Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXXVI, No. 1

Heterogeneous Palladium-Catalyzed Exchange Labelling of Representative Organic Compounds with Tritium Gas

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Summary

A range of organic substrates was successfully exchanged with tritium gas using $NaBH_4$–reduced palladium oxide or chloride as catalyst. Exchange conditions involved a reaction temperature of 100 °C, a reaction time of 3 days, and products were analyzed by radio-gas chromatography and ^3H NMR spectroscopy. Both aromatic and aliphatic compounds underwent exchange, 18 of the 22 substrates incorporated >35% of the available tritium, and most products showed high radiochemical purity. ^3H NMR analyses showed that both alkanes and the alkyl chains of alkylbenzenes were rapidly and evenly labelled. Some aromatic compounds showed general ring exchange while others showed high specificity. These results for bulk palladium catalyst are strikingly different from those obtained with bulk platinum and supported palladium catalysts. The results are discussed in terms of currently accepted mechanisms of heterogeneous metal catalyzed hydrogen isotope exchange reactions.

Keywords: Heterogeneous palladium, tritium gas, tritium NMR, radio-glc.

Introduction

Early studies of hydrogen isotope exchange of organic compounds were performed before the development of ^2H and ^3H NMR spectroscopy permitted detailed analysis of the regiospecificity of exchange. Recent years have seen these NMR procedures applied to exchange over most group VIII metals, particularly over various physical forms of platinum. However, detailed NMR studies of the exchange of aromatic substrates over palladium metal catalysts have been less well documented. Deuterium exchange studies of aromatic molecules by Kemball and co-workers,[1] and Horrex *et al*[2] relied upon mass spectrometric analyses to provide mechanistic insight, while Buchman has investigated tritiation techniques[3] and used chemical methods to show the selective benzylic exchange. More recently, a number of steroids have been exchanged over supported palladium catalysts, and the benzylic sites of labelling identified by ^3H NMR spectroscopy.[4] Other aromatic substrates containing benzylic positions have been labelled with

CCC 0362–4803/95/010001–14

Received 11 March, 1994
Revised 4 August, 1994

tritium or deuterium and the products analyzed by ^3H or ^2H NMR spectroscopy, including naphthalene derivatives,[5] folic acid and methotrexate,[6] and blocked phenylalanine derivatives.[7] Lockley used ^2H NMR spectroscopy to study the influence of catalyst supports in the palladium-catalyzed D_2O labelling of the benzene ring of sodium benzoate.[8]

Interpretation of the mechanism of exchange in complex molecules would be aided by a study of the exchange of simple model compounds over palladium. Exchange in aromatic compounds, particularly over platinum, has been extensively reviewed[9] and in general results have been interpreted in terms of a dissociative π-complex mechanism.[10] The extent to which the dissociative mechanism is applicable to heterogeneous palladium-catalyzed reactions of aromatic molecules with elemental tritium or deuterium has not been explored in detail.

We now report the tritium gas exchange of simple aromatic and aliphatic organic substrates over unsupported palladium, with purity of products and total radioactivity assessed by radio-gas chromatography and regioselectivity of labelling determined by ^3H NMR spectroscopy. Most of the earlier studies[1,2] of palladium-catalyzed exchange of similar model organic compounds were carried out before ^3H NMR spectroscopy was a readily available technique and details of the regioselectivity of the catalytic exchange reactions were not readily obtainable. This information is important in the verification of proposed reaction mechanisms.

Experimental

Catalyst Preparation. — Heterogeneous palladium metal was prepared by reduction of the oxide or chloride with sodium borohydride. In a typical exchange experiment, palladium oxide or chloride (*ca.* 50 mg, Johnson Matthey) was suspended in distilled water (5 mL), 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. After removal of excess water the metal was suspended in absolute ethanol by repeated washings (3x, 10 mL ethanol).

Exchange Methodology. — Suspended catalyst was transferred by pipette into a side arm breakseal reaction tube described elsewhere,[11] the residual ethanol removed under vacuum, the catalyst degassed and tritium gas (*ca.* 300-500 mCi, 111-185 GBq) admitted to the catalyst. After flame-sealing of the reaction tube, the previously degassed organic substrate (0.2 mL of liquid or 0.2 g of solid) was added by the smashing of the internal breakseal. Reactions were run in a thermostatically controlled oven, usually for 72 hours at 100 °C. After reaction, the products were

isolated by distillation under vacuum, through the breakseal back into the side-arm, which was then cut off the reaction ampoule.

