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TRITIUM LABELLING OF 1,2,3,4-TETRAHYDRONAPHTHALENE BY CATALYTIC HYDROGENOLYSIS OF THE PHENYLTETRAZOLYL ETHER OF 1,2,3,4-TETRAHYDRO-6-HYDROXYNAPHTHALENE ON PALLADIUM ON CALCIUM CARBONATE

INTERFERENCE AND APPLICATION OF CATALYTIC HYDROGEN EXCHANGE PHENOMENA

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Abstract—Catalytic hydrogenolysis of the phenyltetrazolyl ether of 1,2,3,4-tetrahydro-6-hydroxynaphthalene with tritium gas in EtOH and Pd/$CaCO_3$ or Pd/C as catalyst, produced 1,2,3,4-tetrahydro-(1,4,6-^{3}H)-naphthalene. The tritium label on the 1- and 4-position resulted exclusively from catalytic hydrogen exchange between tritium gas and 1,2,3,4-tetrahydronaphthalene or its tetrazolyl ether. The radiochemical yield for the substitution of the tetrazolyl group was at a most 30–40% and proceeded partly via a hydrogen transfer from the α-positions.

Catalytic hydrogen exchange between hydrogen gas and benzylic H atoms seemed to be more general as was demonstrated with dihydroanthracene, fluorene, *m*-xylene and ethyl benzene. Exchange experiments in EtOH with deuterium gas indicated that the percentage of labelling depended on the temperature, the duration of exchange and the excess of deuterium gas used. It was possible to prepare in this way 1,2,3,4-tetrahydro-(1,4-^{3}H)naphthalene with a specific activity higher than that of the tritium gas used.

IN THE course of our investigation on the chemical effects of ^{14}C-decay in 1,2,3,4-tetrahydronaphthalene (tetralin) we needed ^{14}C-labelled compounds specifically marked with tritium in the aromatic or aliphatic part of the molecule. Our method of synthesis produced the several possible ^{14}C-labelled tetralins with an OH group in the desired tritium-position.[1]

First we investigated the replacement of a phenolic OH group by deuterium or tritium. As the specific activity of the final compounds had to be about 0·5–1·0 C/mM, we looked for methods which apply hydrogen gas directly as the substituting agent. To our knowledge the only simple and direct replacement of a phenolic OH group by hydrogen has been described by Musliner and Gates.[2] According to these authors a phenolic OH group can be converted into the 1-phenyl-5-tetrazolyl ether by reaction with 1-phenyl-5-chlorotetrazole. Catalytic hydrogenolysis of this ether on Pd/C produces the hydrogen derivative and 1-phenyl-5-tetrazolone. The reaction conditions mentioned by the authors are very mild, generally high yields are obtained at 35°C and one atmosphere of hydrogen pressure within 10–15 hr in C_6H_6, EtOH or THF as solvent.

The results of some of our experiments are summarized in Table I and II. The conclusions which can be drawn from these experiments are mentioned in the text, where reference to these experiments is made as e.g. (I–3), indicating Table I, experiment 3.

We found that hydrogenolysis of the tetrazolyl ether of 6-hydroxytetralin did not proceed within 120 hr in C_6H_6, either with Pd/C, nor with Pd/$CaCO_3$ as catalyst.

