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THE EFFECT OF CATALYTIC REACTION CONDITIONS ON THE INCORPORATION OF TRITIUM IN UNSATURATED COMPOUNDS

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SUMMARY

We have obtained multiple-tritium-labelled 5-α-androstan--3-one, dihydropicrotoxin, dimethyl-propyl-3-chloro-butyl--ammonium chloride, 2,2-di(trifluoromethyl)-3,3-dicyanobicyclohept[2,2,1]ane, dihydroalprenolol, undecanoic acid, dihydro--m,m'-di-tert.-butyl-p-coumaric acid and dihydrofusicoccin. By varying the conditions for the hydrogenation of terminal double bonds one can considerably increase the molar radioactivity of such compounds through isotopic exchange. We discuss some tentative explanations of the effect of the labelling reaction conditions upon the synthesis of compounds with desired properties.

INTRODUCTION

Isotopic exchange[1,2], selective hydrogenation of triple bonds into double bonds[3,4] or of one of several double bonds[5,6] and hydrogenation of multiple carbon-carbon bonds[7-12] are among the most wide-spread methods of introducing the tritium label into biologically active compounds. Platinum[7,11] or palladium[8-10,12] usually serve as catalysts. The usual

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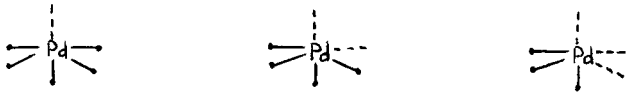
solvents are benzene[13,14], ethyl acetate[15], dioxane[11,12], chloroform[8], methanol[9], ethanol[10], etc. The duration of the reaction and other parameters (temperature, pressure, gas composition, etc.) vary within a very wide range. The efficiency of isotopic exchange is influenced by the temperature of the reaction mixture[16], the nature of the catalyst[16-19] and solvent[16-19], the saturation of the catalyst with hydrogen[18], gas pressure[16-18]. The yield of the labelled end product and its molar radioactivity have proved to be strongly dependent on all these conditions and on the nature of the initial compounds.

It seems to be a question of processes occurring in the hydrogen-catalyst-olefin system. The active centres of a heterogeneous metal catalyst can be represented in the following way[20]:



n=6 n=5 n=4

These structures correspond to the concept of hydrogenation of unsaturated compounds on the face (n=6), edge (n=5) and corner (n=4) of the metallic crystal[21]. The free coordination bonds may be occupied either by solvent molecules or by tritium atoms. These structures differ in selectivity, steric and electron parameters.

The mechanism of hydrogenation on active centres for n=4 can be modelled by considering the hydrogenation steps in the presence of $(Ph_3P)_3RhCl$[22], which forms a dihydride complex. Hydrogenation on active centres for n=5 can be modelled on homogeneous catalysts, which form monohydride complexes[23]. Significantly, if the reduction of olefin occurs in the presence of the dihydride complex, the hydrogenation proceeds quickly and without any by-products[22]. A more involved pattern is observed

in the case of monohydride complexes[23]. The reaction mixture contains the products of double-bond isomerization and migration, with a preponderance of the cis-isomer[23]. The nature of the solvent produces a stronger effect in the presence of such catalysts.

The data obtained in[24,25] allow the process of label incorporation on palladium's active centres (n=4) to be represented in the following way (Diagram 1). The fact that some solvents the molecule of an unsaturated compound incorporates more than two tritium atoms upon hydrogenation is probably due to the ability of these solvents to stabilize monohydride complexes on the catalyst surface and thereby inhibit the formation of dihydride complexes. This should raise the efficiency of isotopic exchange and so considerably increase the molar radioactivity of the reduced compounds.

When alkenes are treated with tritium in the presence of Lindlar catalyst, the hydrogenation rate of non-terminal double bonds is rather low[26]. Apparently, the n=4 active centres are deactivated by lead atoms. In this case both hydrogenation and isotopic exchange can only occur on the n=5 active centres (see Diagram 2). It is not surprising, therefore, that for such catalysts the hydrogenating ability changes in unison with the ability to stimulate isotopic exchange[2]. In the selective hydrogenation of acetylenic compounds one usually employs Lindlar catalyst pre-saturated with hydrogen (Diagram 2), with a catalyst:alkyne ratio of 1:100 (because of the large adsorption capacity of the acetylenic bond, no adsorption of the emerging double bonds occurs until practically nothing remains of the initial compound).