Analytical Procedures. —

Radio-Gas Chromatography. — Volatile compounds were analyzed by radio-gas chromatography.[12] A flame ionization detector (HP5750 Research Chromatograph, HP3373B Integrator) and an ionization 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. — All tritium spectra were obtained with broadband proton decoupling on a Bruker CXP-300 (^{3}H at 320 MHz) instrument. The samples (0.05 to 0.2 mL) were made up to 0.5 mL with starting material or a solvent such as carbon tetrachloride in a 5 mm NMR tube and protiated TMS (10 μL) added as reference material. The tubes were then flame-sealed and placed inside a 10 mm NMR tube with D_2O or C_6D_6 in the annulus to provide the field-locking signal. Spectra were referenced to a ghost TMS signal generated in the tritium spectrum.[13] ^{3}H spectra were usually acquired with a 30 μs pulse, 8K data points, 3 sec recycle time, sweep width 3000 Hz, and 1-10,000 repetitions. Proton (300 MHz) and deuteron (46 MHz) NMR spectra of standards were obtained as previously described.[14]

Results

A range of simple organic substrates was exchanged with tritium gas at 100 °C over a period of 72 hours, catalyzed by sodium borohydride-reduced palladium (II) oxide or chloride. The results derived from radio-GLC and ^{3}H NMR analyses are shown in Table 1. The percent approach to equilibrium (% Approach) 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 number of observed impurities is noted for each substrate and the amounts are recorded as a percentage of the total observed organic tritium content of the sample. The distribution of tritium in the compounds in Table 1 is expressed as the percent tritium in each magnetically distinct position in the ^{3}H NMR spectrum. The NMR spectral peaks of the cyclohexane derivatives were assigned with reference to proton NMR data of deuteriated cyclohexanes,[15] and by comparison with proton-decoupled natural abundance ^{2}H NMR spectra of the starting materials. A comparison of the ^{3}H, ^{2}H and ^{1}H chemical shifts so obtained is given in Table 2 since a detailed summary of the data for these alkyl and aryl cyclohexanes is difficult to

Table 1 - Heterogeneous Palladium-Catalyzed Exchange of Organic Substrates with Tritium Gas.

