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Deuteration study to elucidate hydrogenolysis of benzylic alcohols over supported palladium catalysts

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Abstract

Deuteration in combination with multinuclear NMR spectroscopy was applied to elucidate the pathway of the C–O bond scission of 1-(4-isobutylphenyl) ethanol (4-IBPE) to 4-isobutylethylbenzene (4-IBEB) over Pd/SiO_2, Pd/C, and unsupported Pd black. Information about the pathway was obtained by determining the positions at which deuterium was incorporated by means of ^1H, ^2H, and ^{13}C NMR spectroscopy. The C–O bond scission of 4-IBPE over Pd/SiO_2 and Pd black occurred exclusively by direct hydrogenolysis, whereas both hydrogenolysis and the dehydration–hydrogenation route were observed over Pd/C. The latter was attributed to the acidic nature of the carbon support. Spillover of dissociatively adsorbed hydrogen from the metal surface to the support does not play an important role in the direct hydrogenolysis of 4-IBPE over Pd.

Keywords: Benzylic alcohols; Deuterium; Hydrogenolysis; Palladium; ^1H, ^2H, ^{13}C NMR

1. Introduction

The selective hydrogenation of aromatic ketones to the corresponding alcohols is an important reaction in the fine chemicals industry. Supported Pd catalysts are usually the catalysts of choice for these reactions due to their ability to selectively hydrogenate the carbonyl functional group under mild operating conditions [1,2]. The selective hydrogenation of 4-isobutylacetophenone (4-IBAP) to 1-(4-isobutylphenyl) ethanol (4-IBPE) (Scheme 1) is an intermediate reaction step in the multistep synthesis of ibuprofen [3]. The desired product 4-IBPE is further carbonylated to yield ibuprofen. Ibuprofen can be administered as a racemate because the inactive (R)-enantiomer undergoes *in vivo* inversion of configuration, providing the active (S)-enantiomer [4]. Though 4-IBPE is the desired product, the formation of the undesired 4-isobutylethylbenzene (4-IBEB) is also observed, especially when using acidic supports or at higher hydrogen pressures. Whereas Pd/C is the most commonly used catalyst as mentioned in many patents [3,5,6], Ru/Al_2O_3 [7], and Ni/HY [8] also have been reported for this system. We recently reported on the performance of Pd/SiO_2 for this particular reaction [9]. The formation of the undesired 4-IBEB was observed in all of these studies [7–9].

There are two possible routes for the transformation of 4-IBPE to 4-IBEB (Scheme 2): dehydration–hydrogenation and direct hydrogenolysis [10] of the C–O bond of 4-IBPE. The first route proceeds via the formation of an intermediate, 4-isobutylstyrene (4-IBSty), followed by further hydrogenation to yield 4-IBEB. Chaudhari et al. [7,8] postulated the dehydration–hydrogenation route for the formation of 4-IBEB over Ru/Al_2O_3 and Ni/HY catalysts, although no evidence of the intermediate 4-IBSty was seen on GC analysis. Elucidation of the exact pathway is important from the viewpoint of accurate kinetic modeling, because the acidic support also participates when the transformation of 4-IBPE to 4-IBEB occurs by the dehydration–hydrogenation pathway and thus must be

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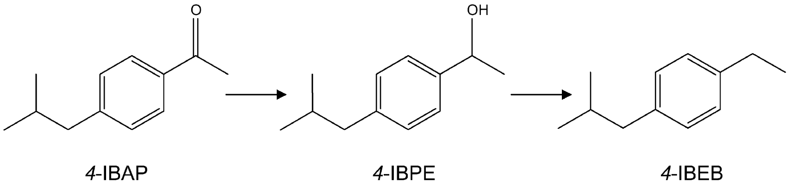
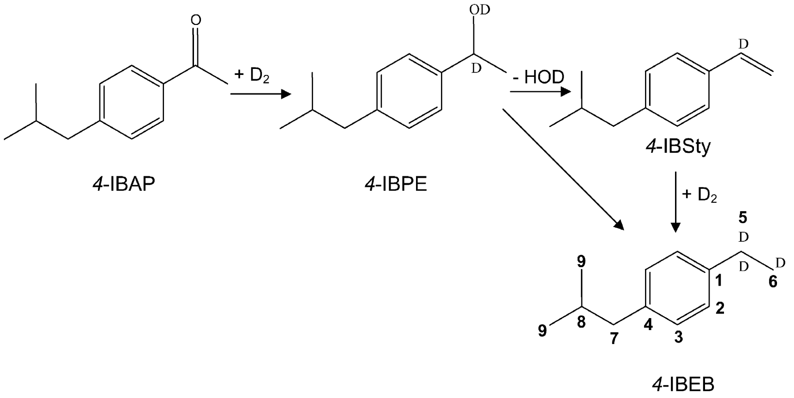


Scheme 1. Reaction scheme for the hydrogenation of 4-isobutylacetophenone over supported Pd catalysts.



