

# Control of catalytic debenylation and dehalogenation reactions during liquid-phase reduction by H<sub>2</sub>

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## Abstract

Heterogeneous catalysis, which is being used more frequently in the fine chemicals industry, does not always provide the desired selectivity because various functional groups become labile to reduction by hydrogen on a noble metal under similar reaction conditions. To study the selectivity of debenylation versus dechlorination in an aromatic compound, the kinetics of the reduction of 4-chloro-N,N-dibenzylaniline on supported Pd catalysts in a buffered solvent under hydrogen reduction conditions were investigated. The turnover frequency on a Pd/C catalyst was 2–40 times higher than that on Pd dispersed on SiO<sub>2</sub>, TiO<sub>2</sub>, and Al<sub>2</sub>O<sub>3</sub>. The effects of hydrogen pressure, organic substrate concentration, temperature, solvent, and catalyst support on the selectivity were not great at a pH of 5.4, whereas the effect of acid or base modifiers was very significant. Only dechlorination reactions occurred under basic conditions, and the use of an acid confirmed a preferential promotion of debenylation reactions; consequently, as the pH decreased from 12 to 0.1, the selectivity for dechlorination decreased from essentially 100% to almost 0. Using a triethylamine/acetic acid buffer system to control pH, it was determined that the inflection point in selectivity corresponds to a pH value equal to the pK<sub>a</sub> of the benzyl-protected amine (4.5 in this case). Consequently, one important finding is that the dechlorination reaction can occur at high rates even under acidic conditions, as long as the pH of the reaction mixture is greater than the pK<sub>a</sub> of the protected amine. Furthermore, generation of an acidic product like HCl during a dechlorination reaction can decrease the system pH and markedly alter selectivity unless a buffer is present. For reactions carried out at a pH of 5.4, the initial rate of organic substrate consumption was modeled by a classical Langmuir–Hinshelwood sequence, with the assumption of two types of active sites, one site to adsorb H atoms and the other to adsorb the organic substrate, yielding a slightly better fit to the data. The Weisz–Prater criterion was applied to verify the absence of mass transfer effects.

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## 1. Introduction

The manipulation of functional groups is essential in multi-step organic syntheses. To avoid side reactions during a chemical transformation involving a multifunctional organic compound, some functionalities may need to be protected while carrying out reactions directed at other functional groups in the substrate (reactant). Such a protective group must attach specifically to the functional group for which it is intended, must be inert under the reaction conditions directed at other functionalities, and must be relatively easy to detach at the end of the

transformation sequence under conditions that will not affect other groups in the substrate.

For example, free amines contain a –N group that is labile under a variety of reaction conditions and thus needs to be protected to ensure its integrity over the course of a synthesis involving multiple steps. Benzyl groups are often the protective group of choice for amines, and at the end of the transformation, the free amine groups can be recreated by removing the benzyl protective group from the N atom by various reactions [1–6]. N-debenylation under catalytic reduction conditions using H<sub>2</sub> [6] is an attractive alternative solution when the use of strong acids like *p*-toluenesulfonic acid [2] or strong bases like Li di-isopropylamide [3] is not desirable; however, catalytic reduction conditions can also lead to undesired side reactions, such as dehalogenation and double-bond reduction [7,8].

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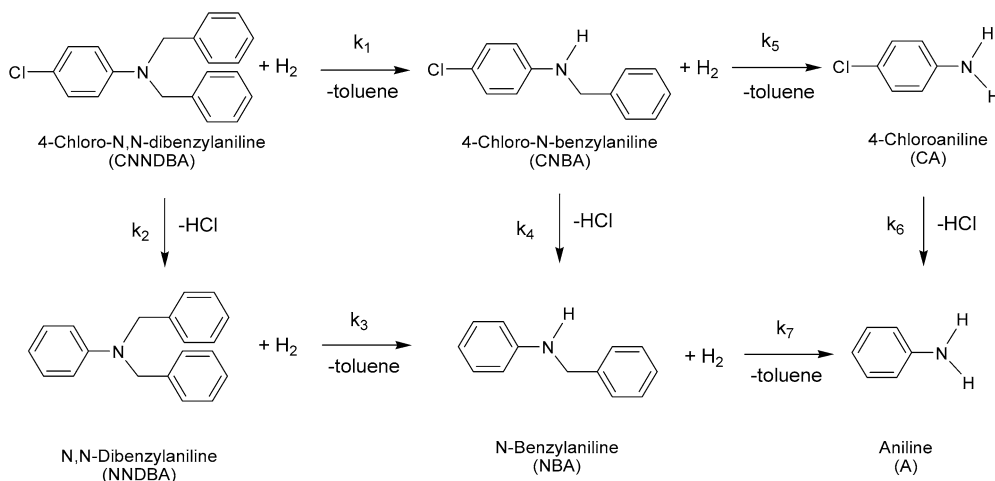


Fig. 1. Reaction network for the reduction of 4-chloro-N,N-dibenzylaniline (CNNDDBA) to aniline.