Compound	Activity (mCi/mL)	% Approach to Equil. [a]	Impurities #, %	% Incorporation per Position *o*	*m*	*p*	Other Positions	Aromatic to Alkyl Labelling
Toluene	503	33.6	1, 10.0	<1	6.4	3.0	CH_3-90.6	9.4 : 90.6
Toluene [b]	848	71.3	-	<1	<1	<1	CH_3-100%	0 : 100
Hexylbenzene	1134	75.6	1, 3.3	<1	4.2	2.6	α-CH_2-12.8; β-CH_2-11.2; γ-CH_2-22.4; δ,ε-CH_2-33.2; CH_3-14.1	6.8 : 93.8
Hexylbenzene [c]	764	50.9	3, 10.5	<1	2.2	0.7	α-CH_2-18.0; β-CH_2-17.8; γ-CH_2-19.2; δ,ε-CH_2-19.6; CH_3-22.5	2.9 : 97.1
Nonylbenzene	1030	68.4	1, 3.4	<1	<1	<1	α-CH_2-15.2; β-CH_2-12.6; γ,δ-CH_2-21.6; ε,ϕ-CH_2-20.4; ω-1,ω-CH_2-19.6; CH_3-10.8	0 : 100
Nonylbenzene [c]	560	37.3	3, 11.5	<1	2.8;	1.1	α-CH_2-10.2; β-CH_2-11.6; γ,δ,ε-CH_2-29.4; ϕ,ω-1,ω-CH_2-27.4; CH_3-17.1	3.9 : 96.1
i-Propylbenzene	947	63.1	-	<1	<1	<1	CH-10.8; CH_3-89.2	0 : 100
m-Xylene	1060	70.7	-	<1	<1	<1	CH_3-100.0	0 : 100
Chlorobenzene	415	27.7	2, 63.9	50.2	30.0	19.8		—
Chlorobenzene [b]	80	6.7	1, 26.0	26.0	37.4	36.6		—
Nitrobenzene	17	1.4	-					
Nitrobenzene [d]	775	65.1	-	5.6	50.4	34.6		
Pyridine	728	61.2	1, 0.1				2/6-95.4; 3/5-3.0; 4-1.4	—
Pyridine [b]	902	75.8	1, 0.8				2/6-68.1; 3/5-19.0; 4-12.8	—
Naphthalene	176	11.7	1, 42.0				α-29.6; β-70.4	—
n-Hexane	1847	100.0	-				α-CH_2-30.8; β-CH_2-30.8; CH_3-38.4	—
2,3 Dimethylbutane	1715	100.0	-				CH-16.2; CH_3-83.8	—
Methylcyclohexane	782	52.1	1, 13.5				CH_3-23.7; 1-axial-6.8; 2-ax.-11.4; 2-eq.-19.4; 3-ax.-16.2; 3-eq.-8.4; 4-ax.-6.8; 4-eq.-7.5	—
Ethylcyclohexane	870	58.0	-				CH_3-18.0; CH_2-6.2; 1-ax.-13.2; 2-ax.-12.0; 2-eq.-13.4; 3-ax.-14.4; 3-eq.-9.8; 4-ax.-7.4; 4-eq.-5.6	—
t-Butylcyclohexane	591	39.4	1, 2.7				CH_3-25.5; 1-ax.-7.3; 2-ax.-8.0; 2-eq.-16.0; 3-ax.-17.2; 3-eq.-16.0; 4-ax.-5.4; 4-eq.-4.7	—
Phenylcyclohexane	674	44.9	2, 11.0	0.4	1.0	<1	1-ax.-10.2; 2-ax.-19.2; 2-eq.-16.2; 3-ax.-21.4; 3-eq.-18.6; 4-ax.-6.3; 4-eq.-6.9	1.4 : 98.6
Dicyclohexyl [b]	464	39.0	3, 44.6				1-ax.-14.6; 2-ax.-17.5; 3-ax.-19.4; 4-ax.-10.1; 2,3,4-eq.-38.4	—

Standard reaction conditions: 50 mg pre-reduced PdO, 0.2 mL substrate, 357 mCi T_2 gas, 72 hours at 100 °C

a — See first paragraph of Results section for definition.

b — Reaction conditions: 75 mg pre-reduced $PdCl_2$, 0.3 mL substrate, 357 mCi T_2 gas.

c — Reaction time 36 hours.

d — Reaction temperature 150 °C.

extract from the literature, and for some compounds the ^3H spectra have allowed for resolution of peaks which were reported as overlapping or completely unresolved in previous publications.

Sixteen different substrates were tritiated, and the extent of the labelling after 72 hours at 100 °C varied considerably from 1.4% incorporation in nitrobenzene to 100% in n-hexane and 2,3 dimethylbutane. The specific activities obtained ranged from 17 to 1850 mCi/mL of substrate (*ca.* 8-250 mCi/mmol, 3-93 GBq/mmol), and all but four of the samples showed incorporation of 35% or more of the available tritium, as determined by radio-gas chromatography. The maximum attainable specific activity was limited to *ca.* 250 mCi/mmol by the small quantity of tritium gas used in the reactions.

Radiochemical impurities were detected in 14 of the 22 samples, ranging from <1 to 63.9% of the total sample activity. The detection of byproducts in samples such as n-hexylbenzene and n-nonylbenzene was only achieved by virtue of their radioactivity, as the mass of impurity present in the reaction products was very small. Impurities were usually volatile and chromatographed in proximity to the starting material, as might be consistent with hydrogenation products. The level of radiochemical impurity in both samples of chlorobenzene was significant, and for one of those samples some 60.6% of the activity was present in the dehalogenation product, benzene. This combination of exchange and dehalogenation of an aryl halide might be expected since heterogeneous palladium is often used as a dehalogenation catalyst at higher tritium pressures.[16] In contrast, significant hydrogenation of the benzene ring (*i.e.* production of halocyclohexanes and cyclohexenes) is unlikely, since even with simple alkenes exchange is dominant over saturation at low tritium pressures.[17]

Discussion

The exchange pattern of palladium-catalyzed hydrogen isotope exchange in alkylaromatic molecules reported in Table 1 is characterized by three features:

1. A dominance of alkyl over aromatic labelling.
2. Uniform exchange levels along the alkyl chain of alkylbenzenes.
3. A preference for meta and para rather than ortho exchange in aromatic rings.

