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Preliminary communication

HYDROGEN–DEUTERIUM EXCHANGE REACTIONS CATALYZED BY ZEROVALENT PHOSPHINEPALLADIUM COMPLEXES

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Summary

Complexes of the type $[Pd(PR_3)_n]$ (n = 3 or 4), which may be conveniently generated in situ, catalyze hydrogen–deuterium exchange reactions between D_2O and various organic substrates, at ambient temperature. The reactions are most rapid for nitroalkanes, where exchange occurs exclusively at the C(1) position and allows the isolation of specifically deuterium-labeled compounds.

We have recently shown that the reactions of tertiary phosphines with certain cyclopentadienyl complexes of palladium and platinum involve hydrogen–deuterium exchange between the hydrogen atoms of the ring and a suitable deuterated solvent [1]. It was found that zerovalent tertiary phosphine complexes were formed during the reactions and their presence, along with adventitious moisture, contributed to the overall exchange process. We have now been investigating the role of zerovalent palladium complexes in hydrogen–deuterium exchange reactions of organic substrates and our preliminary results are presented here.

Since our previous studies had shown that H–D exchange occurred readily in acetone-d_6 [1], we carried out our initial reactions in acetone-d_6 to which 10% D_2O by volume was added. The complexes $[Pd(PBu^n_3)_3]$ and $[Pd(PMePh_2)_4]$ were isolated from the reactions of $[Pd_2(\mu\text{-}Cl)_2(\eta^3\text{-}C_3H_5)_2]$ with the appropriate tertiary phosphine [2], or were more conveniently generated in situ by reaction of $[Pd(\eta^5\text{-}C_5H_5)(C_6H_4N{=}NC_6H_5)]$ with PR_3 [1]. Thus, $[Pd(\eta^5\text{-}C_5H_5)(C_6H_4N{=}NC_6H_5)]$ (approx. 0.03 mmol) was dissolved in $(CD_3)_2CO/D_2O$ (0.5 ml) and the organic substrate was added. Upon introduction of the tertiary phosphine (0.12 mmol), the zerovalent complex $[Pd(PR_3)_4]$ is generated immediately and the H–D exchange process is initiated. In the case of nitromethane as substrate and PBu^n_3, the exchange proceeds significantly in time of mixing, as mon-

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itored by ^1H NMR spectroscopy, and for CH_3NO_2/Pd ratios up to 20 exchange is complete within one hour at ambient temperature. For a 100/1 ratio it is essentially quantitative after 24 h. In the ^1H NMR spectrum the signal at δ 4.4 ppm due to CH_3NO_2 diminishes while the resonances at δ 2.1 and 3.5 ppm, due to CHD_2COCD_3 and HDO respectively, increase in intensity. During the reaction the singlet at δ 4.4 ppm is partly split, indicating the intermediate formation of the partially deuterated species.

The ability of the zerovalent palladium complex to catalyze the exchange process is dependent on the nature of the tertiary phosphine and decreases in the order $PBu^n_3 > PMePh_2 > PPh_3$, which parallels the order of decreasing nucleophilicity [3]. In the case of $[Pd(PPh_3)_4]$ the exchange between CH_3NO_2 and D_2O is very slow, and when $P(OMe)_3$ is added to a solution of $[Pd(\eta^5\text{-}C_5H_5)(C_6H_4N{=}NC_6H_5)]$ and CH_3NO_2 exchange is again very slow at ambient temperature.

Although some protonation of $(CD_3)_2CO$ does occur in these reactions, the use of ketones as substrates (and hence in much lower concentrations) leads to only very slow H—D exchange at ambient temperature. Using $[Pd(PBu^n_3)_4]$ we have found the following order of decreasing rates of H—D exchange for organic substrates: $RNO_2 \gg RCN > R_2CO \gg RCOOR, RX, ROR$. An exception to this order is acrylonitrile which undergoes H—D exchange extremely rapidly, but this case is likely to be complicated by hydration and polymerization reactions [4—6]. It has been shown that $[Pt(PEt_3)_3]$ catalyzes H—D exchange between ketones and D_2O in THF solution at 80°C [6], and the palladium(0) system is also likely to be much more reactive under such conditions.