Scheme 2. Pathways to C–O bond cleavage of 1-(4-isobutylphenyl) ethanol.

accounted for in the kinetic rate expression. Furthermore, for this reaction system, the catalyst is known to deactivate [8,9]; one reason for this could be the polymerization of the intermediate 4-IBSty formed when the C–O bond scission of 4-IBPE proceeds via the dehydration–hydrogenation route. Thus, it is important to understand the exact pathway for the transformation of 4-IBPE to 4-IBEB.

Conclusive evidence of the reaction pathway can be obtained through deuteration studies by determining the positions at which deuterium is incorporated in the resulting 4-IBEB by means of ^{1}H, ^{2}H, and ^{13}C NMR spectroscopy. Burwell [11] demonstrated the power of deuteration experiments in elucidating hydrogenation mechanisms. Within the scope of this topic, Ranade and Prins [12] applied deuteration to conclude that C–O bond scission in 1-indanol hydrogenation over Rh/C occurred only by direct hydrogenolysis on the support. The aim of the present study was to identify the pathway of transformation of 4-IBPE to 4-IBEB over Pd catalysts such as Pd/SiO_2, Pd black, and Pd/C using multinuclear NMR spectroscopy.

2. Experimental

2.1. Materials

4-IBAP was purchased from Alfa Aesar, 4-IBPE was home-made at the Organic Chemistry Department of the Delft University of Technology, and cyclohexane (undeuterated), 5% Pd/C, and Pd black were purchased from Aldrich. The isotopic purity of deuterium gas (Aldrich) was 99.8%. All chemicals were used as received without further purification. The in-house-prepared Pd black was obtained by calcining Pd(II) nitrate precursor (Aldrich) in air at 673 K, followed by reduction in flowing H_2 at 373 K. Preparation of the Pd/SiO_2 has been described elsewhere [9].

2.2. Deuteration

The deuteration experiments were performed in a 500-ml stainless steel autoclave. In a typical deuteration experiment, the desired amount of reactant (4-IBAP) and solvent (cyclohexane) were charged to the reactor along with the prereduced catalyst. The contents ($\sim$200 ml) were flushed with nitrogen three times at room temperature. After the desired reaction temperature was attained, the system was pressurized with deuterium (^{2}H) to the required pressure, and the stirrer was switched on. The semi-batch experiments were carried out at standard conditions of 373 K, 0.15 mol/L of 4-IBAP in cyclohexane, 2.0 MPa ^{2}H pressure, and a stirring speed of 1500 rpm using 0.3 g of catalyst. After the reaction was complete, the reactor was cooled to room temperature and depressurized prudently. Off-line GC analysis was performed with a Chrompack gas chromatograph (CP9001 autosampler), equipped with a CP Sil 8 CB column (50 m × 0.25 mm), under the following conditions: FID temperature, 523 K; injector temperature, 523 K; column temperature ramped uniformly from 323 to 523 K at 6.7 K/min. After the reaction, the catalyst was filtered from the reaction mixture, and the product 4-IBEB was obtained from cyclohexane under reduced pressure. The NMR spectra were recorded on a Varian Inova-300 spectrometer operating at 25 °C at 300 MHz for ^{1}H, 75 MHz for ^{13}C, and 46 MHz for ^{2}H. Samples were prepared in 5-mm tubes using $CDCl_3$ and TMS as an internal standard.

2.3. Surface chemistry

Temperature-programmed decomposition–mass spectroscopy (TPD-MS) measurements were performed in a conventional flow apparatus using a quartz microreactor and He as carrier gas flowing at 50 STP cm^3/min. About 200 mg of