TABLE 1. CATALYTIC HYDROGENOLYSIS OF THE TETRAZOLYL ETHER OF 6-HYDROXY TETRALIN ON Pd/$CaCO_3$

Experiment No.[a]	1	2	3	4	5	6	7	8
Gas used, *a* type	D_2	D_2	HT	D_2	D_2	D_2	H_2	D_2
b mM	2·5	±30	2·5	2·5	2·5	4	±30	±30
c s.a.[b]	--	--	17.2000	--	--	--	--	--
Reaction time (hr)	2	3	3	2·5	2	0·5	2	2·5
Solvent, *a* type	EtOT	EtOH	EtOH	C_6H_6 + 10% Et_3N	EtOT	EtOT	EtOD	EtOD
b mM	140	130	170	5 ml	140	100	170	86
c s.a.[b]	487	--	--	--	1660	858	--	--
Tetralin, *a* s.a.[b]	153	--	22.090	—	332	615	—	—
b NMR.[c] Ar	89	89	--	--*	96	94	100	81
α	55	16	--	--	64	70	47	72
β	100	100	--	--	100	100	100	100
D-at/molec	2·24	3·80	--	--	1·60	1·44	2·12	1·88
c Mass spec., D_0	8·6	--*	--	33·0	—*	--*	--*	--*
(%) D_1	21·5	--	--	58·9	--	--	--	--
D_2	31·0	--	--	6·5	—	--	--	--
D_3	24·3	—	—	1·6	--	—	--	--
D_4	11·7	--	--	--	--	--	--	--
D_5	2·7	--	—	--	--	--	--	--
D-at/molec	2·17	—	--	0·77	--	--	--	--
Remaining gas, s.a.[b]	48	--	13.500	--	41	35	--	--

* Not determined

[a] All reactions were carried out with 0·7 mM of the tetrazolyl ether and 100 mg of Pd/$CaCO_3$ except in exp. 4 and 6 where 50 mg of Pd/C were used.

[b] Specific activity in nC/mM

[c] The ratio of the values for Ar, α and β equals the signal ratio from these protons in the NMR-spectra, taking the signal from the β-protons as internal standard

Use of EtOH gave a great improvement. The hydrogenolysis proceeded very rapidly with either catalyst giving yields of 80–90% of tetralin. Although with Pd/C hydrogenolysis was finished within 30 min and about 2 hr were required with Pd/$CaCO_3$ to obtain the same yield of tetralin, we decided to use Pd/$CaCO_3$ in further experiments. This decision was based on the observation that both catalysts caused the same type of reactions, but that Pd/C increased considerably the hydrogen exchange between the α-hydrogen in tetralin and tetralyl ether on the one side and solvent-hydrogen and/or hydrogen gas on the other side. In order to minimize this exchange reaction, which will be discussed later, we chose Pd/$CaCO_3$ as catalyst.

Hydrogenolysis experiments with deuterium gas and Pd/$CaCO_3$ indicated that in the NMR spectra the ratio of the integrated peak areas of the α-, β-, and aryl protons varied with the duration of the hydrogenolysis. If the β-protons were used as an internal standard a scrambling of the deuterium over the α-positions and the aromatic ring had to be assumed (I-1, 2). However, we could prove that during the hydrogenolysis of the tetrazolyl ether no aromaticity shift took place:

The absence of this aromaticity shift was demonstrated by carrying out the hydrogenolysis of the tetrazolyl ether of 7-hydroxy-(2-^{14}C)tetralin, followed by oxidative degradation of the obtained (2-^{14}C)tetralin to phthalic acid (experiment I).

Mass spectrometric measurements made clear that in most cases the degree of deuterium incorporation was higher than one D-atom per molecule and that the species present were partly non-deuterated and partly labelled with 1 to 5 D-atoms per molecule (I-1). When in similar experiments tritium gas was used, we deduced from the specific activities of the tritium gas and the product ^{3}H-tetralin that again more than one T-atom per molecule was incorporated (I-3).

As the presence of the ^{2}H-label in both rings of tetralin could be explained by a catalytic hydrogen exchange between tetralin (or the tetralyl ether) and deuterium gas, we investigated this exchange with molecular deuterium and tritium. The experiments with deuterium showed indeed that extensive hydrogen exchange took place. It was possible to introduce more than 3 D-atoms per molecule of tetralin (II-9, 11). The correspondence of the mass spectra with the NMR spectra was good when only deuteration of the α-positions in tetralin was taken into account. If however, the exchange reaction was continued for a long period of time, NMR indicated that also hydrogen exchange with the β-positions of tetralin occurred (II-11). Additional confirmation of the α-location of the deuterium in tetralin was obtained in the following way. Deuterated tetralin, obtained by exchange labelling, was converted into ^{2}H-naphthalene by treatment with 2,3-dichloro-5,6-dicyanoquinone (DDQ).[3] The NMR spectrum of the ^{2}H-naphthalene was in excellent accordance with the mass spectrum if again only deuteration of the α-positions was assumed (experiment II). Experiments with tritium gas showed also that extensive hydrogen exchange between tritium gas and tetralin occurred. It was possible to obtain tritiated tetralin with a specific activity much higher than that of the tritium gas used (II-12). Oxidative degradation of the product ^{3}H-tetralin to phthalic acid demonstrated that all the activity was located in the aliphatic ring (experiment III).