Selectivity control is also important because in some instances the dehalogenation reaction is desired and debenzylation must be suppressed. Studer and Blaser pointed out that “little is known about the selective removal of benzyl groups in molecules containing aromatic halogens, and reports of benzylated anilines are scarce and often incomplete” [9]. Thus they used 4-chloro-N,N-dibenzylaniline—a compound subject to both N-debenzylation and dehalogenation—to examine the factors determining selectivity to debenzylation products [9]. Reduction under one atmosphere of H<sub>2</sub> in the presence of a Pd/C catalyst results in the reaction network illustrated in Fig. 1. Studer and Blaser demonstrated that debenzylation is favored in the presence of acids, whereas dehalogenation is favored in the presence of bases. The choice of catalyst had no significant effect on selectivity, but carbon-supported Pd was found to be more effective for debenzylation compared with oxidic Pd or Pd(OH)<sub>2</sub>. Polar solvents appeared to favor dehalogenation, whereas nonpolar solvents seemed to favor debenzylation [9].

Our study was undertaken to obtain additional knowledge about the factors that channel the reaction pathway to either debenzylation or dehalogenation, with an emphasis on the role of pH. The substrate used by Studer and Blaser (4-chloro-N,N-dibenzylaniline [CNNDDBA]) was again chosen as a model compound. In their original work, Studer and Blaser stopped short of developing a kinetic model based on reaction rates measured at different temperatures, pressures, and reactant concentrations; therefore, another objective of our study was to acquire appropriate rate data over a range of reaction conditions to enable us to propose a kinetic model to describe the disappearance of the CNNDDBA substrate. It is well known that acidic conditions promote debenzylation [9–11], whereas basic conditions inhibit debenzylation and favor dechlorination [9,12,13]. A protonated nitrogen atom is positively charged and electron-attracting, and thus it is expected to behave differently than a neutral amine nitrogen atom, which can act as an electron donor. When starting with a neutral reaction mixture (pH = 7), the pH can drop rapidly if the parallel dehalogenation reaction is significant, because this reaction generates HCl in situ, which can then increase the rate of debenzylation. This process not

only makes it difficult to determine the effect of other reaction parameters on selectivity, but also complicates a precise study of the effect of pH on these reactions. To overcome this difficulty, we used buffered systems to maintain different pH levels and examine the selectivity in greater detail. We also investigated the influence of several solvents and of different supports for palladium.

## 2. Experimental

### 2.1. Materials

Methanol (99.8%), tetrahydrofuran (99.9%, inhibitor-free), acetic acid (glacial, 99.8%), triethylamine (99.5%), concentrated sulfuric acid (98%), hydrochloric acid (37% in water), chloroform (99.8%, stabilized with ethanol), sodium carbonate (powder, 99.5%), sodium sulfate (granular, 99+%), lithium hydroxide monohydrate (98+%), aniline (99%), 4-chloroaniline (99+%), benzyl chloride (99+%), tetradecane (99+%), and aniline (99%) were all purchased from Aldrich. N-benzylaniline (98%, GC) and N,N-dibenzylaniline (99%, GC) were purchased from TCI America. The 5% Pd/C catalyst was purchased from Johnson Matthey (A102038-5, ~50% wet). Its mean particle diameter was 30 μm and the pore size distribution was reported to be <2 nm, 0.3 ml/g; 2–10 nm, 0.2 ml/g; 10–20 nm, 0.1 ml/g; 20–30 nm, 0.05 ml/g; 30–100 nm, 0.1 ml/g; 100–500 nm, 0.35 ml/g; and 500–1000 nm, 0.3 ml/g. The Pd/Al<sub>2</sub>O<sub>3</sub>, Pd/SiO<sub>2</sub>, and Pd/TiO<sub>2</sub> catalysts were prepared in our laboratory as described previously [14,15]. Hydrogen (99.999%) and argon (99.999%) were purchased from MG Industries. The CNNDDBA substrate was prepared from 4-chloroaniline and benzyl chloride according to a procedure developed by Blaser and Studer [9], as described previously [14]. Characterization of the white CNNDDBA precipitate gave a melting point of 377–378 K (377–378 K [9]), and its <sup>1</sup>H NMR spectrum in acetone d-6 gave the following chemical shifts (δ, in ppm): 4.72 (s,4H), 6.71 (d,2H), 7.08 (d,2H), and 7.22–7.36 (m,10H).

