Synthesis of Regio- and Stereospecifically Deuterium Labelled 2-Benzylindanes

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Indenes, Indenes, Deuterium Labelling, Homogeneous Catalytic Hydrogenation,
Stereochemistry

2-Benzylindanes (1, 1a) are hydrogenated to benzylindanes (2) using tris-(triphenylphosphine)-rhodium(I)-chloride in benzene by a strict cis-1,2 addition of hydrogen to the double bond. Thus, stereo- and regio-specific deuterium labelling at the five-membered ring of various benzylindanes has been carried out. The high selectivity of deuterium incorporation is shown independently by 1H NMR and mass (MIKE*) spectrometry of selected 2-benzylindanes.

Introduction

In the course of our mass spectrometric investigation of the intramolecular hydrogen exchange in gaseous radical cations of α,ω-diphenylalkanes [1–3] we required a synthetic access to various stereospecifically deuterium labelled 2-benzylindanes 2.

\[ 2: X = H, 3\textsuperscript{a}, 4\textsuperscript{a}-OCH\textsubscript{3}, F, -CH\textsubscript{3}, -OH, -N(CH\textsubscript{3})\textsubscript{3}, 3\textsuperscript{a}, 5\textsuperscript{a}-OCH\textsubscript{3}) \]

It is well known that in heterogeneous catalytic hydrogenation of alkenes partial isomerization and/or migration of the double bond occurs [5, 6]. In the case of olefins labelled with deuterium at the \(\text{CH} = \text{CH} = \text{CH}\) group or of using deuterium gas, non-regio-specific and isotopically impure labelling results [6]. As another consequence, the overall hydrogenation of the alkene may generate, in part, the products of trans-addition of \(\text{H}_2 (D_2)\) to the double bond along with that of cis-addition.

Indenes represent a class of alkenes containing a particularly reactive allylic group. Accordingly, heterogeneous catalytic hydrogenation of 2-benzylindenes over various Pd and Pt catalysts in alcoholic solvents, produces 2-benzylindanes with \(\geq 35\%\) incorrect incorporation of the label [7].

We wish to report here on the successful application of tris-(triphenylphosphine)-rhodium(I)-chloride (Wilkinson’s catalyst) [8] to the stereo- and regiospecific deuterium labelling of indanes 2 by homogeneous catalytic hydrogenation and deuteration of the corresponding indene precursors 1.

Scheme 1.

\[ \text{D}_2 \text{O, NEt}_3, \text{Pyr} \]

* MIKE spectrometry: Mass analyzed ion kinetic energy spectrometry.
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2: $X = H, 3',-F, -CH_3, -OH, -N(CH_3)_3; 3',5'-(OCH_3)_2$;

It is well known that in heterogeneous catalytic hydrogenation of alkenes partial isomerization and/or migration of the double bond occurs [5, 6]. In the case of olefins labelled with deuterium at the $>CH=CH-$grouping or of using deuterium gas, non-regio-specific and isotopically impure labelling results [6]. As another consequence, the overall hydrogenation of the alkene may generate, in part, the products of trans-addition of $H_2$ (D$_2$) to the double bond along with that of cis-addition.

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Results and Discussion

Using RhCl[P(C6H5)3]3 in ca. 0.2 m benzene solution hydrogenation of 1 takes place slowly (24–36 h) at room temperature with ≈ 99% regio- and stereoselectivity, as shown by 1H NMR and mass spectrometry (vide infra). Thus, using D2 gas, [1R,2-D2]-indanes (2a) are obtained from 1 with ≈ 98% isotopic purity. In the same way, [1c,3,3-D3]-indanes (2b) and [1,1,2,3,3-D3]-indanes (2c) are produced from 2-benzyl-[1,1,3-D3]-indenes (1a), which are synthesized from 1 by basic H/D exchange [8]. The 2-benzylindanes are isolated in nearly quantitative yields, irrespective of the substituent X (Scheme 1).