Palladium-catalyzed exchange with T_2 or D_2 gas has previously been reported to give a higher proportion of side-chain relative to aromatic exchange than platinum,[1a,1d,2-7,18] and this low ratio of aromatic to aliphatic labelling was also observed in D_2O exchange of alkylaromatics over palladium catalysts.[19] The data in Table 1 emphasize the scale of this effect, and show that exchange in aromatic positions represents less than 10% of total tritium incorporation in all of the

Table 2: Tritium, Deuterium and Proton Chemical Shifts of Substituted Cyclohexanes.

	Isotope	1ax	2ax	3ax	4ax	2eq	3eq	4eq	CH_3	other
Methyl-	^3H	1.313	0.892	1.236	1.130	1.652	1.675	1.629	0.878	
	^2H	1.301	0.862	1.219	1.114	1.640	1.665	1.618	0.862	
	^1H	1.317	0.867	1.200	1.100	1.683	1.717	1.667	—	
Ethyl-	^3H	1.226	0.878	1.208	1.153	1.693	1.730	1.632	0.878	1.107 CH_2
	^2H	1.133	0.856	1.196	1.088	1.679	1.713	1.629	0.856	1.196 CH_2
t-Butyl-	^3H	0.961	0.933	1.199	1.098	1.758	1.758	1.648	0.851	
	^2H	0.947	0.916	1.180	1.080	1.744	1.744	1.628	0.832	
	^1H	0.983	0.900	1.200	1.100	1.767	1.767	1.650	—	
c-Hexyl-	^3H	1.016	0.945	1.168	1.068	1.682 [a]	1.657 [a]	[a]	—	
	^2H	1.031	0.956	1.181	1.100	1.691	1.691	1.691	—	
Phenyl-	^3H	2.326	1.300	1.263	1.126	1.767	1.712	1.629	—	7.162*m* , 7.098*p* , 7.032*o*
	^2H	2.333	1.302	1.302	1.137	1.768	1.711	1.711	—	7.156*m* , 7.084*p* , 7.084*o*

- First set of data for each compound is proton-decoupled tritium NMR chemical shift information (320 MHz, neat solution, ghost referenced).
- Second data set is from natural abundance proton-decoupled deuterium NMR spectra (46 MHz, 2.5 mL substrate, 0.1 mL TMS).
- Proton data are from reference 15, and are corrected for ^2H isotope effect. Data were acquired at 60 MHz, 39 °C, on 20% v/v CCl_4 solutions, with an error of $\pm$ 0.017 ppm.

a. The 2eq and 3eq assignments may be reversed and the 4eq triton was unresolved from either the 2eq or 3eq tritons.

alkylbenzenes studied, in some cases not being detected at all. The extent of the preference for methyl over aromatic exchange in toluene appeared to be distinctly different between pre-reduced PdO and $PdCl_2$ catalysts. Repeated experiments confirmed the distinction shown in Table 1, namely, that the aromatic exchange was undetectable (<1%) over $PdCl_2$ derived catalyst but approached 10% over $NaBH_4$ reduced PdO.

The most directly comparable of the previous studies of exchange with hydrogen gas over palladium metal films or bulk metal were also conducted for mechanistic reasons, namely the D_2 labelling of benzene,[1a] toluene,[2] t-butylbenzene,[1b] and p-xylene.[1c] In these earlier studies, the observed rate of methyl hydrogen exchange was more rapid than aromatic positions in toluene and p-xylene, with the ortho position of toluene much slower than the meta and para positions. In the contrary case of t-butylbenzene the meta and para hydrogens were more readily exchanged than the methyl hydrogens, and these were considered similar to the methyl hydrogens of neopentane.