We noticed that in the presence of Pd/$CaCO_3$ EtOH exchanged its OH hydrogen rapidly with tritium gas (II-13, 14). If however, the exchange reaction was carried out at room temperature with deuterium gas and a solution of tetralin in EtOT, practically no activity was found in the remaining deuterium gas, although the tetralin contained still more than one D-atom per molecule (II-15). The specific activity of the obtained ^{2}H-tetralin was less than 1% of the specific activity of the EtOT used. Therefore we conclude that the presence of tetralin seriously hampered the catalytic hydrogen exchange between EtOH and hydrogen gas, and moreover, that the hydrogen exchange of the α-positions of tetralin took place exclusively with molecular hydrogen.

The observed catalytic exchange of the H atoms in the benzyl positions of tetralin with molecular hydrogen seemed not to be confined to tetralin only. It was possible

TABLE 2. CATALYTIC HYDROGEN EXCHANGE EXPERIMENTS AT 25°C

Experiment No.[a]	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Compound, *a* type	Tetra.[d]	Tetra.[d]	Tetra.[d]	Tetra.[d]	—	—	Tetra.[d]	Diha[e]
b mM	1·12	10	2	1·5	—	—	1·42	0·7
Gas used, *a* type	D_2	D_2	D_2	HT	HT	H_2	D_2	D_2
b mM	8	25	9	2·5	2·5	2·5	2·5	8
c s.a.[b]	—	—	—	17000	17000	—	—	—
Reaction time (hours)	110	3	175	4	3	2	2	3
Solvent, *a* type	EtOH	EtOH	EtOH	EtOH	EtOH	EtOT	EtOT	EtOH
b mM	170	170	170	86	86	80	80	70
c s.a.[b]	—	—	—	—	—	520	343	—
Compound isolated, *a* s.a.[b]	—	—	—	24000	165	±500	<2	—
b NMR,[c] Ar	100	100	100	—	—	—	100	100
α	16	67[5]	26	—	—	—	63	18
β	100	100	94	—	—	—	100	—
D-at./molec.	3·36	1·30	3·20	—	—	—	1·48	2·56
c Mass spec., D_0	1·2	23·9	1·8	—	—	—	19·1	—*
(%) D_1	1·6	39·8	6·0	—	—	—	35·9	—
D_2	10·1	26·4	20·5	—	—	—	30·7	—
D_3	35·1	8·8	36·9	—	—	—	11·4	—
D_4	47·9	1·4	29·3	—	—	—	3·7	—
D_5	3·5	—	4·7	—	—	—	0·1	—
D_6	0·8	—	0·8	—	—	—	—	—
D-at./molec.	3·41	1·25	3·03	—	—	—	1·46	—
Rest gas, s.a.[b]	—	—	—	—*	12100	235	27	—