The stereo- and regiospecificity of the labelling is shown by 1H NMR spectrometry of, e.g., the unsubstituted 2-benzyl-[1R-2-D2]-indane (2a) (X = H) (Fig. 1) and by mass spectrometry of 2-(3'-methoxybenzyl)-[1c,3,3-D3]-indane (2b) (X = 3'-OCH3) (Fig. 2), respectively. These examples afford complementary structural information and are representative for all of the various substituted and labelled indanes 2.

2a shows an AB-system (δH A = 2.65 ppm, δH B = 2.95 ppm, JAB = −15.8 Hz) due to the C1 methylene group, a singlet at 2.75 ppm due to the benzylic methylene group, and a broad singlet at δ 2.64 ppm, which has to be assigned to the CHD group (JCHD is estimated to be ca. 2.0 Hz, corresponding to the expected value of ca. 0.15 · JHH [9]). Since the shielding of a proton at five-membered rings by a vicinal cis-substituent is well known [10], we have to assume that HA = HB and HD = HD. Hence, the resonance at δ 2.64 ppm reflects the cis-position of the CHD-proton (H4), showing an isotope effect (Δδ = −17 ppm) of reasonable magnitude [11]. There is no resonance within the region of the H5 signals (see sinusuous arrow in Fig. 1); hence, the trans-C1 position bears no hydrogen but rather ≈ 99% deuterium atoms (D5). In turn, it follows that no deuterium is incorporated in the C1 methylene group.

This interpretation of the 1H NMR spectrum, showing stereo- and regiospecific deuteration of 1, is corroborated by the mass spectrometric analysis of the complementarily labelled indane 2b (X =...
Scheme 2.

3'-OCH₃) (Fig. 1 and Scheme 2). The 3'-methoxy derivative is discussed instead of the unsubstituted 2b (X = H) for the sake of clearness [12].

![Diagram](image)

Fig. 2. Partial mass spectrum (70 eV) (a) and MIKE* spectrum (b) of 2b (X = 3'-OCH₃), showing incomplete (a) and complete (b) exchange of the four hydrogen atoms (C) at C₂⁻, C₂, C³, and C⁴ prior to fragmentation (cf. Scheme 2).

The major mass spectral fragmentation of ionized 2b (X = 3'-OCH₃) is the formation of C₈H₁₉O⁺ (m/z 122). This McLafferty type fragmentation requires the cleavage of the C²⁻–C² bond, being preceded by the transfer of a hydrogen atom at a γ-position (viz. C¹ or C₃) to an ortho-position (viz. C² or C⁴) of the alkyl anisole moiety [3]. This H⁺ transfer has been shown to be reversible, leading to an exchange of the hydrogen atoms at the γ and the ortho positions, the extent of which increases with increasing life-time of the molecular ions [2, 3]. Because of steric reasons the hydrogen atoms trans to the benzyl group (H⁺ and H⁺) cannot be transferred to the ortho-positions, restricting the exchange to only the four H⁺, H⁺, H⁺, and H⁺ atoms.

Whereas the hydrogen exchange is incomplete in the 2b⁺⁺ (X = 3'-OCH₃) molecular ions fragmenting within ca. 1 µs in the ion source of the mass spectrometer (Fig. 2a), it has reached equipartition in the long-lived (ca. 10 µs) metastable 2b⁺⁺ ions [13], fragmenting in the second field-free region of the instrument. This follows from the MIKE* spectrum of 2b⁺⁺ (X = 3'-OCH₃) (Fig. 2b) showing C₈H₁₉O⁺⁺ (m/z 123) and C₈H₁₉D₂O⁺⁺ (m/z 124) exclusively and with the statistically expected abundance ratio of unity. As a consequence, the cis-positions of 2b (X = 3'-OCH₃) must have been labelled completely (≥ 98% D₂).

In accordance to this result, the reciprocally deuterated 2-(3'-methoxybenzyl)-[1r,2-D₂]-indane 2a (X = 3'-OCH₃), bearing no deuterium atom at the cis-positions, shows C₈H₁₀O⁺⁺ (m/z 122) as the only fragment ions formed from the metastable molecular ions (Fig. 3).