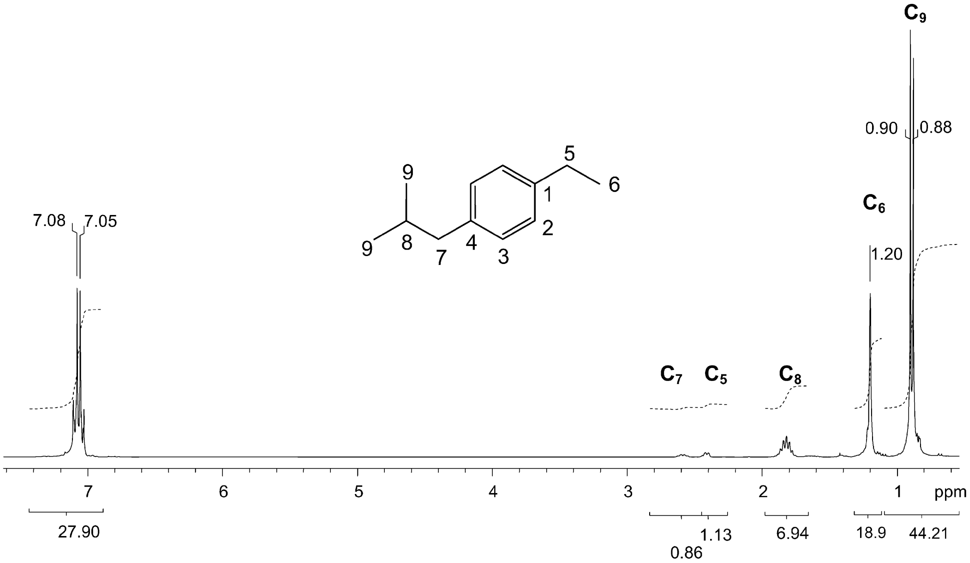


Fig. 1. ^{1}H NMR spectrum of 4-IBEB obtained by 4-IBAP deuteration over Pd/SiO$_2$.

sample (5% Pd/C) was heated at a rate of 10 K/min up to 1173 K. The desorption of gaseous species from the sample were monitored with a quadrupole mass spectrometer (Balzers) connected on-line with the reactor. Mass spectra were recorded in multiple-ion detection (MID) mode using a channeltron detector. The evolved CO and CO$_2$ were calibrated as described by Wang and McEnaney [13] using thermal decompositions of calcium carbonate and calcium oxalate.

Titration curves were used to determine the surface acidity of the commercial 5% Pd/C sample [14]. Weighed amounts of material (∼280 mg) were mixed with a KCl solution (7 ml, 0.1 M). Increasing amounts (50–500 µl) of aqueous NaOH (0.5 M) solution were added. After sealing and equilibration with gentle agitation for 72 h at room temperature, the pH values of the solutions were determined using a Metrohm 580 ion-activity meter. The Boehm titration method was used to quantify the various types of acidic surface groups [15]. The results are expressed as mmol OH$^-$ equivalent/g$_{\mathrm{carbon}}$.

NH$_3$-TPD to determine the surface acidity of the SiO$_2$ sample (50 mg) was carried out in a Micromeritics TPR/TPD 2900 at 473–723 K after three consecutive saturation steps with pure NH$_3$ at 473 K.

3. Results and discussion

Deuteration experiments offer a possibility way to differentiate the pathways of transformation of 4-IBPE to 4-IBEB (Scheme 2). If the transformation proceeds through the dehydration–hydrogenation route, then deuterium incorporation should be observed at carbon 6, whereas no deuterium incorporation on this carbon would be expected if the transformation proceeded by direct hydrogenolysis of the C–O bond. Under the chosen experimental conditions, saturation of the aromatic ring did not occur for any of the catalysts studied. In the absence of proton-deuterium exchange, three deuterium atoms (two on carbon 5 and one on carbon 6) should be theoretically incorporated into the product 4-IBEB if dehydration–hydrogenation is the main pathway, and two deuterium atoms (on carbon 5) if hydrogenolysis is the predominant route. As seen from the ^{1}H NMR spectrum (Fig. 1), extensive deuterium incorporation is observed on carbon 5 and carbon 7 when Pd/SiO$_2$ is used as a catalyst, indicating H/D exchange at the benzylic positions. As the integral for a single proton (assumed not subjected to exchange) on carbon 8 (1.8 ppm) is 6.94, theoretically an integral of 13.88 would be expected for the two hydrogens on carbon 5 (2.4 ppm, 2H) and carbon 7 (2.6 ppm, 2H) in the absence of any addition/exchange of deuterium. The observed integrals of 0.86 on carbon 7 and of 1.13 on carbon 5 imply 94% incorporation of deuterium on carbon 7 and 92% on carbon 5.

In the normal ^{13}C NMR spectrum, carbon atoms with no bonded deuterium appear as singlets, because the carbon nucleus is decoupled from the hydrogen nucleus. Multiplicity arises due to the coupling of a carbon nucleus with a deuterium atom [12]. The ^{13}C NMR spectrum in Fig. 2 clearly shows that no significant deuterium incorporation occurs on the aromatic carbons 1–4 or on carbons 6, 8, and 9; otherwise, they would exhibit multiplicity. The extensive deuterium exchange on carbon 7 can be explained by the fact that the benzylic C–H bond is weaker than the others and leads to the formation of a conjugated adsorbed system after the C–H dissociation (Scheme 3). Repeated C–H dissociation and D–* addition can account for essentially complete exchange at carbon 7.