TABLE 2—*continued*

Experiment No.[a]	17	18	19	20	21	22	23	24
Compound, *a* type	Diha[e]	Fluo.[f]	E.B.[g]	Xyl.[h]	Tetr.[d]	Tetr. D[i]	Tetr.[d]	Tetr.[d]
b mM	1·81	2	2	2	0·8	0·5	1	2
Gas used, *a* type	D_2	D_2	D_2	D_2	HT	H_2	D_2	H_2
b mM	±20	5	5	5	2·5	>30	3	25
c s.a.[b]	—	—	—	—	17000	—	—	—
Reaction time (hours)	12	12	36	36	3·5	3	3	4[k]
Solvent, *a* type	EtOD	EtOH	EtOH	EtOH	C_6H_6 + 10% Et_3N	EtOH + 20% benzene	THF[10]	EtOD
b mM	170	170	170	170	7·5 ml	10 ml	10 ml	170
c s.a.[b]	—	—	—	—	—	—	—	—
Compound isolated, *a* s.a.[b]	—	—	—	—	340	—	—	—
b NMR,[c] Ar	100	100	100	100	—	—	100	—
α	3·3	3·9	19^5	135	—	—	60	—
β	—	—	61	—	—	—	100	—
D-at./molec.	3·73	1·69	1·0	0·61	—	—	1·60	—
c Mass spec., D_0	<1	—*	—*	—*	—	26·3	—*	19·5
% D_1	<2	—	—	—	—	39·6	—	35·5
D_2	3·7	—	—	—	—	24·6	—	20·5
D_3	19·5	—	—	—	—	7·8	—	10·5
D_4	70·8	—	—	—	—	1·6	—	4·3
D_5	<2	—	—	—	—	<1	—	1·7
D_6	<1	—	—	—	—	—	—	—
D-at./molec.	3·67	—	—	—	—	1·23	—	150
Rest gas, s.a.[b]	—	—	—	—	—*	—	—	—

* Not determined.

[a] All reactions were carried out with 100 mg of Pd/CaCO$_3$ as catalyst, except exp. 12 (300 mg), 10 (200 mg), 18 (350 mg) and 22 where 50 mg of Pd/C was used.

[b] Specific activity in nC/mM.

[c] The ratio of the values for Ar, α and β equals the signal ratio from these protons in the NMR-spectra.

[d] Tetr. = tetralin.

[e] Diha = 9,10-dihydroanthracene.

[f] Fluo = fluorene.

[g] E.B = ethyl benzene.

[h] Xyl. = m-xylene.

[i] Tetr. D = tetralin obtained in exp. 10.

[j] THF = tetrahydrofuran.

[k] Reaction temperatures 60° C.

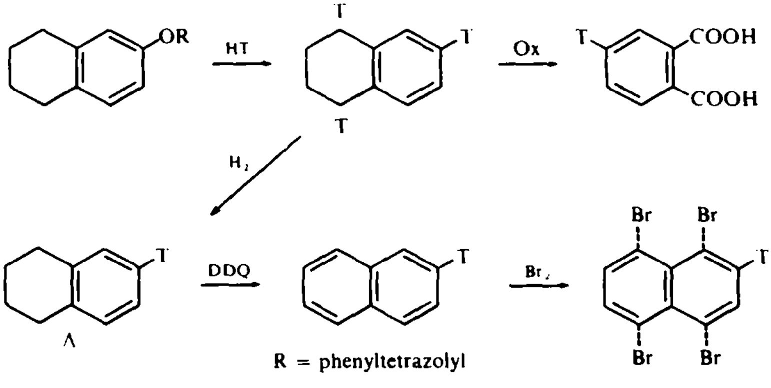
to substitute up to 90% of the hydrogen in the benzyl positions of 9,10-dihydroanthracene by deuterium without any introduction of deuterium into the aromatic rings as was shown by NMR and mass spectra (II-**16**, **17**). This confirmed the results obtained with tetralin where continued exchange introduced deuterium also into the β-positions, but not into the aromatic ring.

Exchange labelling of fluorene, ethyl benzene and *m*-xylene was investigated also (II-**18**, **19**, **20**). These reactions were not as fast as the forementioned ones, but within 36 hr the α-positions in fluorene and ethyl benzene and the Me groups in *m*-xylene could be labelled for 85, 50 and 10% respectively. The fact that unlabelled EtOH could be used as solvent indicated again that in the presence of the mentioned compounds the hydrogen exchange between EtOH and hydrogen gas was hampered.