![Diagram](image)

Fig. 3. Partial MIKE* spectrum of 2a (X = 3'-OCH₃).
Conclusion

The results of the $^1$H NMR and mass spectrometric analysis of deuterium labelled 2-benzyl-indanes (2) confirm independently that the homogeneous catalytic hydrogenation of 2-benzyl-indenes to 2-benzyl-indanes using RhCIP($C_6H_5$)$_3$ in benzene solution occurs with complete ($\geq 99\%$) regio- and stereo-specifity. This warrants the use of this catalyst for deuterium (and tritium) labelling of all kinds of 1H-indenes in general.

Experimental

MELTING points were measured with an Electrothermal melting points apparatus and are uncorrected. Boiling points were taken during the distillative purification using a Kugelrohr apparatus, Model GKR-50 (Buchi). All synthetic steps were recontrolled by thin layer chromatography (Kieselgel, Merck) mostly using petroleum ether/ethyl acetate (3:1) as eluent. IR-spectra were recorded with a Model 377 instrument (Perkin Elmer). $^1$H NMR spectra with a WP 80 instrument (90 MHz, Bruker). 70 eV and low energy mass spectra were measured with a MAT 311A instrument (Varian MAT) at 3 kV accelerating voltage, 300 $\mu$A emission current and ca. 250 °C ion source temperature. MKE* spectra were obtained with a (high resolving) ZAB-2F mass spectrometer (Vacuum Generators) at 6 kV and 100 $\mu$A. Using this technique the magnetic sector selects the metastable ion which is to be investigated by its decompositions which occur after having passed the magnet. The ionic products thus formed are then analysed by scanning the following electrostatic sector field.

2-Benzyl-indene (1) was prepared according to Campbell et al. [14] by dehydration of 2-benzyl-1-indanol in 90% formic acid. This method cannot be applied to, e.g., 2-(3'-methoxybenzyl)-1-indanol because of partial cyclo dehydration to 4b,9b,9a,10-tetrahydro-indeno[1,2-al]indene [15] which, however, can be omitted by heating the alcohol in dimethyl sulfoxide (DMSO) [16]. The complete synthesis of the various substituted 2-benzyl-indenes and -indanones will be given in another context [15], restricting the present description to the preparation of the indanes discussed above.

2-(3'-Methoxybenzyl)-1-indene 1 ($X = 3'$-OCH$_3$)

2-(3'-Methoxybenzyl)-1-indanone was prepared as described by Thompson [17] as an oil (b.p. 160 °C/0.07 mbar [17]), which solidified within one day to give white crystals which had a m.p. of 58–59 °C after recrystallisation from ethanol.

2-(3'-Methoxybenzyl)-1-indanol was obtained by reduction of the ketone with LiAlH$_4$ in diethyl ether in 86% yield as an approx. 1:1 mixture of the cis and the trans isomers (white needles of m. p. 44–47 °C).

Calcd C 80.28 H 7.13
Found C 80.37 H 6.99

IR (KBr): $v$ (cm$^{-1}$) 3390 (br), 3020 (m), 2940 (s), 2840 (m), 1600 (s), 1580 (s), 1260 (s), 1150 (s), 1050 (s), 780 (m), 750 (s), 700 (m). The stereoisomers can be separated [15] but are easily identified in the mixture by $^1$H NMR spectrometry (CDCl$_3$/TMS/ D$_2$O) due to the resonance of their carbinol protons H*: $\delta$ (ppm) 2.3–3.3 (mult., 5 H), 3.80 (sing., 3 H(OCH$_3$), 4.88 (dubl., J$_{1H,1'HH}$ = 6.0 Hz), 5.04 (dubl., J$_{1H,2HH}$ = 4.8 Hz; 1 H$^1$), 6.6–6.9 and 7.1–7.3 (mult., 8 H$^{13}$O). Mass spectrum (70 eV) of the mixture: m/z 254 (M$^+$; 5% B), 236 (M$^+-$H$_2$O, 4% 133 (M$^+-$CH$_3$C$_6$H$_4$OCH$_3$; 30%), 122 (C$_6$H$_5$OCH$_3$, 100%), 121 (C$_6$H$_5$OCH$_3$, 32%). The mass spectrometric identification of the pure stereoisomers will be discussed in a separate paper [15].