Besides CD$_2$-type carbon atoms, some CH$_2$- and CHD-type carbon atoms on carbon 5 are also seen on the detailed ^{13}C NMR spectrum (Fig. 3). The triplet (28.38, 28.121, 27.862 ppm) and the quintet (28.28, 28.02, 27.77, 27.52, 27.26 ppm) both with coupling constant (J) of ca. 19 Hz are attributed to the mono- and bi-deuterated carbon 5 (Fig. 3a). The peak at 26.96 in Fig. 3a is assigned to the CH$_2$-type carbon. Similarly, mono- and bi-deuterated carbon are also seen on carbon 7 as a triplet (44.45, 44.71, 44.96 ppm) and a quintet (43.79, 44.04, 44.30, 44.55, 44.80 ppm) with the same coupling constant (Fig. 3b). In addition, some residual CH$_2$-type

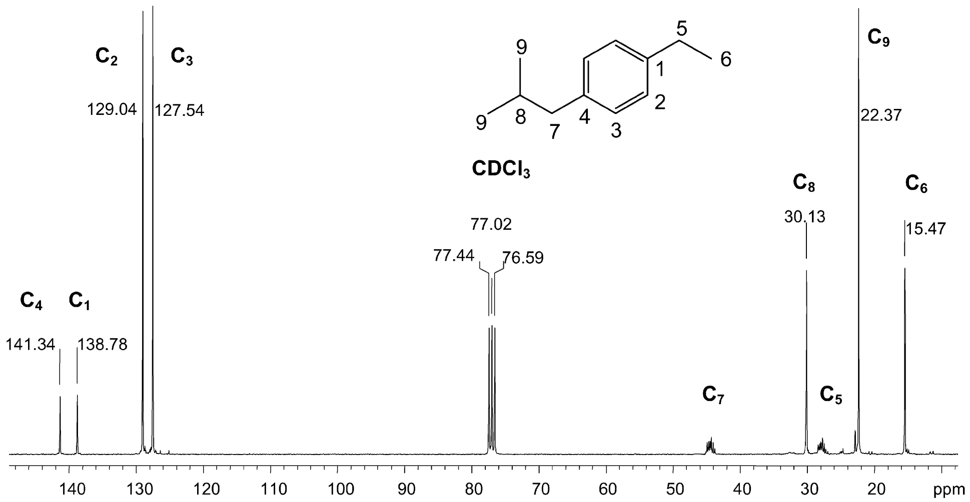
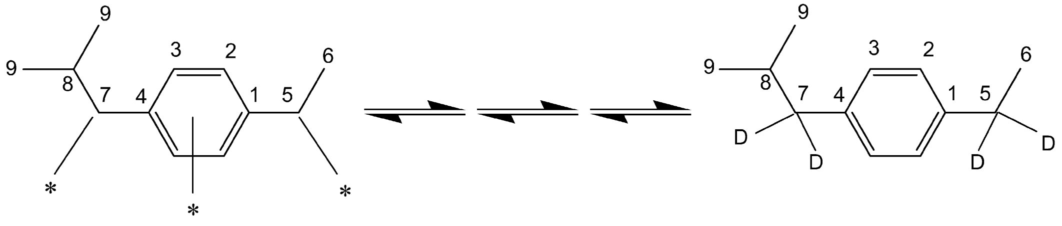


Fig. 2. ^{13}C NMR spectrum of 4-IBEB obtained by 4-IBAP deuteration over Pd/SiO_2.



Scheme 3. H/D exchange/addition occurring on carbon 5 and carbon 7 of 4-IBEB.