Both unsupported[3] and supported palladium catalysts[4-7] have been employed in T_2 and D_2 labelling of biochemicals to yield specifically α-CH (benzylic) labelled products. The present results (Table 1) show that extensive and uniform alkyl labelling is possible with bulk palladium, with little variation in the extent of exchange between protons of different alkyl carbons. While alkyl labelling in previous studies has been explained in terms of intermediates involving primary π-complex adsorption and π-allylic exchange (Figure 1A),[2,10,20] the present results (Table 1) are more readily discussed in terms of direct adsorption of the alkylbenzenes *via* the alkyl substituents (Figure 1B), with ring adsorption playing a minor role. Initial adsorption may occur at any of the alkyl carbons. The observed pattern is also in strong contrast to the pronounced α-CH exchange observed for both HTO and T_2 labelling over bulk platinum catalysts,[11] in which the π-allylic mechanism seems to be clearly required. We interpret the current results to mean that the exchange of long-chain alkylbenzenes over bulk palladium occurs *via* rapid interchange between mono-, di- and possibly tri-adsorbed alkyl species (*e.g.* the species in Figures 1B, 1C and 1D), as previously invoked to explain extensive multiple exchange in alkanes.[21] Hence the alkyl chain of alkylaromatic molecules reacts with the catalyst in essentially the same manner as would an alkane.

It is not clear why this general exchange of alkyl groups in palladium-catalyzed exchange has not previously been emphasized. In the case of tritium labelling experiments over palladium black,[3] the substrates were usually drug candidates which contained only an α-CH or CH_2, with no further saturated carbons in the chain, thus yielding the phenomenon unobservable. Uniform alkyl labelling may be suppressed on supported palladium catalysts, especially at low metal

coverages, if the mechanism depends on the formation of αβ-diadsorbed intermediates and requires ensembles of metal atoms.

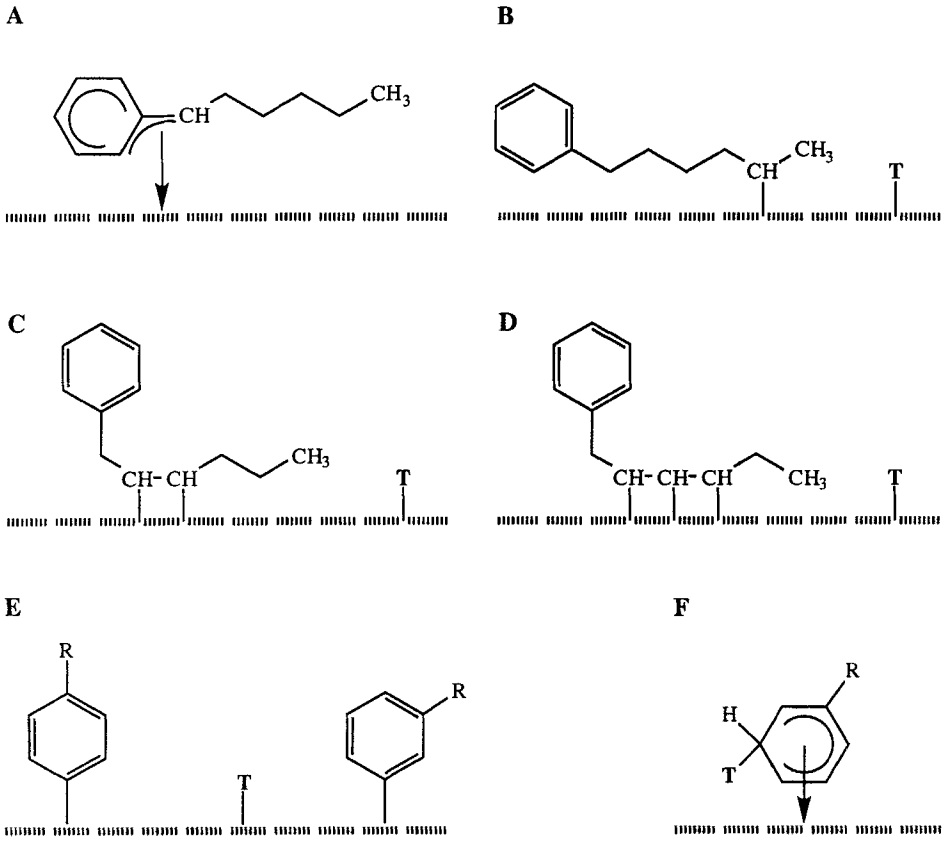

Figure 1: Possible reaction intermediates in heterogeneous palladium catalyzed exchange. (A). π-Allylic intermediate for alkyl exchange, (B). σ-Bonded intermediate for exchange in the alkyl chain of an alkylbenzene, (C). αβ-Diadsorbed alkyl exchange intermediate, (D). αβγ-Triadsorbed alkylbenzene, (E). Dissociative π-complex intermediates, (F). Associative π-complex intermediate.