The mixture of the stereoisomeric indanols (1.28 g, 5.0 mmol) was heated to 170–175 °C in 4 g (50 mmol) of dry, freshly distilled DMSO under N$_2$ atmosphere for 20 h. After cooling, the reaction mixture was worked up by adding water and extracting the emulsion with petroleum ether (50–70) several times. The organic layer was washed with water and dried over MgSO$_4$. After evaporation of the solvent 1 (X = 3'-OCH$_3$) was obtained as an oil (b.p. 165–170 °C, 0.07 mbar), yield 0.93 g (78%). Recrystallisation from ethanol gave white crystals, m. p. 30–31 °C.

Calcd C 86.41 H 6.82
Found C 86.71 H 6.66

IR (neat): $v$ (cm$^{-1}$) 3055 (m), 2910 (m), 2840 (m), 1600 (s), 1585 (s), 1260 (s), 1155 (s), 1050 (s), 780 (m), 755 (s), 720 (s), 705 (m). $^1$H NMR (CDCl$_3$)/TMS: $\delta$ (ppm) 3.28 (br. sing., 2 H$^1$), 3.79 (quasi sing., 2 H$^2$ and 3 H(OCH$_3$)), 6.57 (br. sing., 1 H$^1$), 6.65–7.45 (mult., 8 H$^{13}$O). MS (70 eV): m/z 236 (M$^+$, 42% B), 235 (M$^+-$H, 4%), 128 (M$^+-$C$_6$H$_5$O, 19%), 121 (C$_6$H$_5$OCH$_3$, 100%), 115 (C$_6$H$_5$+*, 12%), 91 (C$_6$H$_4$+*, 10%).

2-Benzyl-[1.1.3-D$_3$]-indene 1a ($X = H$) and 2-(3'-methoxybenzyl)-[1.1.3-D$_3$]-indene 1a ($X = 3'$-OCH$_3$)

5 mmol of the indene are added to a mixture of D$_2$O (99.75%, Merck) (3.0 g, 150 mmol), pyridine (5 g, distilled twice from CaH$_2$), and triethylamine (0.5 g, 5 mmol, freshly distilled, b. p. 87–88 °C). The tightly stopped bulb was heated to 80 °C.
(bath) overnight with stirring (some h will suffice to achieve equilibrium). The volatile components are removed carefully under oil pump vacuum. The residue, containing ca. 87% of the d₃-indene, is subjected twice to the same procedure and is then purified by recrystallization from ethanol (1b (X = H); yield 84%; m. p. 47–48 °C) or by short-path distillation (1a (X = 3'-OCH₃); 95%). Deuterium content is typically 99% (98.1% d₂, 1.8% d₃, by mass spectrometry, 9 eV electron impact ionization).

**Homogeneous catalytic hydrogenation and deuteriation of 2-benzylindenes 1** and 1a (X = H and 3'-OCH₃):

2-Benzyl-1(1t,2-D₃)-indane 2a (X = H)