In this work we continue to look at how the conditions of introducing tritium into unsaturated compounds influence the yield and molar radioactivity of the labelled product. We also

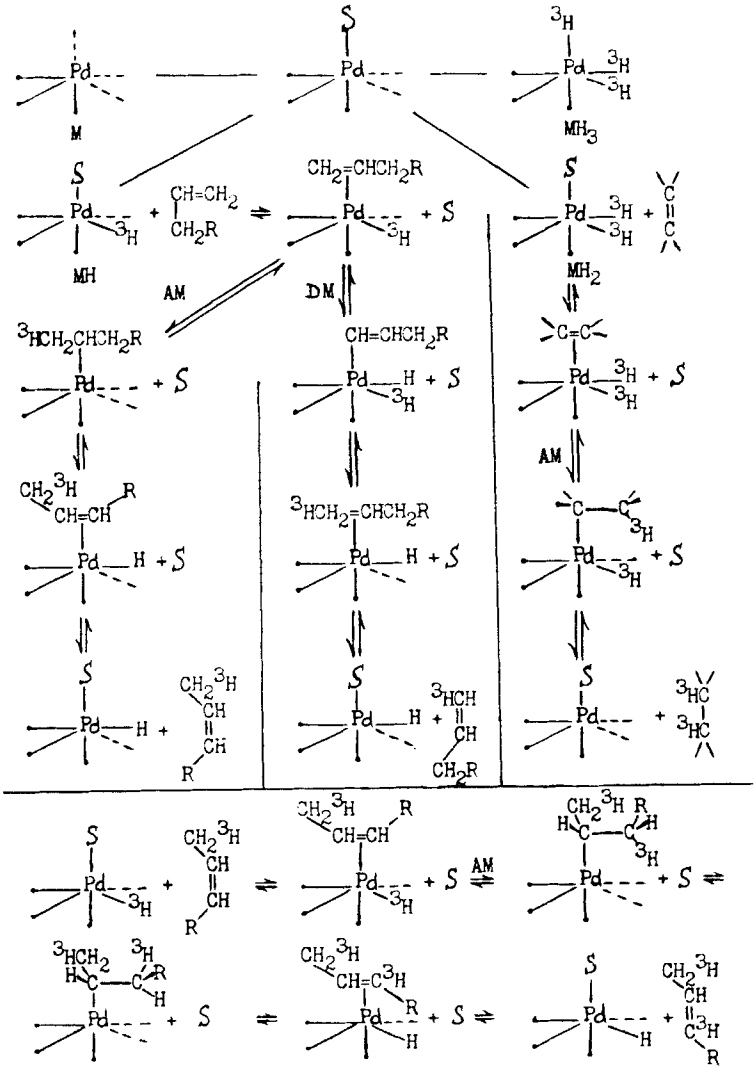


Diagram 1

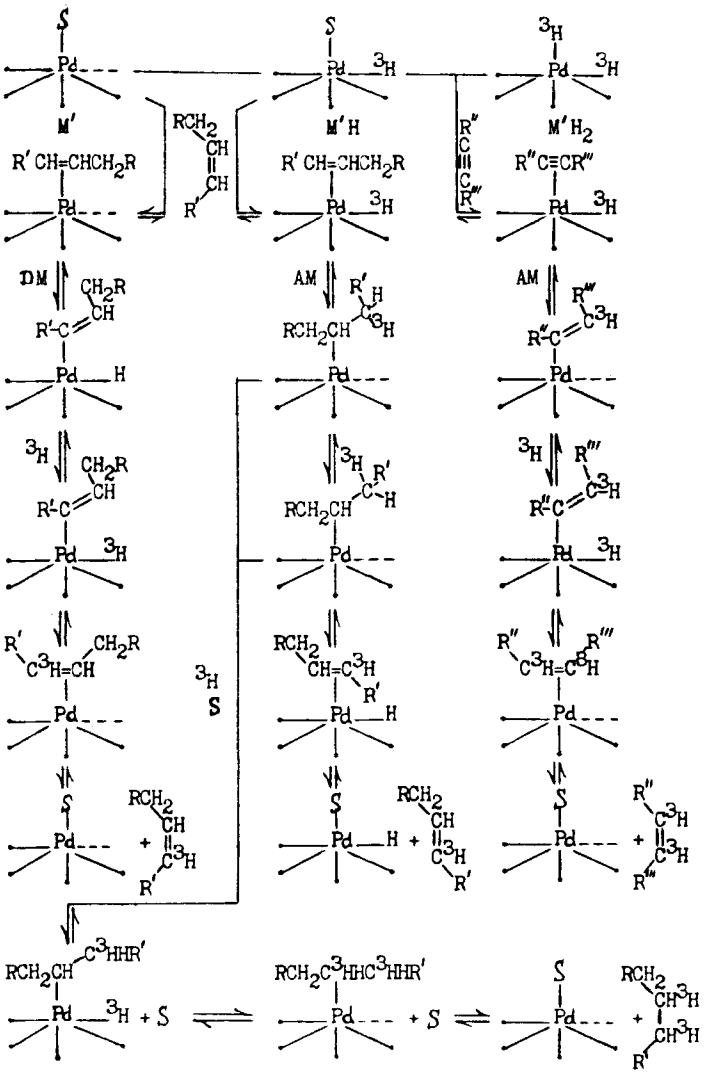


Diagram 2

discuss a possible explanation of the results, based on the above concept of the processes occurring on the catalyst surface.

MATERIALS AND METHODS

We used undec-10-enoic acid ($C_{11:1}$), 5α-androst-16-en-3-one, picrotoxin dimethylallyl-3-chlorobutyl ammonium chloride,

2,2-di-(trifluoromethyl)-3,3-dicyano-bicyclohept[2.2.1]-ene-5, alprenolol, m,m'-di-tert.-butyl-p-coumaric acid and fusicoccine. Solvents and catalysts were prepared and purified by standard procedures. Methylundec-10-enoate ($MEC_{11:1}$) and methyl-m,m'--di-tert.-butyl-p-coumarate (MECA) were obtained according to[27], and bromphenacyl esters according to[28].

Gas-liquid chromatography (GLC) was performed on a CHROM-5 chromatograph (Czechoslovakia) with a 3x1200mm column filled with CHROMOSORB W-AW, 80-100 mesh, phase: 10% SILAR 10C, carrier gas: nitrogen, v=25 ml/min, column temperature 110°C, flame--ionization detector. Mass spectra were recorded on a HITACHI M 80-A mass spectrometer (Japan) equipped with an ion source operating in the electron-shock mode and the secondary-ion (SIMS) mode, and an M-003 data-processing system. Reversed phase