## 2.2. Reaction apparatus

Reduction of CNNDDBA in H<sub>2</sub> was conducted in a 500-ml jacketed glass autoclave (Ace Glass) provided with a turbine agitator operated with an electrical stirrer motor (IKA-Eurostar), a thermometer, a pressure gauge, and a sampler [14]. The reactor temperature was controlled by a water bath provided with a recirculation pump (Fisher Scientific). The reactor was connected to a house vacuum system and to pressure regulators attached to hydrogen and argon cylinders. The gases were passed through a drying column (Supelco) before entering a gas flow meter (model GFM 171 TOT 1-10, Aalborg Instruments) equipped with a flow totalizer.

## 2.3. Reaction procedures

The reduction experiments were carried out in a semibatch mode at constant pressure and temperature in the jacketed Ace Glass autoclave. The solvent containing CNNDDBA was charged to the reactor, and the powder catalyst was subsequently added under mild agitation. The system was sealed and placed under an inert atmosphere by three consecutive cycles of evacuation followed by pressurization with Ar to 240 kPa. Then hydrogen was introduced, and the reactor was pressurized three times to 240 kPa in the absence of agitation. (Because of suppressed mass transfer into the solvent when the stirrer was idle, no hydrogen uptake was observed.) The system was then brought to the desired H<sub>2</sub> reaction pressure and allowed to stabilize until the gas flow meter indicated no flow. The reaction was started by rapidly raising the agitation rate to 700 RPM (zero-time point), and the desired reaction temperature was maintained using the water bath. H<sub>2</sub> was flowed through the gas meter and totalizer to maintain a constant H<sub>2</sub> pressure and to quantify consumption. Between four and six 3-ml samples were removed at different intervals, with the time and the total hydrogen uptake recorded when each sample was withdrawn.

Because of the low solubility of the reactant in many organic solvents, reactions were conducted in mixtures containing tetrahydrofuran (THF), which is the best solvent for CNNDDBA. The effects of solvent, catalyst support, catalyst pretreatment, and buffer pH on the reaction rate and selectivity were then examined, and rate data (concentration vs. time) were collected at different H<sub>2</sub> pressures (115, 156, 194, and 263 kPa), temperatures (278, 298 and 330 K), and CNNDDBA starting concentrations (9.5, 19.0, 28.3, and 37.8 μmol/ml). To minimize and control the effect of changing pH, reduction experiments were conducted in a THF solvent buffered at pH levels of 12.0, 6.0, 5.2, 4.7, 3.5, and 0.1, as measured by a pH meter (Corning model 450). All buffers with the exception of the pH = 0.1 system were prepared from triethylamine and acetic acid such that they maintained the reaction mixture within a narrow pH range ( $\pm 0.25$  pH units) throughout the course of the reaction [14]. The system with a pH of 0.1 was prepared by adding a mixture of acetic acid and H<sub>2</sub>SO<sub>4</sub> to a solution of CNNDDBA in THF. At low pH levels, the dechlorination reaction was totally suppressed and no HCl

was produced; therefore, even though the H<sub>2</sub>SO<sub>4</sub>/acetic acid mixture was not actually buffering at a pH of 0.1, the pH of the reaction mixture did not drift during the hydrogen addition.

Each sample was transferred via a filter-pipette to a vial containing 10 ml of chloroform and 10 ml of 5% aqueous sodium carbonate and shaken vigorously, and then the layers were allowed to settle. About 3 ml of the bottom chloroform phase was pipetted out, diluted 50% with chloroform, and dried over sodium sulfate before being injected directly into the GC column. (Important note: If the CNNDDBA substrate and the nitrogen-containing products are not fully deprotonated by, e.g., treating the samples with sodium carbonate, then the results of the GC analyses are inaccurate because the protonated fraction (RNH<sup>3+</sup>, R<sub>2</sub>NH<sup>2+</sup>, R<sub>3</sub>NH<sup>+</sup>) will not elute through the column, due to the strong interaction of the ionic compounds with the highly polar support.) An internal standard method using tetradecane was used to determine a response factor ( $RF_i$ ), for each component  $i$  in the reaction network. The response factors relative to the tetradecane internal standard ( $RF_{IS} = 1$ ) were as follows:  $RF_{CNNDDBA} = 1.33$  for 4-chloro-N,N-dibenzylaniline,  $RF_{NNDBA} = 1.03$  for N,N-dibenzylaniline,  $RF_{NBA} = 1.11$  for N-benzylaniline,  $RF_{CA} = 1.66$  for 4-chloroaniline, and  $RF_A = 1.21$  for aniline. The response factor for 4-chloro-N-benzylaniline (CNBA), which was not available from a commercial source, was calculated theoretically as 1.31 based on its molecular weight [16]. Programming details with the H-P 5890 Series II chromatograph fitted with a Rhino capillary column (15 m  $\times$  0.025 mm  $\times$  1 μm film thickness) are provided elsewhere [14]. Mass balances (μmol CNNDDBA reacted vs.  $\sum$  μmol products formed) agreed to within  $\pm 5\%$ .

