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A COMPARISON OF HETEROGENEOUS AND HOMOGENEOUS PLATINUM-CATALYZED EXCHANGE PROCEDURES FOR THE ISOTOPIC HYDROGEN LABELLING OF SYNTHETIC HORMONES AND STEROIDS[1].

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Two type one-step methods involving radiation-induced or catalytic procedures are currently available for the general deuteration and/or tritiation of synthetic hormones and steroids[2]. Of the radiation-induced techniques, the Wilzbach gas exposure procedure[3] is the most useful but is limited only to tritium. Where possible, the catalytic method involving exchange with isotopic water in the presence of heterogeneous Group VIII transition metals is to be preferred. Platinum is the most active metal catalyst for exchanges of this type. Heterogeneous exchange suffers from certain disadvantages, namely: (a) the reaction occurs on a metal surface and is thus susceptible to conventional surface poisons (b) rate of exchange is relatively slow and is preferably performed in a vacuum sealed ampoule at temperatures up to 180°C (c) many large molecules, particularly biologically important compounds, are not readily adsorbed on heterogeneous surfaces and therefore do not label easily (d) catalytic-induced degradation is observed with many steroid type molecules in the presence of heterogeneous platinum.

It is the purpose of the present communication to report preliminary experiments involving the use of a new homogeneous platinum catalyst[5] for the deuteration and/or tritiation of synthetic hormones and steroids and to compare the results with exchange on heterogeneous platinum. The homogeneous catalyst has already been used to label simple molecules such as benzene and the monosubstituted benzenes[5] however, this is the first report of the method being applied to the synthetic hormones and steroids.

In Tables 1 and 2, the homogeneous platinum catalyzed exchange results are compared with analogous reactions on the two most useful heterogeneous type catalysts, namely sodium borohydride prereduced platinum and self-activated platinum oxide. In order to typify the exchange behaviour expected for the synthetic oestrogens and steroids, six representative compounds have been selected for Table 1. These are trans-stilbene, bibenzyl, hexestrol, oestrone, cholesterol and testosterone. Trans-stilbene and bibenzyl were chosen since these are the parent compounds of the two common series of synthetic oestrogens i.e., non-steroids or oestrogens which do not possess the perhydrocyclopentenenophenanthrene nucleus.

The results (Table 1) show that the homogeneous platinum catalyzed procedure is satisfactory for the tritiation of all six compounds. The same conclusion can be reached for deuteration except with cholesterol where extensive degradation to ketonic by-products occurs simultaneously with increase in deuterium incorporation. When compared with heterogeneous exchange, the homogeneous procedure is faster and can be performed at significantly lower temperatures, thus minimizing possible thermal catalytic degradation. The cut-off in the low voltage mass spectra (Table 2) suggests that homogeneous exchange at 100°C can be selective to certain positions in the molecule and this is confirmed by n.m.r. In oestrone, cholesterol and testosterone, deuteration is confined to positions close to the points of unsaturation whereas in hexestrol, trans-stilbene and bibenzyl exchange occurs in both ring and side-chain hydrogens, ortho positions adjacent to alkyl groups being deactivated similar to the orientation observed in the alkylbenzenes[5].

These isotope orientation results indicate that the mechanism of homogeneous exchange in the synthetic oestrogens and steroids is the same as that proposed for simpler molecules[6] such as the alkylbenzenes where it is suggested that deuteration in the ring occurs by either the homogeneous associative or dissociative π-complex mechanism and exchange in the α-position of alkyl groups is due to a homogeneous π-allylic mechanism.

The present results indicate that the homogeneous method is attractive for the labelling of a wide range of steroids and synthetic hormones. When compared with heterogeneous metal catalysis, the homogeneous procedure has the additional advantage of simplicity since, with many compounds, reaction can be performed under reflux at atmospheric pressure. In practice it is predicted that the homogeneous method will probably replace the corresponding heterogeneous procedures[4,7] for the deuteration and tritiation of many compounds whereas for the labelling of other compounds the two techniques will be used in a complementary manner.