high-pressure liquid chromatography (HPLC) was performed on a GILSON chromatograph (France) with a 4.6x250mm column and a MILICHROM chromatograph (USSR) with a 2x60mm column. Radioactivity was measured by a scintillation counter with a tritium registration efficiency of ~30% in dioxane scintillator[29] and with the help of a XX2301 radioactivity flow monitor (Leningrad, USSR).

HANDLING DILUTED TRITIUM

1 mg of substance and 0.1 ml of chosen solvent were placed in an ampoule, 2 mg of catalyst was added, the ampoule was frozen with liquid nitrogen, evacuated and filled with a tritium-protium mixture (1:1000) to a pressure of 400 hPa, then the ampoule was thawed and the mixture was stirred throughout the reaction. Once the reaction was completed, the ampoule was re-frozen with liquid nitrogen, and excess tritium was removed by evacuation. The contents of the ampoule were diluted by

methanol, the catalyst was filtered off, labile tritium was removed through isotopic equilibration with proton solvents followed by their evaporation. The remainder was dissolved in 0.3 ml of acetone, then the solution's concentration was determined by chromatography and its radioactivity was measured by the scintillation counter. In the case of $MEC_{11:1}$ (Figure) the kinetic study was performed in a special ampoule[16]: 10 μl aliquots were taken with a microsyringe, dissolved in 20 μl of acetone and analysed by GLC.

