Tetrahedron Letters,Vol.26,No.11,pp 1375-1378,1985 0040-4039/85 \$3.00 + .00
Printed in Great Britain

TRITIUM EXCHANGE LABELING OF COMPOUNDS CONTAINING $-NO_2$, -I, -C=C-, AND -C=O GROUPS

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Abstract: A new method of exchange labeling of compounds containing hydrogen-sensitive groups with adsorbed tritium on supported metal catalysts, is discussed.

In an earlier publication[1], we reported that halogenated aromatics when exposed to a tritium plasma from microwave discharge activation (MDA) are tritiodehalogenated and tritium saturated in the phenyl ring. When labeled with gas-phase-generated tritium atoms benzene and toluene yield predominantly $[^3H]$cyclohexane and $[^3H]$methylcyclohexane, but when labeled with adsorbed tritium on supported metal catalysts, give almost exclusively $[^3H]$benzene and $[^3H]$toluene[2]. In this communication, we report the use of adsorbed tritium on supported metal catalysts for labeling nitrocyclohexane, cyclohexanone, cyclohexene, iodobenzene, 3-iodotoluene and 2-iodothiophene without causing their reduction and ipso substitution. In view of the sensitivity of the $-NO_2$, -I, -C=C-, and -C=O groups towards hydrogenation[3], their inertness towards activated adsorbed tritium is noteworthy. No reports have appeared in the literature on direct labeling of these compounds with tritium.

Table 1 lists the relative radiochemical yields of labeled products and by-products from nitrocyclohexene, cyclohexanone, cyclohexene, iodobenzene, 3-iodotoluene, and 2-iodothiophene. These compounds were selected for their sensitivity towards hydrogen and for their ease of analysis. The H-T exchange labeling is efficient; activities of many samples were in the range of multimillicuries. The values given in Table 1 refer to relative radiochemical yields of the labeled products obtained on SE-30 column, which gives generally higher values (range: -6 to 40%) than Carbowax-20M column, probably due to difference in polarity (column and substrate) and their uneven tritium back-exchange at high temperatures[2].

Exchange reaction between substrate and activated adsorbed tritium species occurs at the surface of the catalyst, involving in sequence dissociative adsorption of the substrate, H-T exchange, and desorption of the labeled product[4]. The H-T exchange is only effective with activated adsorbed tritium species. Without MDA, Ni catalyst on alumina-silica support even when exposed to considerably higher T_2 pressure than normally used, showed no H-T exchange activity.

Table 1. Maximum Percent Yields[a] of Labeled Substrates and Major Impurities in Reactions with Active Adsorbed Tritium on Supported Metal Catalysts on SE-30 Column

Metal Catalyst	Nitrocyclohexane	Cyclohexanone	Cyclohexene	Iodobenzene	3-Iodotoluene	2-Iodothiophene
A. Alumina(I) group						
Pt + I	91.70	73.78	37.63-G[b]	38.54-A 7.23-B	n.i.[c]	5.35
Pd + I	95.83	75.83	73.98	n.i.	———	23.80
Rh + I	95.68	75.77	44.56-K 25.98-G	n.i.	5.96	27.29
Ru + I	76.91	77.63	6.65-J 9.62-F	n.i.	n.i.	8.75
plain I	19.00	78.92	n.i.	n.i.	n.i.	14.63
plain I, act.[d]	37.77	85.65	n.i.	n.i.	11.78-H	9.07
B. Alumina-silica (II) group						
Pt + II	29.89	86.85	15.56 72.11-D	7.37,91.04[e] 7.23-B	76.65	52.87
Pd + II	47.12	87.06	68.56 8.12-A 7.19-D_2	2.76	49.61	81.84
Rh + II	10.80 19.12-I	82.14-F	18.99 67.66-D_1	48.74 3.65-C	50.99	69.17
Ru + II	31.68	———	25.48 70.86-D	23.41-K 17.54-E 11.69-C	68.5 5.22-C 3.10-E	———
Ni + II	61.10	54.85	5.17 75.34-D	77.55	69.46	63.90
plain II	n.i.	32.04	0.88 33.00-D	n.i	n.i	68.21
plain II, act.[f]	9.96 10.49-L	40.80	12.83 57.40-D	2.76	79.7	67.75
C. Activated carbon (III) group						
Pd + III	n.i.	65.51	29.21-A	68.15-A	———	34.39
Pd + III, act.[d]	29.73	73.37	n.i.	———	n.i.	n.i.