Where aromatic exchange does occur (Table 1) over reduced bulk metals, the initial step is believed[10] to involve π-complex adsorption, and subsequent exchange may take place through either a dissociative (Figure 1E) or an associative (Figure 1F) intermediate. The meta/para orientation observed for many aromatic molecules labelled over platinum has previously been

advanced as evidence that labelling proceeds *via* the dissociative mechanism, and it has been assumed that this would be true for all the Group VIII metals. However, most of the supporting evidence for the dissociative mechanism has involved D_2O or HTO exchange reactions over bulk platinum, and may not be directly transferable to the current discussion (*i.e.* palladium catalyst, T_2 isotope source). In a previous palladium study where reaction conditions involved higher T_2 gas pressure (1 atmosphere) and lower temperature (RT) predominantly ortho ring exchange was observed in toluene, while >90% of incorporated tritium was in the methyl group.[22] It is not clear which of the reaction parameters contributed to this vastly different aromatic labelling pattern, but it is difficult to interpret this dominance of the ortho position in the aromatic exchange on the basis of a dissociative mechanism.

In chlorobenzene, a molecule in which the labelling must be entirely in the aromatic ring, the distribution of tritium showed a slight enhancement of the ortho positions (per H atom) over pre-reduced PdO and showed a slight deactivation of the ortho positions over pre-reduced $PdCl_2$ (Table 1). This contrasts with previously published platinum results where very marked deactivation of the ortho position was observed in exchange with both tritium gas[11] and tritiated water.[23] This result suggests that the steric effect of bulky substituents, assumed to dominate the exchange pattern in platinum catalysis of aromatics, may be of less significance in palladium exchange. A possible indication for slight ortho deactivation on palladium metal films in exchange of chlorobenzene and bromobenzene with deuterium gas was observed in the early studies of Kemball *et al.* over various metals[1c] but the accuracy of the analytical methods available at that time precluded unequivocal statements. The present work clarifies the difference between platinum and palladium in halobenzene exchange catalysis and this distinction may well extend to the mechanism by which the aromatic rings of many substrates are exchange labelled on the two metals. One of the strongest arguments used in support of the π–dissociative mechanism for aromatic exchange over platinum catalyst is the observation of a strong steric effect on the regioselectivity of labelling.[10,23] Since there appears to be little steric effect in several of the present results, we do not see as clear a case for assertion of the π–dissociative mechanism over the alternative π–associative scheme.

The exchange of nitrobenzene over palladium is slow at 100 °C but facile at 150 °C. The ortho positions are strongly deactivated and the exchange per hydrogen atom is slower in the meta than the para position. This result parallels that for platinum exchange[11] and is in accord with a previous study of nitrobenzene exchange with both tritium gas and tritiated water over several

metals.[24] The orientation result is interpreted in terms of a π–dissociative mechanism, in which the steric influence of the bulky nitro substituent appears to exert its hindering influence beyond the ortho position to the meta site.

Exchange in pyridine occurs predominantly at the positions adjacent to the nitrogen atom (2,6 positions) over both pre-reduced PdO and $PdCl_2$. This exchange pattern is that previously observed in the equivalent platinum exchange system[11] and in exchange of pyridine with tritiated water.[25] A similar pattern of exchange has been observed with D_2 over a powdered platinum catalyst at 100 °C.[26] An investigation of H-D exchange in pyridine over a Pt(110) single crystal surface using high resolution electron energy loss spectroscopy (HREELS) likewise showed exclusively 2,6 exchange.[27] This highly specific exchange pattern suggests an exchange mechanism involving formation of an adsorbed intermediate by charge transfer from the nitrogen atom and π-electrons of the aromatic ring. These results and issues have been discussed in detail for platinum,[25,27,28] and a π–dissociative mechanism was favoured.[25] It is apparent that the same mechanism operates on the bulk palladium catalyst, and the 2 and 6 positions of the adsorbed pyridine molecules are close to the metal surface, where they are ideally placed for exchange labelling.