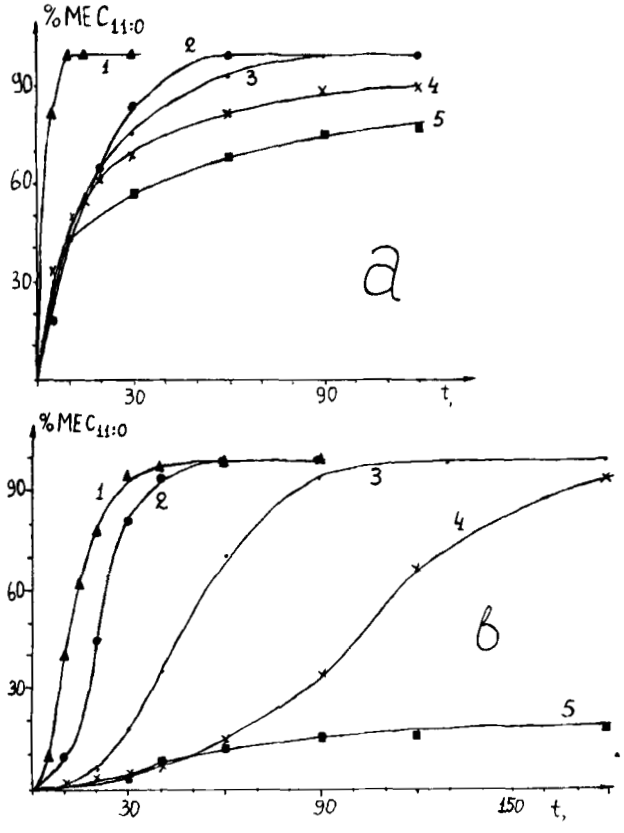


FIGURE. Dependence of the degree of $MEC_{11:1}$ hydrogenation (a) in the presence of 5% $Pd/BaSO_4$ or (b) in the presence of $(Ph_3P)_3RhCl$ on the choice of solvent: 1 - methanol, 2 - ethyl acetate, 3-dioxane, 4-benzene, 5-chloroform.

The effect of the choice of solvent on the molar radioactivity of $MEC_{11:0}$ was examined in the presence of 10% Pd/C, 5% $Pd/BaSO_4$ and 5% PdO/Al_2O_3 (TABLE 1).

TABLE 1. Effect of the choice of solvent and catalyst on the molar radioactivity of methyl undecanoate

Solvent	Catalyst		
	10% Pd/C	5% $Pd/BaSO_4$	5% PdO/Al_2O_3
Dioxane	1.8*	2.1	1.7
Chloroform	2.1	2.4	2.5
Dimethylsulfoxide	0.4	0.07	0.4
Benzene	3.2	3.9	3.0
Heptane	1.3	2.0	1.6
Methanol	0.8	1.2	1.3
Dimethyl formamide	1.2	0.7	1.0
Ethyl acetate	1.6	1.9	2.5
Acetic acid	0.8	1.3	0.9

*Molar radioactivity, TBq/mole

TABLE 2 presents the dependence of the yield and molar radioactivity of dihydro-m,m'-di-tert.-butyl-p-coumaric acid, used as a model compound with non-terminal double bonds, on the duration of the reaction and the choice of solvent.

TABLE 2. Effect of the choice of solvent and the duration of the reaction on the yield and molar radioactivity of m,m'-di-tert.-butyl-p-coumaric acid (catalyst: 5% $Pd/BaSO_4$)

Solvent	Duration (min)	Yield (%)	Molar Radioactivity
Benzene	35	42	1.14
	60	53	1.18
	120	67	1.20
Dioxane	35	30	1.08
	60	39	1.16
	120	53	1.45
Ethyl acetate	35	56	1.52
	60	75	2.03
	120	93	2.04

DEUTERATION AND TRITIATION OF FUSICOCCIN

2 mg of fusicoccin, 4 mg of 5% $Pd/BaSO_4$, 0.4 ml of benzene were placed in an ampoule, frozen with liquid nitrogen and evacuated, then deuterium was introduced up to a pressure of 400 hPa. After defrosting the ampoule was put on a magnetic mixer and the reaction mixture was stirred for 1 h. Then the catalyst was filtered off and the reduced fusicoccin was thrice evaporated with methanol (3 ml every time).