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[a] The yield was based on the peak area in the radiochromatogram, and the recovery of the injected radioactivity was, in general, above 90%[2].

[b] The capitol letters refer to identified impurities, corresponding to the following: A = cyclohexane, B = cyclohexene, C = benzene, D_1 = dimer 1, tricyclo[6,4,0,$0^{2,7}$]dodecane, D_2 = dimer 2, tricyclo[6,4,0,$0^{2,7}$]dodec-3-ene, D = D_1+ D_2, E = toluene, F = cyclohexanol, G = 2-cyclohexen-1-ol, H = 3-methyl-2-cyclohexen-1-ol, I = cyclohexanone, J = 2-cyclohexen-1-one, K = 3-methyl-2-cyclohexen-1-one, L = cyclohexylamine, M = iodocyclohexane. A possible source of the methyl group was from tritiated methane, a likely trace contaminant in T_2 gas.

[c] The abbreviation, n.i.,indicates that either no substantial radioactive peaks appear in the radiochromatogram or the peaks have not been identified.

[d] Activated by heating at 400°C in a stream of hydrogen for 24 hours.
[e] Obtained by using a different labeling apparatus.
[f] Activated by heating at 600°C in hydrogen for 1.75 hours.

We investigated alumina (I), alumina-silica (II), and activated carbon (III) alone and as catalyst support to transition metals. I and II differ in acidity, distribution of OH groups, and reactive sites for accepting T atoms[5] while III has hydrophobic surfaces. On their own, after T exposure, I and II catalyze H-T exchange between adsorbed tritium and nitrocyclohexane, cyclohexanone, 2-iodothiophene to yield the labeled substrates. Hydrogen activation of II enhances its additional ability to catalyze the H-T exchange between 3-iodotoluene and adsorbed tritium. It also increases the yield of [^{3}H]cyclohexene and its dimer from cyclohexene. Alumina (I) catalyzes no dimer formation from cyclohexene but forms [^{3}H]cyclohexen-1-ol instead. On its own, after T exposure, activated carbon (III) cannot effect any H-T exchange.

When the surface characteristics of supports I and II were modified by transition metals, their exchange efficiency was increased many times so that they acquire the ability to label a large number of compounds, such as cyclohexanol, phenol, bromophenol, bromotoluenes, bromocyclohexane, chlorotoluenes, iodocyclohexane, iodotoluenes, iodohexane and 3-iodothiophene[2].

The values in Table 1 reflect inter-support and inter-metal differences of the catalysts. [^{3}H]nitrocyclohexane and [^{3}H]cyclohexanone are formed on transition metals plus I or II but higher labeling efficiency prevails with the former group of catalysts. Labeled iodobenzene, 3-iodotoluene and 2-iodothiophene are formed more readily with the latter group of catalysts. Cyclohexene reacts with adsorbed tritium on (Ni + II) to yield, in addition to [^{3}H]cyclohexene, labeled cyclohexene dimers: [^{3}H]tricyclo[6,4,0,$0^{2,7}$]dodecane and [^{3}H]tricyclo[6,4,0,$0^{2,7}$]dodec-3-ene in high yields[6]. (Pd + II) forms almost exclusively [^{3}H]cyclohexene. In comparison, transition metals + I form from cyclohexene and adsorbed tritium products tentatively identified as [^{3}H]3-methyl-2-cyclohexen-1-ol, [^{3}H]2-cyclohexen-1-ol and [^{3}H]2-cyclohexen-1-one. (Pd + III) reduces cyclohexene to [^{3}H]cyclohexane and dehalogenates and ring-saturates iodobenzene to [^{3}H]cyclohexane.

Not all compounds can be labeled in this manner[2], e.g. nitrobenzene, being an aromatic nitro compound and more sensitive to hydrogen[3b], reacted with adsorbed tritium to yield other labeled products instead of labeled nitrobenzene.