The rate of exchange might be expected to be related to the pK_a value of the substrate involved, but no such simple relationship is found. The pK_a values for some of the substrates are as follows: CH_3NO_2 (pK_a 10.6), CH_3CN (25), $(CH_3)_2CO$ (20) and $CH_3CO_2C_2H_5$ (25). The low value for nitromethane is consistent with the rapid exchange observed for the nitroalkanes, but CH_3CN undergoes exchange much more rapidly than ethyl acetate although they have identical pK_a values [7]. Conversely, acetylacetone has $pK_a = 9$ but shows no visible sign of H—D exchange by ^1H NMR spectroscopy. In this case at least, the situation may be complicated by coordination of the substrate, or its corresponding anion.

In the presence of excess D_2O (and $(CD_3)_2CO$) complete deuteration of nitromethane occurs upon introduction of $[Pd(PBu^n_3)_4]$, but for the higher nitroalkanes deuteration occurs only at the C(1) position. Thus, for nitroethane and 1-nitropropane the quartet at δ 4.6 ppm and the triplet at δ 4.5 ppm, respectively, disappear upon treatment with $[Pd(PBu^n_3)_4]$ in $(CD_3)_2CO/D_2O$; for nitroethane the methyl resonance becomes a singlet, although this is largely obscured by the tributylphosphine multiplets, and for 1-nitropropane the multiplet at δ 1.7—2.1 ppm due to the C(2) hydrogens becomes less complex on deuteration at C(1), although the signal is again partially hidden by the broad PBu^n_3 resonances. The septet at δ 4.6 ppm in 2-nitropropane vanishes upon similar treatment and the doublet at δ 1.5 ppm becomes a single line.

Thus, it is possible to prepare selectively deuterated nitroalkanes by this method. In a typical experiment, 1-nitropropane (8.2 ml) was mixed with D_2O (30 ml), and ethanol (5.4 ml) was added as co-solvent. ($[Pd(\eta^5\text{-}C_5H_5)(C_6H_4N{=}NC_6H_5)]$ is insoluble in water, whereas 1-nitropropane is only slightly soluble, and a co-solvent was deemed necessary. Since acetone contains six hydrogen atoms which may exchange with D_2O, ethanol was chosen since exchange at the hydroxyl function only should occur). $[Pd(\eta^5\text{-}C_5H_5)(C_6H_4N{=}NC_6H_5)]$ (0.33 g), followed by PBu^n_3 (0.93 ml, 4 mol equiv.), was introduced and the solution was stirred under nitrogen for 48 h. The ethanol was then removed by rotary evaporation and the residue was extracted with diethyl ether. The ether layer was separated, dried over Na_2SO_4, and the ether was removed by rotary evaporation. The pure product was obtained by distillation at atmospheric pressure. Typically yields of 80—90% were achieved. The product was shown to be deuterated at the C(1) position to the extent of approximately 90%, by integration of its ^1H NMR spectrum and by consideration of its mass spectrum [8].

It has been shown that $[Pt(PEt_3)_3]$ reacts with water by oxidative addition to give $[PtH(PEt_3)_3]^+OH^-$ [6,9], and a mechanism involving base catalysis has been proposed for the H—D exchange in ketones catalyzed by $[Pt(PEt_3)_3]$ [6]. Our attempts to promote H—D exchange in 1-nitropropane using NaOD in D_2O have been unsuccessful, although this could be due to solubility effects. This result, however, together with the extremely low conductance observed for the related $[Pd(PEt_3)_4]/H_2O$ system ($[Pt(PEt_3)_n]/H_2O$ (n = 3 or 4) in pyridine yields the 1/1 electrolyte, $[PtH(PEt_3)_3]^+OH^-$) [6], suggests a different mode of operation for the palladium(0) system. This may simply mean the existence of ion pairs or, in the most extreme situation, coordination of the hydroxide to the metal center; clearly the equilibrium lies further to the left for palladium than for platinum in equation 1.

$$[MH(OH)(PR_3)_2] \underset{-PR_3}{\overset{+PR_3}{\rightleftharpoons}} [MH(PR_3)_3]^+\text{---}OH^- \rightleftharpoons [MH(PR_3)_3]^+OH^- \qquad (1)$$

Alternatively, the H—D exchange may occur by initial oxidative addition of the substrate C—H bond, followed by exchange with D_2O:

$$PdL_n + R\text{—}H \rightleftharpoons HPdRL_n$$

$$HPdRL_n + D_2O \rightleftharpoons DPdRL_n + HDO$$

$$DPdRL_n \rightleftharpoons PdL_n + R\text{-}D$$

The system described above provides a very mild route to partially deuterated nitroalkanes, and under more vigorous reaction conditions will doubtless lead to the deuteration of many other, less activated, classes of organic compounds.

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