Deuterated fusicoccin was separated on the GILSON chromatograph, 70% aqueous methanol, flow rate 1 ml/min, phase PARTISIL 5 ODS-3, retention time 11.58 min (detection at 210 nm). Analysis on the MILICHROM chromatograph, 65% aqueous methanol, flow rate 0.1 ml/min, phase NUCLEOSIL 5 C18, retention time 6.86 min (detection at 190 nm - 1.00(*); 210 - 1.32; 210 - 1.03; 220 - 0.37).

(*)Relative absorption at the chosen wavelength

The mass spectrum of the deuterated analogue was obtained by the SIMS method[30] involving the ionization of an unmodified molecule by the Xe^+ beam in a glycerin solution with NaCl. Analysis by this method[31] showed the molecule to have incorporated 3.2 deuterium atoms on an average.

The tritiation procedure was similar to that of deuteration. Tritium-labelled dihydrofusicoccin was purified on the GILSON chromatograph, 65% aqueous methanol, flow rate 1 ml/min, phase SERVACHROM 10 C18, retention time 13.47 min (detection by radioactivity). The product was analysed on the MILICHROM chromatograph, 65% aqueous methanol, flow rate 0.1 ml/min, phase SERVACHROM 5 C18, retention time 7.47 min (detection at 190 nm - 1.00; 200 - 1.33; 210 - 1.07; 230 - 0.02). The yield and molar radioactivity values for the labelled compounds are listed in TABLE 3. The radiochemical purity was 95-97%.

DEUTERATION OF METHYL UNDEC-10-ENOATE

The procedure used for the deuteration of $MEC_{11:1}$ was similar to the deuteration of fucicoccin. Deuterated $MEC_{11:1}$ was separated on the GILSON chromatograph, 75% aqueous methanol, flow rate 0.5 ml/min, 3.3x150mm column, phase SEPARON C18 5 μm, retention time 24.1 min (detection at 190 nm). In the GLC analysis the retention time was 5.00 min for $MEC_{11:0}$, 6.77 min for $MEC_{11:1}$. The mass spectrum of deuterated $MEC_{11:0}$ obtained under the above conditions showed the molecule to have incorporated 2.9 deuterium atoms on an average.

TRITIATION OF UNDEC-10-ENOIC ACID

The tritiation of $C_{11:1}$ was performed by a procedure similar to the deuteration of fusicoccin. 1.75 mg of $[^3H]C_{11:0}$ was purified by column chromatography on 0.2 g of silica gel L (Czechoslovakia) (60-100 μm). Successive elution by 10 ml of

benzene, 10 ml of ethyl acetate and 10 ml of ethanol was used. Aliquots of three fractions were methylated by diazomethane and analysed by GLC. The first fraction contained 5% of the saturated acid, while the ethyl acetate fraction had 95% of the acid. The purity of the labelled product was analysed on the MILICHROM chromatograph, 90% aqueous methanol, flow rate 0.1 ml/min, phase NUCLEOSIL 5 C18. Aliquots were analysed in the form of bromphenacyl esters, the retention times for the $C_{11:1}$ and $C_{11:0}$ derivatives were 3.88 min and 4.77 min respectively (detection at 260 nm). The yield and molar radioactivity values for the labelled acid are presented in TABLE 3, the radiochemical purity was 95-97%.

MULTIPLE TRITIUM LABELLING OF DIHYDRODERIVATIVES OF 5α-ANDROST-16-EN-3-ONE, PICROTOXIN, 2,2-DI-(TRIFLUOROMETHYL)-3,3-DICYANO--BICYCLOHEPT/2.2.1/7-EN-5, M,M'-DI-TERT.-BUTYL-p-COUMARIC ACID, ALPRENOLOL, DIMETHYLALLYL-3-CHLOROBUTYL AMMONIUM CLORIDE

The tritiation procedure was similar to that used for the deuteration of fusicoccin; ethyl acetate was the solvent for the first four compounds, methanol for the last two (TABLE 3).