Tentatively we explain the above mentioned results by assuming that the chemisorption on the Pd/$CaCO_3$-surface is stronger for tetralin and similar aromatic compounds than for EtOH.[4] The assumption that aromatic compounds are stronger absorbed on the catalyst surface than EtOH was supported by the following facts. If C_6H_6 was used as solvent no hydrogen exchange took place between tetralin and tritium gas, even the use of Pd/C and the presence of about 10% of Et_3N in this solvent gave the same result (II-**21**). On the other hand, the addition of about 20% of C_6H_6 to the solvent EtOH was sufficient to decrease the hydrogen exchange with tetralin considerably (compare the mass spectra of II-**10** and II-**22**). In a non-aromatic solvent like THF again extensive hydrogen exchange between tetralin and hydrogen gas was observed (II-**23**).

Having this knowledge about exchange labelling, we looked into the results obtained by the catalytic hydrogenolysis of the tetrazolyl ether of 6-hydroxytetralin. After preparing tritiated tetralin in this manner, we located all the T-atoms in the molecule in the following way (experiment IV). The α-located tritium in the ^3H-tetralin was removed by catalytic exchange with hydrogen gas. This was proved by the observation that the specific activity of the resulting ^3H-tetralin (A) was comparable with the specific activity of the phthalic acid produced by oxidative degradation of the original ^3H-tetralin. The location of the aromatically bound tritium was found after conversion of ^3H-tetralin (A) into ^3H-naphthalene, followed by bromination of this compound. Because the specific activity of the obtained 1-bromonaphthalene was equal to the specific activity of ^3H-naphthalene, the tritium had to be located on the 2-position. The reactions are summarized in Scheme I.

SCHEME I



As we had already found that the labelling of the α-positions of tetralin occurred exclusively by exchange with hydrogen gas, we investigated if the ether group substitution occurred by hydrogen gas also. This could not be established by a determination of the specific activity of the aromatically bound tritium in ^{3}H-tetralin, produced by hydrogenolysis with tritium gas. Because of the exchange between benzylic hydrogen and hydrogen gas, dilution of the gas with α-hydrogen interfered, unless very large amounts of labelled hydrogen were used. We tried therefore to suppress the exchange by adding some C_6H_6 to the solvent EtOH, but the amount of exchange was still too high to neglect. Although we found that the hydrogenolysis of the tetrazolyl ether did not proceed in pure C_6H_6, the reaction did proceed when 10% of Et_3N was added and Pd/C was used as catalyst (I-4). Mass spectra indicated however, that this time too dideutero-tetralin was formed, possibly because of interfering hydrogen exchange reactions.

Because we had established that the α-hydrogen of tetralin did not show any exchange with tritiated EtOH and that at the same time the exchange between EtOH and hydrogen gas was practically absent, we assumed that the same could be true for the tetrazolyl ether of 6-hydroxytetralin. Therefore we carried out the hydrogenolysis of this ether with deuterium gas, using tritiated EtOH as solvent (I-1, 5). The specific activity of the remaining deuterium gas was indeed only 2 to 4% of the specific activity of the EtOT used, indicating a strong hampering of the hydrogen exchange between EtOH and hydrogen gas.

However, the specific activity of the product tritiated deuterotetralin, although much lower than the specific activity of the EtOT, was 6 to 15 times higher than half the specific activity of the remaining deuterium gas. Oxidation of the tritiated deutero-tetralin to phthalic acid demonstrated that most of the tritium was located on the α-positions, however, the specific activity of the obtained phthalic acid was still too high to be explained by introduction solely from the gas phase (experiment V).

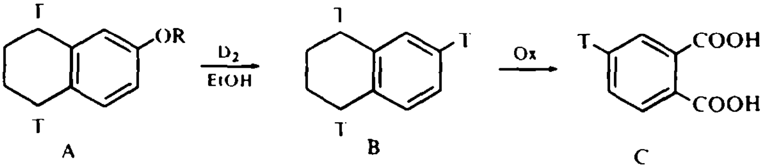
The observation that α-located tritium was present in the above mentioned tritiated deutero-tetralin makes it clear that still hydrogen exchange between EtOT and α-hydrogen in the tetrazolyl ether of tetralin had occurred. We found that such a H-T-exchange also took place with tetralin if the exchange reaction was carried out at 60°, as was demonstrated in (II-24). Because heating to about 60° was necessary to start the hydrogenolysis of the tetrazolyl ether, the temperature dependence of the mode of the exchange reaction explained this apparent contradiction with previous results.