In a 10 ml cylindric glass tube 2.10 mg (10 mmol) of 1 (X = H) are dissolved in 5 ml of dry benzene, and 45 mg (0.05 mmol) of RhCl[(C₅H₅)₂]₂ added. The tube is shut by a septum cap, connected to a micro-hydration apparatus by a syringe needle adaptor and flushed with nitrogen and then deuterium gas. Under vigorous magnetic stirring the stoichiometric amount of D₂ is absorbed at ambient temperature in ca. 12–15 h, but stirring is continued another 12–24 h until absorption has ceased. (Towards the end of the deuteration reaction the light-red solution gets deep-red, indicating irreversible reaction of the catalyst). The solution is filtered through kieselgel/benzene, the solvent then evaporated and the residue purified by Kugelrohr distillation (b.p. 145–150 °C/0.01 mbar), affording 2a (X = H) as a colourless oil in nearly quantitative yield. 1H NMR (CDCl₃/TMS): δ (ppm) 2.65 and 2.95 (AB-system, J = -15.8 Hz, 2 H²; see discussion), 2.64 (br. sing., 1 H³), 2.75 (sing., << H³), 6.8–7.6 (mult., 9 H₄; see discussion), Deuterium content (MS, 70 eV): 96.9% d₂, 2.2% d₃, 0.9% d₄ ≥ 98.0% [3].

2-(3'-Methoxybenzyl)-1(1t,2-D₃)-indane 2a (X = 3'-OCH₃)

This compound was obtained in the same way from the corresponding indene (1, X = 3'-OCH₃) as a colourless oil (b.p. 155–160 °C, 0.01 mbar). 1H NMR (CDCl₃/TMS): δ (ppm) 2.65 and 2.97 (AB-system, J = -16.0 Hz, 2 H²), 2.63 (br. sing., 1 H³), 2.73 ppm (sing., 2 H²; and, in part, H³), 3.76 (sing., 3 H²; see discussion), 6.7–6.95 (mult., 3 H₄; see discussion), and 7.0–7.35 (mult., 5 H₄; see discussion). Deuterium content (MS, 70 eV): 97.1% d₂, 2.7% d₃, 0.2% d₄ ≥ 98.5%.

2-Benzyl-1(1c,3,3-D₃)-indane 2b (X = H) and 2-(3'-Methoxybenzyl)-1(1c,3,3-D₃)-indane 2b (X = 3'-OCH₃)

These isotopomers were synthesized in the same manner by using the corresponding indenes 1a (X = H and X = 3'-OCH₃) (see above) and D₂ gas. 1H NMR (CDCl₃/TMS) of 2b (X = H): δ (ppm) 2.6–2.85 (mult., H², 2 H²). 6.9–7.45 (mult., 3 H₄; see discussion), Deuterium content (MS, 70 eV): 99.6% d₂, 2.7% d₃, 0.4% d₄ ≥ 98.8%. 1H NMR of 2b (X = 3'-OCH₃): δ (ppm) 2.6–3.0 (mult., H², 2 H²). 3.78 (sing., 3 H²; see discussion), 6.7–6.9 (mult., 3 H₄; see discussion), and 7.05–7.3 (mult., 5 H₄; see discussion). Deuterium content (MS, 70 eV): 96.4% d₂, 3.0% d₃, 0.5% d₄, 0.1% d₅ ≥ 98.6%.

2-Benzyl-1(1,1,2,3,3-D₅)-indane 2c (X = H)

This isotopomer was obtained from 1a (X = H) using D₂ gas. 1H NMR (CDCl₃/TMS): δ (ppm) 2.75 (sing., 2 H²), 6.8–7.6 (mult., 3 H₄; see discussion). Deuterium content (MS, 70 eV): 87.1% d₂, 1.2% d₃, 11.1% d₄, 0.6% d₅ ≥ 97.8%.

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[7] As a marked example, the deuteriation of 2-benzyl-
[1,1,2,3,3-D₅]-indene 1a (X = H, see scheme 1) in ethanol
over palladium on charcoal (Merek) affords 19% [D₅]-, 68% [D₄]-, and 9% [D₃]-indane 2 (X = H); use of [D₅]-ethanol gives 7% [D₄]-, 83% [D₃]-, and 10% [D₂]-hydrocarbon.
[12] The mass spectrometric fragmentation of 2 (X = H) is preceded by a partial epimerization of the C{sup 2}H{sub 2} and D{sup 2}H{sub 2} groups which is suppressed in the presence of a 3{sup 3}-methoxy substituent [3].
[13] For reviews on metastable ions, see, e.g.: a) K. Lev-