[16,17-$^3H_2$]5-α-Androstan-3-one was purified by TLC on SILUFOL. (Czechoslovakia) in the hexane-ethyl acetate (6:1) system R_f~0.5. The label-carrying zone was extracted by ethyl acetate (10ml x 3). Analysis by GLC, column temperature 260°C, retention time 3.14 min.

Tritium-labelled dihydropicrotoxin was purified by TLC on SILUFOL (Czechoslovakia) in the chloroform-methanol (19:1) system R_f~0.45. The label-carrying zone was extracted by ethyl acetate (10ml x 3). Analysis by HPLC on GILSON, 90% aqueous methanol, 1 ml/min, PARTISIL 5 ODS-3, retention time 3.27 min (detection at 210 nm).

[Propyl-$^3H_2$]dimethyl-propyl-3-chloro-butyl ammonium chloride was purified and analysed by TLC on SILUFOL in the isopro-

panol-0.1N HCl (2:1) system R_f~0.25. The label-carrying zone was extracted by the same system (3ml x 3). The extract was lyophilized, the remainder was dissolved in 1 ml of methanol and filtered through 0.1 g of SERVACHROM 30 μm C18. The phase was washed with 5 ml of methanol, the eluate was evaporated, and the remainder was dissolved in methanol.

[5,6-$^3H_2$] 2,2-Di-(trifluoromethyl)-3,3-dicyano-bicyclohept [2.2.1]-ane was purified by HPLC on GILSON, 70% aqueous methanol, 1 ml/min, SERVACHROM 10 C18, retention time 5.31 min (detection on radioactivity). Analysis by HPLC on GILSON (80% methanol, 1 ml/min, retention time 4,65 min, monitoring at 210 nm; column: PARTISIL ODS-3 4.6x250mm) or MILICHROM (75% aqueous methanol, 0.1ml/min, retention time 5.62 min; column: SERVACHROM 5 C18 2x60mm; relative absorbance: 190nm - 1.00, 200 nm - 1.22, 210nm--0.11)

[Propyl-2,3-$^3H_2$]dihydroalprenolol was purified by filtration through 0.1 g of SERVACHROM C18 30μm. The phase was washed with 5 ml of methanol, the eluate ws evaporated, and the remainder was dissolved in methanol. Analysis by HPLC on MILICHROM, 35% acetonitrile in 0.02 M KH_2PO_4 (pH 2 titration by trifluoroacetic acid) and 0.2% trietylamine, 0.1 ml/min; column; NUCLEO - SIL 5 C18, 2x60mm; retention time - 5.33 min; relative absorbane: 220 nm - 1.00, 240 nm - 0.01, 270 nm - 0.23, 280 nm - 0.08.

[2,3-$^3H_2$]Dihydro-m,m'-di-tert.-butyl-p-coumaric acid (CAo) was purified by column chromatography on 0.8 g of WOELM silica gel (FRG) (carrier-substance ratio 1:40) and eluted with 12 ml of hexane (the solution's radioactivity was 0.22GBq), 12 ml of ether (130 GBq) and 12 ml of ethanol (7.4 GBq). MECAo was analysed by HPLC on GILSON, 70% aqueous methanol, 1 ml/min, SERVACHROM 10C18, retention time 5.31 min (monitoring on radioactivity) or elution with 80% aqueous methanol, 1 ml/min, PARTISIL 5 ODS-3, retention time 4.65 min (detection at 210 nm).

Also HPLC on MILICHROM, 75% aqueous methanol, 0.1 ml/min SERVACHROM 5C18, retention time 5.62 min, relative absorbance: 190 nm-1.00 200 nm-1.22, 210 nm-0.49, 220 nm-0.11.
The GLC analysis of MECAo was performed at column temperature 200°C, retention time 2.87 min for MECAo, 9.27 min for MECA.