From the results of experiment V it follows that the hydrogenolysis of the tetrazolyl ether took place at least partly with hydrogen which had not originated from the gas phase. Exactly the same conclusion was derived from a similar experiment in which Pd/C instead of $Pd/CaCO_3$ was used as catalyst (I-6), only the exchange labelling of the α-positions of the tetrazolyl ether was much more intensive.

It is not easy to say which part of the aryl located hydrogen originated from the gas phase. Hydrogenolysis with a large excess of hydrogen gas in EtOD, produced deuterated tetralin without deuterium in the aromatic ring (I-7). If however, the reaction was carried out in EtOH with a large excess of deuterium gas, only about 0·5 D-atom per molecule was introduced into the aromatic ring (I-2). Curiously, the use of EtOD and a large excess of deuterium gas produced deuterated tetralin with only 0·75 D-atom per molecule in the aromatic ring (I-8). As the excess of deuterium gas was always more than 20 times the amount of hydrogen which could be exchanged from the α-positions, we assume that the α-hydrogen, exchanged on the catalyst surface, stayed immediately available for the hydrogenolysis. This can explain why the specific activity of the phthalic acid, obtained after oxidation of tetralin which was produced by hydrogenolysis in EtOT (I-5), was higher than the specific activity of the remaining deuterium gas (experiment V).

If indeed the α-hydrogen of the tetrazolyl ether of 6-hydroxytetralin takes part in the catalytic hydrogenolysis of the tetrazolyl group, it could be checked by using α-tritiated tetrazolyl ether as the substrate (see Scheme II):

SCHEME II



R = phenyltetrazolyl

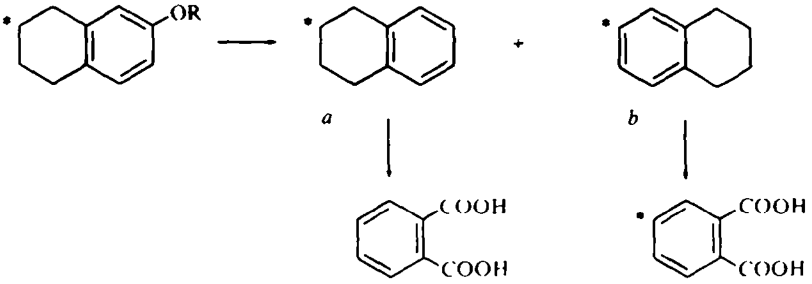
We found (experiment VI) that catalytic hydrogenolysis caused a decrease in the specific activity of 0·72 μC/mM in going from A (s.a. = 2·53 μC/mM) to B (s.a. = 1·81 μC/mM). Oxidative degradation of B gave phthalic acid with a s.a. = 0·091 μC/mM. Thus 11% of the lost α-located tritium activity was found back in the aromatic ring. This aryl located tritium could not be introduced from the gas phase as the specific activity of the gas phase was too low (0·135 μC/mM). Moreover, from the NMR spectrum of compound B it was concluded that 0·32 D-atom per molecule was present in the aromatic ring. Taking into account the amounts of reactants used, we calculate that at a most 0·06 μC/mM could be introduced from the gas phase into the aromatic ring. If the lost amount of activity were present in the liquid phase, we calculate that only 0·004 μC/mM could be introduced from the solvent ethanol.

The calculation of the amount of tritium introduced into the aromatic ring is based on the observed deuterium incorporation. This calculation gives indeed a maximum value because a possible isotope effect is effective in the opposite direction. We found for example in experiment IV that the s.a. of the aromatically bound tritium was only 18% of that of the tritium gas used.