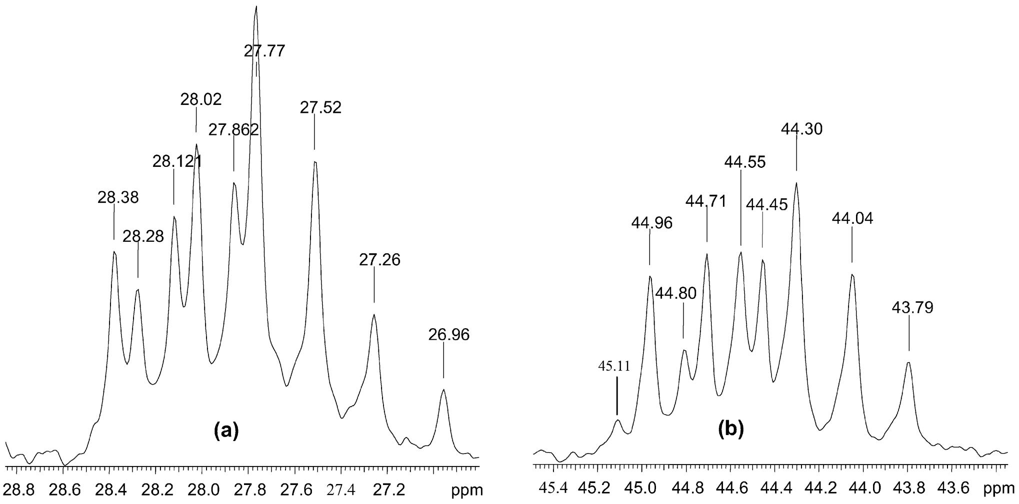


Fig. 3. ^{13}C NMR spectra of 4-IBEB indicating (a) multiplicity on carbon 5 and (b) multiplicity on carbon 7.

carbon 7 is seen at 45.11 ppm. The source of the hydrogen may be either the substrate or the solvent, as was also suggested by Ranade and Prins [12]. An experiment in which the catalyst was reduced with hydrogen instead of deuterium gave results similar to those shown in Fig. 3, although the degree of deuteration was obviously lower (by 7%).

Two peaks, at 2.4 and 2.6 ppm, in the proton-decoupled ^{2}H NMR spectrum provide conclusive evidence of deuterium incorporation on carbon atoms 5 and 7, respectively (Fig. 4). Furthermore, minor peaks (0–2 ppm) are observed in the ^{2}H NMR spectrum, possibly due to artefact.

The essential absence of deuterium on carbon 6 (Fig. 4) demonstrates that the transformation of 4-IBPE to 4-IBEB over a Pd/SiO_2 occurs exclusively by direct hydrogenolysis of the C–O bond. The elimination of H_2O from 4-IBPE leading to 4-IBSty can be excluded. The hydrogenolysis of 4-IBPE can occur through one of two possible mechanisms: (i) an S_N2-type mechanism, in which the surface hydrogen displaces the hydroxyl group from its attachment to the carbon atom [10], or (ii) a more stepwise mechanism starting with the dissociation of the C–O bond and temporary bonding of the OH group and of the hydrocarbon residue (Scheme 3) on the Pd surface.

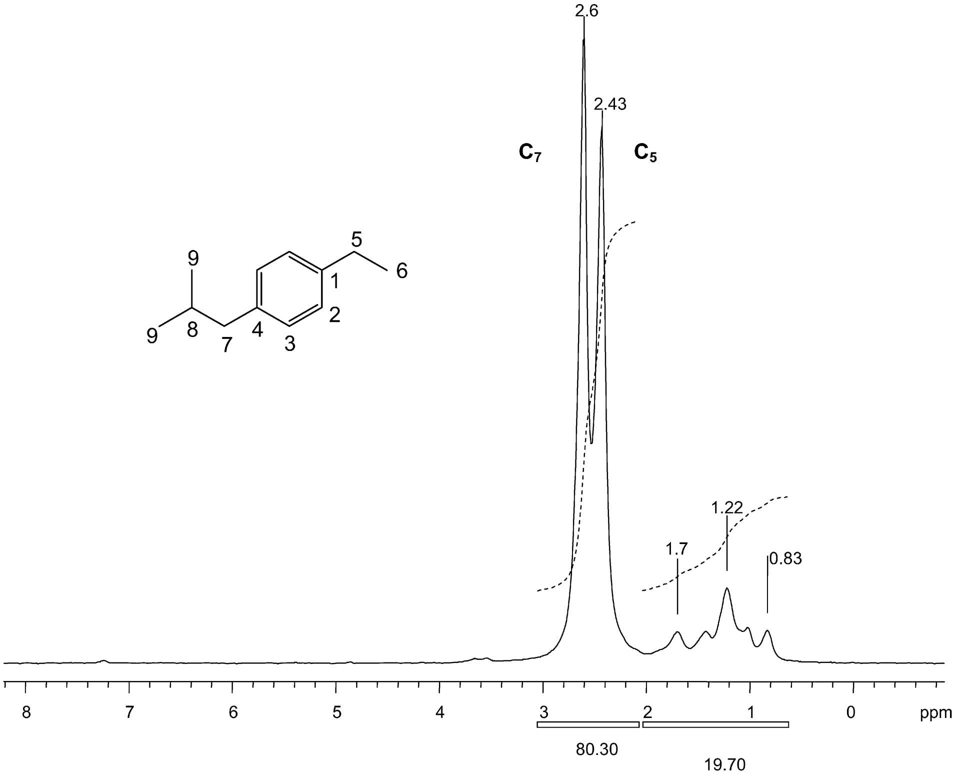


Fig. 4. Proton decoupled ^{2}H NMR spectrum of 4-IBEB product of the deuteration of 4-IBAP over Pd/SiO$_2$.