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TABLE 1. [a]

Run	Compound	Catalytic System	Compound (g)	Catalyst (g)	D_2O (g)	Reaction Time (hr)	Reaction Temp. °C.	% D
1	*trans*-Stilbene	heterogeneous S.A.	0.050	0.020	2.03	47	110	2.8
2	*trans*-Stilbene	heterogeneous $NaBH_4$	1.01	0.206	32.9	48	150	60.3
3	Bibenzyl	heterogeneous S.A.	0.050	0.010	2.08	47	110	50.0
4.	Bibenzyl	heterogeneous $NaBH_4$	0.050	0.010	2.06	47	150	90.0
5	Bibenzyl	heterogeneous $NaBH_4$	1.53	0.209	28.8	24	120	71.5
6	Hexestrol	heterogeneous $NaBH_4$	0.70	0.205	43.7	48	130	34.3
7	Oestrone	heterogeneous $NaBH_4$	0.050	0.010	2.09	47	150	7.0
8	Oestrone	heterogeneous S.A.	0.050	0.010	2.10	48	152	15.3
9	Oestrone	heterogeneous S.A.	0.050	0.010	2.13	97	152	19.2
10	Oestrone	heterogeneous $NaBH_4$	0.50	0.198	30.1	48	160	18.2
11	Cholesterol	heterogeneous S.A.	0.050	0.010	2.06	48	110	8.8
12	Testosterone	heterogeneous $NaBH_4$	0.050	0.010	2.20	48	90	4.3
13	*trans*-Stilbene	homogeneous [b]	0.061			2.5	92	11.2
14	Bibenzyl	homogeneous [b]	0.061			2.5	92	10.5
15	Hexestrol	homogeneous [b]	0.061			2.5	92	12.2
16	Oestrone	homogeneous [b]	0.061			2.5	92	15.3
17	Cholesterol	homogeneous [b]	0.073			2.5	92	2.9
18	Testosterone	homogeneous [b]	0.059			2.5	92	10.5

[a] S.A. = self-activation

[b] Reaction conditions involved 3ml of a solution of CH_3COOD (67 mole % in D_2O) containing HCl(0.01M) and K_2PtCl_4 (382 mg).

TABLE 2.

DEUTERIUM DISTRIBUTION OF COMPOUNDS REPORTED IN TABLE 1.

Run (Table 1)	Compound	Catalyst	Deuterium Distribution														
			d_0	d_1	d_2	d_3	d_4	d_5	d_6	d_7	d_8	d_9	d_{10}	d_{11}	d_{12}	d_{13}	d_{14}
2	*trans*-Stilbene	heterogeneous	-	-	-	-	1.2	7.3	26.3	26.3	19.7	10.6	5.4	2.1	1.2		
5	Bibenzyl	heterogeneous	-	-	-	-	-	-	0.7	3.4	10.7	22.5	26.3	19.5	11.1	4.3	1.3
6	Hexestrol	heterogeneous	5.8	6.6	5.6	8.5	10.9	8.2	6.4	4.9	4.0	4.0	4.0	4.6	3.7	4.9	4.2
			d_{15}	d_{16}	d_{17}	d_{18}	d_{19}	d_{20}									
			4.0	3.2	2.5	1.7	1.5	0.8									
13	*trans*-Stilbene	homogeneous	9.1	55.2	28.0	7.6											
15	Hexestrol	homogeneous	3.5	15.1	27.9	26.8	17.6	7.0	2.1								
16	Oestrone	homogeneous	0.1	2.6	13.8	35.5	40.5	7.7									
17	Cholesterol	homogeneous	45.7	32.4	8.7	13.1											
18	Testosterone	homogeneous	2.2	11.6	26.0	28.2	27.1	5.0									