In a similar experiment (experiment VII), but with a shorter reaction time (10 min instead of 1 hr), we found that in the reaction from A to B, 28% of the lost α-located tritium activity was present in compound C. However, from NMR data and the amounts of reactants used we calculated that at a most 7% of the lost α-located activity could be introduced from the gas phase into the aromatic ring. Introduction via the solvent ethanol could incorporate at a most 0·6% of the lost activity in the aromatic ring.

We conclude therefore that the tritium activity found in phthalic acid C, is introduced directly from the α-positions, whether or not via the catalyst. The observation that at shorter reaction time the percentage of tritium transferred from the α-positions into the aromatic ring increases, is fully understandable from the hydrogen exchange between α-hydrogen and hydrogen gas. The possibility that the substitution of the tetrazolyl group proceeds quantitatively by a hydrogen transfer from the α-positions, can not be excluded because we have indications that a fairly large isotope effect is involved in the hydrogen exchange of α-located tritium.

Scheme III



EXPERIMENTAL

Materials. Tetrazolyl ether of 6-hydroxytetralin was prepared as described by Den Hollander *et al.*[5] Other starting compounds were commercially available; their purity was checked by gaschromatography (GLC). Pd/$CaCO_3$ (10%) and Pd/C (10%) were obtained from E. Merck A.G. and Drijfhout en Zn's N.V., respectively. Deuterium gas was obtained from Baker Chemicals. Purity was stated to be at least 99·5%. Tritiated hydrogen and tritiated ethanol were prepared from tritiated water by reduction with Mg, respectively by reaction with NaOEt. Hydrogenolysis of the tetrazolyl ether and the purification by GLC of the product tetralin were carried out as described by Den Hollander *et al.*[5] The hydrogen exchange experiments were done in the same way. Ethyl benzene and *m*-xylene were purified by GLC on SE 30 (15% w/w on Chromosorb-W). Dihydroanthracene and fluorene were purified by crystallization.

Experiment I. An aromaticity shift could be detected by degradation of ^{14}C-labelled tetralin which was produced by hydrogenolysis of a starting compound in which one of the rings was specifically labelled (see Scheme III).

As follows from Scheme III, determination of the specific activities of the obtained tetralin and phthalic acid affords immediately evidence on the presence of tetralin labelled in the aromatic ring (*b*).

Starting from 7-hydroxy-(2-^{14}C)tetralin with a specific activity of 0·428 μC/mM[1], its phenyltetrazolyl ether was prepared and the hydrogenolysis was carried out as described. ^{14}C-labelled tetralin with a specific activity of 0·426 μC/mM was isolated in 85% yield. This tetralin was oxidized to phthalic acid with potassium permanganate as described by Den Hollander *et al.*[5] The specific activity of the obtained phthalic acid was less than 0·005 μC/mM, indicating that 1, no aromaticity shift had occurred and 2, the specificity of the ^{14}C-label in 7-hydroxy-(2-^{14}C)tetralin was greater than 99%.

Experiment II. The deuterated tetralin obtained in (II–10), was converted into deuterated naphthalene by treatment with 2,3-dichloro-5,6-dicyano quinone (DDQ) and purified by GLC as described.[5] The NMR signal ratio from the α- and β-protons of the deuterated naphthalene was 77 : 100, indicating a labelling percentage of 0·96 D-atom per molecule if the β-protons were taken as an internal standard. Mass spectroscopy showed that D_0 = 30·7%, D_1 = 45·3%, D_2 = 24·0% and D_3 = 0·4%, thus indicating a labelling percentage of 0·945 D-atom per molecule. The conclusion that β-deuteration is absent supports the same conclusion from (II–10). The discrepancy between the expected and observed deuterium percentage of naphthalene (0·64 and 0·95 D-at/molec, respectively) is caused by an isotope effect.[1]

Experiment III. Tritiated tetralin with a specific activity of 24 μC/mM obtained in (II–12), was diluted to a specific activity of 4·48 μC/mM. After oxidation with $KMnO_4$, phthalic acid with a specific activity of 0·083 μC/mM was obtained. As we have shown that during the oxidation hydrogen exchange phenomena do not take place with the aromatic ring,[5] at least 98% of the tritium activity was located in the aliphatic ring.