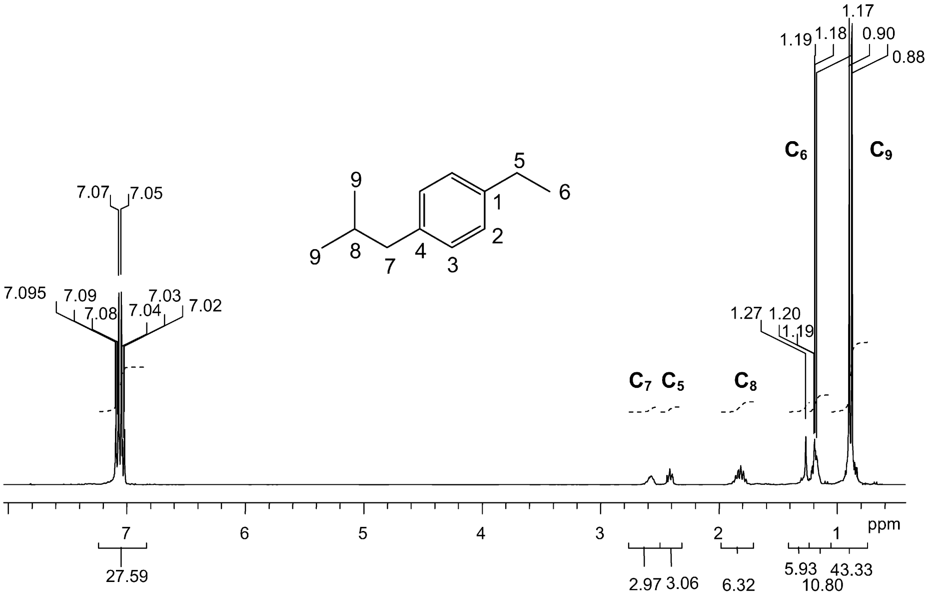


Fig. 5. ^{1}H NMR spectrum of 4-IBEB obtained by 4-IBAP deuteration over Pd/C.

The ^{1}H, ^{2}H, and ^{13}C NMR spectra of 4-IBEB obtained by 4-IBAP deuteration over 5% Pd/C differed considerably from those obtained using the 5% Pd/SiO$_2$ catalyst. Apart from the 78 and 74% deuterium incorporation on carbons 7 (2.6 ppm, 2H) and 5 (2.4 ppm, 2H), respectively, as seen in the ^{1}H NMR spectrum of the product 4-IBEB (Fig. 5), significant deuterium incorporation also occurred on carbon 6 (1.19 ppm). This finding was further confirmed by the multiplicity of the peak corresponding to carbon 6 in the ^{13}C NMR spectrum (Fig. 6). The proton-decoupled ^{2}H NMR spectrum (Fig. 7) indicates the presence of deuterium on carbon 6 (1.24 ppm) in addition to that on carbon 5 (2.4 ppm) and carbon 7 (2.6 ppm). This indicates that the transformation of 4-IBPE to 4-IBEB occurs through a combination of the dehydration–hydrogenation pathway and the direct hydrogenolysis pathway over a Pd/C catalyst. Based on the ^{1}H NMR spectrum, an integral of 18.96 would be expected for the hydrogens on carbon 6 (1.2 ppm, 3H), because the integral for a single proton on carbon 8