The slow exchange of naphthalene parallels that with D_2O over heterogeneous palladium.[29] A considerable yield of one byproduct was observed and consideration of the several peaks in the alkyl region of the ^3H NMR spectrum (between 0.5 ppm and 2.1 ppm) leads to the conclusion that hydrogenation to decalin occurred. Hydrogenation of one ring to give tetralin would lead to resonances in the 1.8 and 2.8 ppm region, but since these were not detected, tritiated tetralin was not a significant reaction product. Naphthalene was labelled most extensively in the β position, but the degree of specificity (70.4% β) was less than that previously reported for platinum catalyzed exchange of naphthalene with tritium gas (90.8% β).[11] Again steric effects appear to be less important in the palladium catalysis.

Alkanes undergo facile exchange on these palladium catalysts and in general for straight, cyclic and branched alkanes, the incorporated tritium is distributed fairly evenly throughout the molecules. The relative exchange rates (per hydrogen atom) between methyl, methylene or methine positions show no consistent pattern over the various alkanes. The probabilities of primary and secondary C-H bond cleavage in propane have been calculated[30] and these indicate a slight preference for secondary C-H activation. Kemball and co-workers have reported detailed studies of multiple exchange of alkanes with deuterium over palladium films[31] and over supported

palladium.[32] It was concluded that palladium is the most effective metal for multiple exchange, which proceeds by an αβ-process rather than through αα- or αγ- intermediates. A theoretical model in support of this conclusion has been developed recently.[33] The current observation that tritium is distributed generally throughout the alkanes is consistent with a process in which the interconversion of αβ-intermediates in a multiple exchange process is rapid.

Conclusions

The isotope distributions reported in this study show several differences between heterogeneous palladium and the more widely studied platinum as hydrogen isotope exchange catalysts. A number of the labelling patterns are unique to palladium, and comparison of the present results with those of earlier studies indicate that this uniqueness is a function of both the particular metal and its physical form. The present results lead us to propose the following features for palladium black catalyzed exchange with T_2:

- alkyl exchange will dominate ring labelling in alkylbenzenes.
- alkyl groups on aromatic rings and in alkanes will be readily and uniformly labelled.
- aromatic rings will be preferentially labelled in the least hindered positions.
- molecules containing heteroatoms are likely to be most labelled adjacent to the heteroatom.
- under conditions of high substrate to T_2 molar ratio (*ca.* 250:1) hydrogenation of aromatic substrates will be a minor factor.

The absence of any clear steric effect in the exchange of chlorobenzene, and the slow labelling of naphthalene are not readily interpretable in terms of the π-dissociative exchange mechanism previously proposed for platinum systems. However, the strong meta/para regioselectivity of exchange in nitrobenzene and the alkylbenzenes are as observed in platinum catalysis, and are consistent with the π-dissociative mechanism.

The dominance and uniformity of alkyl exchange in alkylbenzenes leads us to propose direct dissociative adsorption involving an alkyl C-H bond for those substrates, and the lack of any α-CH preference mitigates against the operation of a π-allylic mechanism in these reactions.

The importance of the physical form of palladium catalysts was clearly illustrated in a recent publication[8] where the aromatic exchange pattern could be changed substantially [*i.e.* from 96% (meta plus para): 3.7% (ortho) to >99% (ortho)] by changing from palladium black to 1% Pd/C catalyst. Thus we believe there are many properties of both bulk and supported palladium catalysts which are incompletely characterized in terms of their influence on hydrogen isotope exchange reactions.

A full understanding of the mechanism of the hydrogen isotope exchange catalysis requires a detailed knowledge of the structure of the active metallic site, the nature of the species adsorbed at that site[34] and the manner in which the structure of the catalytic site may be influenced by the adsorbate.[35] It is probable that palladium differs from platinum in several of these respects, and it is important to analyze exchange products by a direct technique such as ^{2}H or ^{3}H NMR spectroscopy to gain insight into the subtle effects of the reaction environment on regioselectivity.

Acknowledgements

We thank the Australian Research Council and the Australian Institute of Nuclear Sciences and Engineering for their support.

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