Experiment IV (see Scheme I). Tritiated tetralin produced by hydrogenolysis with tritium gas (I–3) was purified by GLC and diluted to 4·15 μC/mM. Part of this diluted tetralin was oxidized to phthalic acid with a specific activity of 0·583 μC/mM. Another part of the diluted tetralin was subjected to catalytic hydrogen exchange with a large amount of hydrogen gas (in EtOH with Pd/$CaCO_3$ as catalyst). The specific activity of the obtained tetralin (A) was 0·503 μC/mM. This proved that all aliphatically bound tritium was removed by hydrogen exchange. Treatment of this tetralin (A) with DDQ[3] gave naphthalene with a specific activity of 0·500 μC/mM. Because of the large isotope effect involved in this reaction when α-located tritium is removed, this result can not be considered as a proof for the absence of α-located tritium. The position of the tritium in the product naphthalene was determined by bromination.[5] The isolated 1-bromonaphthalene had a specific activity of 0·490 μC/mM, indicating a specificity of the tritium location greater than 96% (corrected for 4% 2-bromonaphthalene present).

Experiment V. Tritiated tetralin with a specific activity of 332 nC/mM (I–5) was oxidized to phthalic acid with a specific activity of 53 nC/mM. This specific activity was 2·6 times as high as half the specific activity of the remaining gas (20·5 nC/mgrat.), and only 3·2% of the specific activity of the EtOT used (1660 nC/mM).

Experiment VI. The α-labelling of 6-hydroxy tetralin by hydrogen exchange was checked with molecular deuterium. NMR spectroscopy indicated that only about one D-atom per molecule was introduced into the α-positions if the exchange reaction between 1 mM of 6-hydroxytetralin and 20 mM of deuterium gas was carried out for 18 hr at room temperature in 10 ml of EtOH in the presence of 100 mg of $Pd/CaCO_3$.

Similarly tritiated 6-hydroxytetralin was prepared. After purification by GLC on SE-30 (15% w/w on Chromosorb-W) and dilution with carrier, the tetrazolyl ether was prepared (*vide infra*). One millimole of the tritiated tetrazolyl ether (s.a. = 2·53 μC/mM) was converted into tritiated deutero-tetralin by hydrogenolysis of a solution in 10 ml of EtOH with 2 mM of deuterium gas in the presence of 100 mg of $Pd/CaCo_3$ (1 hr at 30°C). After purification by GLC (*vide infra*) its s.a. was found to be 1·82 μC/mM and from the NMR data we calculated that the α-positions and the aromatic ring contained 2·14 and 0·32 D-atoms per molecule, respectively. The s.a. of the remaining deuterium gas was 0·135 μC/mM.

The tritiated deutero-tetralin was then oxidized to phthalic acid, that was isolated after conversion to dimethyl phthalate.[5] After purification by GLC on SE-30 (15% w/w on Chromosorb-W) its s.a. was 0·091 μC/mM.

Experiment VII. The same starting material and the same amounts of reactants were used as in experiment VI, only the reaction time was shortened to 10 min at 30°C. The s.a. of the obtained tritiated deutero-tetralin was 2·04 μC/mM, and from the NMR data it followed that the α-positions and the aromatic ring contained 2·32 and 0·28 D-atom per molecule, respectively. The s.a. of the phthalic acid, obtained after oxidation of the tritiated deutero-tetralin was 0·192 μC/mM.

Measurements. Specific activities of solid or liquid compounds were determined by gas chromatographic concentration determination and liquid scintillation counting on a Nuclear Chicago Unilux I, model 6850. The specific activity of tritium gas was determined by internal proportional gas counting or by quantitative oxidation of a known amount of gas to tritiated water, followed by liquid scintillation counting. NMR-spectra were recorded on a Varian A-60. Mass spectra were recorded on a CH5-Varian Mat.

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