TABLE 3. Yield and molar radioactivity of multiply labelled compounds obtained through reduction of unsaturated carbon-carbon bonds

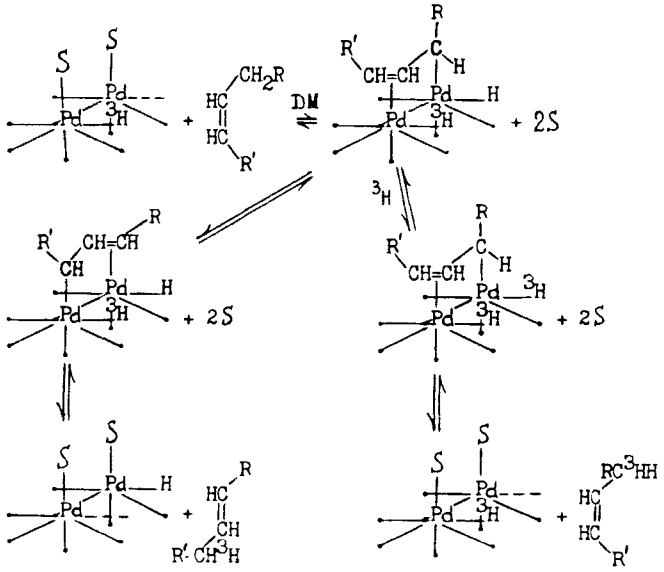
Original compound	Yield(%)	Molar Radioactivity (PBq/mol)
5α-Androst-16-en-3-one	83-85	1.50-1.70
Picrotoxin	75-80	1.30-1.40
Dimethyl-allyl-3-chloro-butyl ammonium chloride	80-90	0.45-0.50
Undec-10-enoic acid	80-90	2.96-3.03
2,2-Di-(trifluoromethyl)-3,3 dicyanobicyclo[2.2.1]-en-5	50-55	0.78-1.07
Alprenolol	80-90	1.96-2.04
Fusicoccin	75-80	3.00-3.10
m,m'-Di-tert.-butyl-p-coumaric acid	96-99	1.70-1.75

RESULTS AND DISCUSSION

With the right choice of hydrogenation conditions it is possible to raise the molar radioactivity of the end product through isotopic exchange (Diagram 1). Indeed, having looked at the way the choice of solvent and catalyst affected the labelling efficiency upon the hydrogenation of $MEC_{11:1}$ (TABLE 1), we found that the tritium incorporation was at its highest in the presence of 5% $Pd/BaSO_4$, with benzene as solvent. Kinetic studies (Figure) revealed a general trend of decreasing $MEC_{11:0}$ synthe-

sis rate in the order: methanol, ethyl acetate, dioxane, benzene, chloroform, in the presence of both heterogeneous (5% $Pd/BaSO_4$) and homogeneous /$(Ph_3P)_3RhCl$/ catalysts. Apparently, the interaction of solvent molecules with the active centres of the n=4 catalysts (Diagram 1) causes the same type of change in their catalytic activity in both cases. The real contribution of the isotopic exchange processes shown in Diagram 1 is also evidenced by the results of deuteration on 5% $Pd/BaSO_4$ in benzene of fusicoccin /$R\text{-}OC(CH_3)_2CH{=}CH_2$/, whose terminal double bond cannot migrate. Mathematical treatment of the mass-spectrometry data hydrogenation not just two (21% yield), but three (22% yield), four (34% yield) and five (6% yield) deuterium atoms.

A similar diagram is proposed in [32] for the processes occurring in the solid-phase (no solvent) protium treatment of 1-butene in the presence of platinum catalysts, though the authors did not consider the processes involved in the dissociative mechanism of adsorption (DM) of the unsaturated compound or the cooperative interaction of the active centres [24] (Diagram 3).



They did consider different types of active centres for catalysts with different degrees of coordinational non-saturation (similar to the structures n=4, n=5, n=6). The paper describes a procedure for quantifying the ratio of the inactive regions on the catalyst surface (n=6) and active centres responsible for direct hydrogenation (dihydride centres), and for isomerization and the formation of semi-hydrogenated forms (monohydride centres).