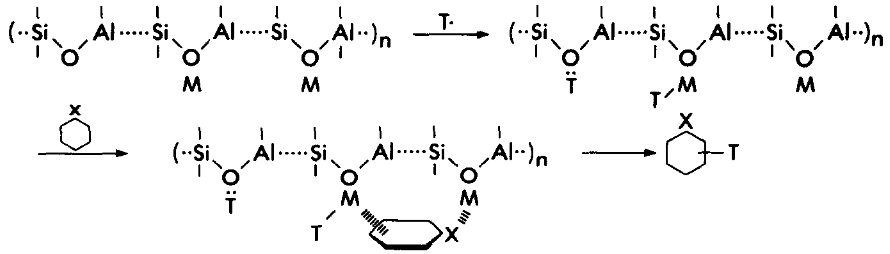

Figure 1. A proposed mechanism for protecting the hydrogen-sensitive groups for direct labeling with activated adsorbed tritium on supported metal catalysts.

Although the lifetime of the activated adsorbed species has not been determined, it remains active for at least 30 minutes in vacuo after the termination of glow discharge[2]. The labeling efficiency is greatly influenced by moisture, extraneous material in the plasma, conditions of the labeling apparatus and the catalyst. Of the compounds studied, the catalytic exchange labeling of iodobenzene is the most susceptible to adverse influences[2].

Apparently, a new mechanism of tritium labeling is involved; it is possible that we are protecting these hydrogen sensitive groups by binding them to metal atoms as ligands so as to make them unavailable for reaction with activated adsorbed tritium (Figure 1). It may also be that the adsorbed tritium is spatially fixed in the adsorbed state so that it can undergo exchange with its immediate neighbors but cannot participate in the reduction of some sensitive groups in distant locations. The surface metal atoms on the catalyst are present in coordination complexes or as metal clusters; its d orbital electrons can overlap with the p orbital electrons of N, O, I atoms and -C=C- bond[7] in the adsorbate molecules. Such complexation and stabilization lead to the direct labeling of H sensitive molecules with tritium.

Acknowledgement. The authors acknowledge research support from NIH CA 33537 (to CTP) and RR 01237 (to R.M. Lemmon, LBL) and thank H. Morimoto (National Tritium Labeling Facility, LBL) for T_2 gas services, G.Y. Cao for discussion, F. Constant of Engelhard Industries Division for plain alumina (I) catalyst support and Camille Sata for technical assistance.

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6. The cyclohexene dimers were identified by comparison of retention indexes with a known analog, tricyclo$[6,4,0,0^{2,7}]$dodec-3,11-diene and its hydrogenated products on SE-30 and Carbowax-20M columns and by analysis of a highly converted sample by GC/MS. The analog was prepared according to D. Valentine et al. (J. Am. Chem. Soc. 86, 5205 (1964)).
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10. Experimental Procedure: Sixteen pellets of the supported metal catalysts were exposed to about 5 torrs of tritium gas in a microwave plasma for 20 minutes according to a previous reported procedure[1]. After removing the excess tritium by evacuation, followed by flushing with He, the tritium-charged catalyst was immediately transferred in air to a vial containing the substrate in a ratio of 3 pellets to 0.1 ml of the substrate. Radioactivity incorporated into the substrate was measured by liquid scintillation counting. Product analysis was by gas-liquid radiochromatography on both SE-30 and Carbowax-20M columns (stainless, 10' length, 1/8" dia.) using a Hewlet-Packard 5880A Gas Chromatograph with Level IV integration. The radioactivity of the column effluent, after mixing with n-propane, was measured with a heated proportional counter at 250°C. The radioactive peaks were integrated with a Tracor-Northern Model 7200 multichannel analyzer, operating in the MCS mode, and the output was by a Teletype Corp. Model 43 keyboard printer. The radioactive components were identified by their retention indexes on SE-30 and Carbowax-20M columns, according to the method described by Buchman et al.[8]

    Supported metal catalysts containing Pt, Pd, Rh, and Ru on alumina and Pd on activated carbon were from Engelhard Industries Division (Newark, N.J.) and those containing Ni, Pt, Pd, Rh, and Ru on alumina-silica were prepared according to Cao and Peng[9], using 1/8" pellets of catalyst support #980-25 (Davison Chemical, Baltimore, MD).

(Received in USA 14 September 1984)