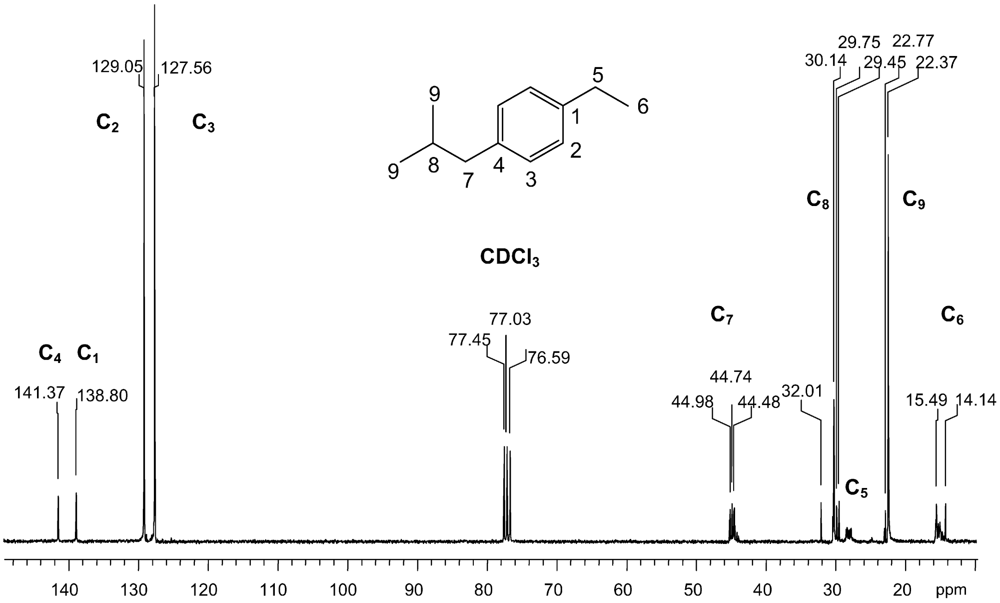


Fig. 6. ^{13}C NMR spectrum of 4-IBEB obtained by 4-IBAP deuteration over Pd/C.

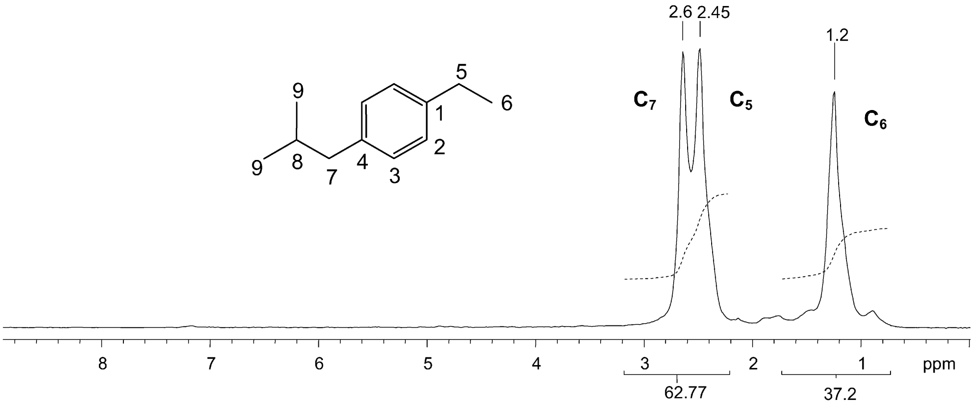


Fig. 7. Proton decoupled ^{2}H NMR spectrum of 4-IBEB product of the deuteration of 4-IBAP over Pd/C.

(1.8 ppm) is 6.32. The integral of 10.8 on carbon 6 suggests 43% deuterium incorporation, compared with the theoretically expected 33%. However, it was not possible to distinguish between the presence of CH_2D-type carbons or CHD_2- and CD_3-type carbons on carbon 6. This result is in contrast to that presented by Ranade and Prins [12], who concluded that the C–O bond scission of 1-indanol over a Rh/C catalyst occurred solely by direct hydrogenolysis. This can be explained by the fact that carbon supports are frequently activated before deposition of the active metal by treatment with mineral acids that oxidize the surface. This oxidative treatment leads to the creation of surface acidic sites [16,17] that might impart acidity to the Pd/C catalyst, thereby promoting the dehydration of the 4-IBPE in our case. This assumption suggests that the C–O bond scission pathway depends on the acidity of the support used.

TPD-MS measurements are useful for characterizing the type of surface oxygen groups present on the carbon [18]. In an inert atmosphere, the surface oxygen complexes desorb primarily as CO and CO_2. CO_2 appears at relatively low temperatures and is attributed to the decomposition of carboxylic acid and/or anhydride groups—acidic groups in which C is bonded to two oxygen atoms. On the other hand, CO desorption occurs at higher temperatures from the decomposition of different types of surface oxygen complexes: phenolic, carbonyl, quinone, ether, and pyrone groups—weakly acidic, neutral, and basic groups in which C is bonded to one oxygen atom. The TPD profile of the 5% Pd/C (Fig. 8) shows the presence of CO_2 and CO peaks. CO_2 evolution ranges from 300 K to around 1050 K, with a maximum at 550 K and shoulders at around 750 K. The former peak can be assigned to carboxylic acid groups; the latter, to lactonic groups [18]. The groups that are decomposed above 810 K produce mainly CO and CO_2 and are attributed to the anhydride groups. The CO_2 desorption peak shows the presence of acidic sites on the 5% Pd/C catalyst.