What determines the metal-hydrogen ratio in the catalyst's active centres? The dissociative chemosorption of molecular hydrogen on metal crystals is known to be followed by a migration of the hydrogen isotopes towards the centres where catalytic reactions take place[33-35]. The efficiency of this process seems to depend on the conditions of the reactions discussed here (hydrogen isotope pressure, temperature, solvent, etc.): in turn, it conditions the preferential formation of the products of isotopic exchange, isomerization and hydrogenation (Diagram 1-3).

For instance, lowered tritium pressure (133 hPa) made it possible to obtain [G-^{3}H]PGF$_{2\alpha}$ with a molar radioactivity of 59.2 TBq/mol and a yield of 30% through isotopic exchange, under DM, in the presence of 5% PdO/Al_2O_3[2] while at a tritium pressure of 400 hPa the double bonds are rapidly hydrogenated -- a process characteristic of adsorption on dihydride centres.

A temperature rise causes the migration of hydrogen isotopes to accelerate, so that the degree of label incorporation in saturated compounds must also grow as centre II gets enriched with tritium (Diagram 4).

This was indeed observed in the labelling of methyl stearate[16,36]. The drop in the molar radioactivity of methyl stearate at temperatures above 37°C[16] is apparently due to a rapid conver-

sion of the monohydride centre (I) into a dihydride centre, where isotopic exchange is impossible under DM.

When the tritium label was introduced into methyl oleate[18,37] through isotopic exchange in the presence of Lindlar catalyst (n=5) the degree of label incorporation under the dissociative mechanism of adsorption proved comparable to the label incorporation under the associative mechanism of adsorption. Apparently the adsorption ability of the active centres (n=5) is well below that of the active centres (n=4), mostly because of steric factors, so that cooperative interactions come to play a more prominent part (Diagram 3). This approach provides an explanation of the high likelihood of label incorporation at the allyl positions of polyenic fatty acids[37].

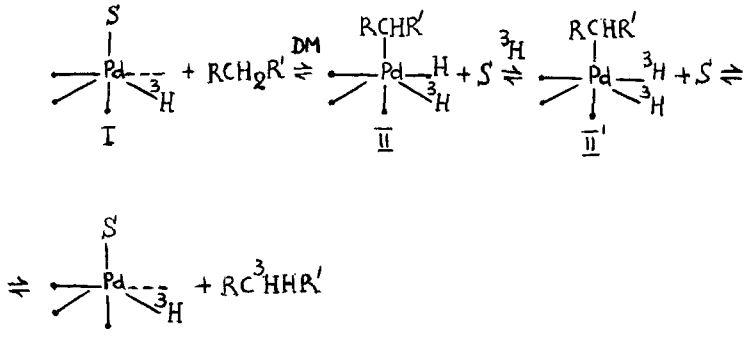


Diagram 4

The study of the effects of catalytic reaction conditions on label incorporation into unsaturated compounds has yielded the following results.

The best solvent for labelling by isotopic exchange on Lindlar catalyst is dioxane[26]: it binds palladium atoms firmly enough, apparently through the free oxygen pairs, and thus prevents the easy formation of palladium hydrides, while it can be displaced by alkene molecules.

For the hydrogenation of compounds with non-terminal double bonds in the presence of 5% $Pd/BaSO_4$, the best results were obtained with ethyl acetate as solvent (TABLE 2). This may mean that the more screened non-terminal double bonds ineffectively displace benzene from the catalyst's active centres, causing a lower final molar radioactivity[38]. Therefore alkenes with sterically impeded double bonds will be reduced with higher yields and better molar radioactivities in non-aromatic solvents.

The conditions evolved for the reduction of unsaturated compounds made it possible to obtain multiple-tritium-labelled biologically active compounds with a yield of 50-99% and a molar radioactivity range of 0.45-3.10 PBq/mol (TABLE 3). The radiochemical purity of the labelled compounds was no less than 95-97%.

Explanations were found for a number of phenomena in the labelling process using the current concepts of the structure and functioning of active centres on heterogeneous catalysts.

This, in turn, led to the optimization of terminal -double--bond hydrogenation conditions, making it possible to obtain labelled biologically active compounds (through reducing one double bond) with molar radioactivities above 3 PBq/mol.

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