hydrogenation or dehalogenation byproducts.

All the orientation results are consistent with aromatic exchange taking place by the dissociative π -complex mechanism,¹⁶ and alkyl exchange in α -CH positions probably occurs by way of the π -allylic process.¹⁸ Alkanes appear to undergo direct dissociation and exchange through a hydrocarbon radical adsorbed on the catalyst surface, as previously described.³⁶ Recent work has made it clear that the adsorption of a substrate onto a catalyst surface can change the structure of the surface,⁴⁵ and the minor differences in regioselectivity of exchange processes with HTO or T_2 as the isotope source may be due to these surface modifications.

Heterogeneous exchange labelling methods are often regarded as unreproducible, and this may be a result of the variety of inferential techniques formerly used for analysis of reaction products. It is clear that the direct observation of labelled positions through the application of ^3H NMR spectroscopy^{2,46} is a much more satisfactory approach. The application of radio-gas chromatography followed by ^3H NMR analyses of tritiated products is a very powerful combination for volatile substrates. In the future, the rigorous determination of isotope incorporation patterns in substrates coupled with the ability to carefully characterize catalyst reaction sites will allow accurate prediction of exchange pathways and catalyst properties.⁴⁷

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