The titration method gives additional information on the character of the oxygen surface functionalities. The titration curve for 5% Pd/C shown in Fig. 9 indicates the presence of weak carboxylic acid groups as well as phenolic groups on the carbon surface. The presence of these groups might impart sufficient acidity to the carbon support to account for the observed

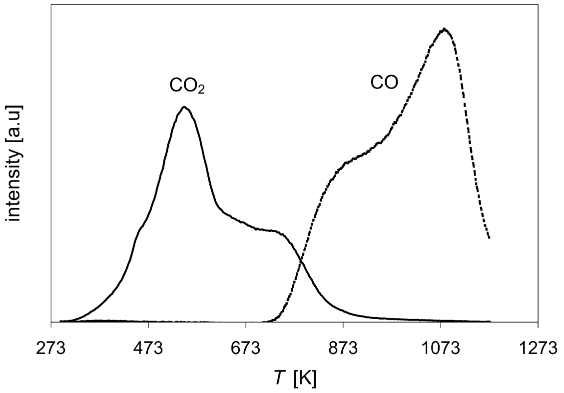


Fig. 8. TPD profiles of 5% Pd/C catalyst.

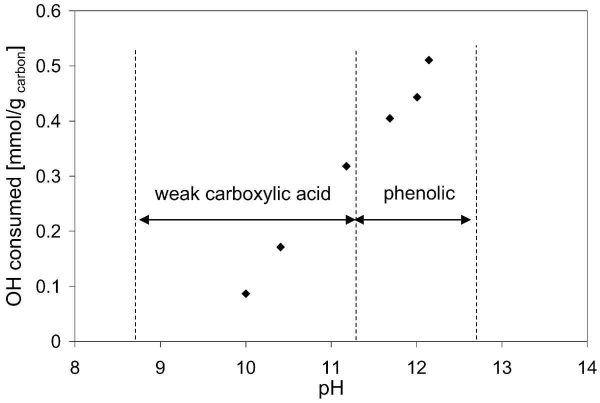


Fig. 9. Base adsorption capacity of 5% Pd/C as a function of pH.

dehydration of 4-IBPE to 4-IBSty over 5% Pd/C. The NH_3-TPD spectrum of the SiO_2 support (not shown here) did not show any desorption of NH_3, indicating that the SiO_2 support did not have sufficiently strong acidic sites. This might explain why we did not observe the dehydration–hydrogenation pathway when using Pd/SiO_2.

To investigate whether the hydrogen dissociated on the Pd or the hydrogen that spilled over onto the support after dissociation on Pd was responsible for the hydrogenolysis of the C–O bond, we performed a hydrogenation run over a Pd black catalyst. The formation of 4-IBEB (Fig. 10) implied that the hydrogenation occurred on the Pd surface without the involvement of any hydrogen spilled over on the support. Furthermore, the initial reaction rate ($\text{mmol}/\text{m}_{\text{Pd}}^2/\text{s}$) for the hydrogenation run over Pd black was in the same order of magnitude as that over a Pd/SiO_2 catalyst. Clearly, hydrogen spillover is not involved in the direct hydrogenolysis of the C–O bond of 4-IBPE over Pd.

4. Conclusion

In this study, deuteration in combination with multinuclear NMR spectroscopy elucidated the pathway of the C–O bond scission of 1-(4-isobutylphenyl) ethanol (4-IBPE) to 4-isobutylethylbenzene (4-IBEB) over Pd/SiO_2, Pd/C, and unsupported Pd black. The C–O bond scission of 4-IBPE was seen to occur exclusively by the direct hydrogenolysis route over Pd/SiO_2 and Pd black, whereas the dehydration–hydrogenation route also played an important role when Pd/C was used. This is attributed to the relatively higher acidity of the carbon support compared with the SiO_2 support. Experiments performed with unsupported Pd black suggest that the hydrogen dissociated on the metal surface plays the major role in the direct hydrogenolysis on Pd with no involvement of the support.

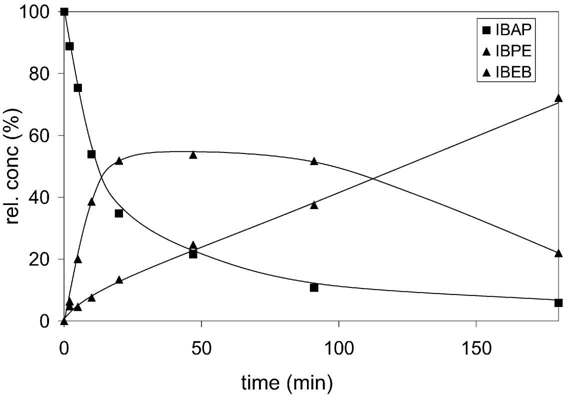


Fig. 10. Relative concentration versus time profile for the hydrogenation of 4-IBAP over a commercial Pd black catalyst Reaction conditions: $w_{\text{cat}} = 0.1$ g, $T = 373$ K, $P_{H_2} = 2.0$ MPa, $C_{\text{IBAP}} = 0.27$ mol/L.

Acknowledgments

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