## 2.4. Catalyst characterization

The concentration of surface Pd (Pd<sub>s</sub>) atoms (i.e., the active component in each catalyst) must be known not only to calculate a turnover frequency (TOF; molecules reacted per second per surface metal atom), but also to calculate the dispersion and average crystallite size of Pd. The Pd<sub>s</sub> atoms were counted both by hydrogen chemisorption using the method of Benson et al. [17] and by carbon monoxide chemisorption using the method of Yates and Sinfelt [18] in an experimental system described previously [19]. The 5% Pd/C catalyst, which was used without pretreatment in the reduction of CNNDDBA, was dried directly in the chemisorption cell at 393 K under high vacuum (ca. 10<sup>-7</sup> kPa) before CO isotherms were obtained for total and reversible uptakes. To check the measurement of Pd<sub>s</sub> atoms, irreversible H<sub>2</sub> adsorption at 298 K was determined after a pretreatment consisting of 2 h at 573 K under 50 cc/min of flowing H<sub>2</sub>, followed by a 30-min flush with helium and then evacuation to 10<sup>-7</sup> kPa. XRD line-broadening measurements were also conducted with the 5% Pd/C catalyst to calculate a volume-weighted average crystallite size.

Table 1  
Irreversible uptakes on and dispersions for Pd catalysts

Catalyst	Irreversible chemisorption		Dispersion	
	$\mu\text{molCO}/\text{g}_{\text{cat}}$	$\mu\text{molH}_2/\text{g}_{\text{cat}}$	CO/Pd	H/Pd
2.0% Pd/Al <sub>2</sub> O <sub>3</sub>	78.2	43.4	0.42	0.46
1.8% Pd/TiO <sub>2</sub>	46.7	24.9	0.28	0.29
2.0% Pd/SiO <sub>2</sub>	15.2	11.4	0.081	0.12
5.0% Pd/SiO <sub>2</sub>	43.9	27.9	0.093	0.12
5.0% Pd/C	61.4 <sup>a</sup>	23.9 <sup>b</sup>	0.13	0.10

<sup>a</sup> As received after evacuation and drying.

<sup>b</sup> After pretreatment in H<sub>2</sub> at 573 K and evacuation.

Table 2  
Initial rates, TOFs and selectivities for CNNDBA reduction in hydrogen over Pd catalysts

Catalyst	Initial activity for CNNDBA disappearance		Selectivity (%)
	Rate ( $\mu\text{mol}/(\text{s g}_{\text{cat}})$ )	TOF <sup>a</sup> (s <sup>-1</sup> )	
2.0% Pd/Al <sub>2</sub> O <sub>3</sub>	0.41	0.005	14
1.8% Pd/TiO <sub>2</sub>	2.37	0.051	12
2.0% Pd/SiO <sub>2</sub>	1.26	0.082	20
5.0% Pd/SiO <sub>2</sub>	2.62	0.060	26
5.0% Pd/C <sup>b</sup>	11.2	0.182	7

Reaction conditions: 298 K, THF solvent buffered at pH = 5.4,  $p_{\text{H}_2}$  = 194 kPa, 28.7  $\mu\text{mol}$  CNNDBA/ml initially.

<sup>a</sup> Based on CO chemisorption.

<sup>b</sup> Before reduction.

### 3. Results

#### 3.1. Catalyst characterization

The dispersion ( $D = \text{Pd}_s/\text{Pd}_{\text{total}}$ ) of each Pd catalyst, as determined by chemisorption measurements assuming adsorption ratios of  $\text{CO}/\text{Pd}_s = \text{H}/\text{Pd}_s = 1$ , is listed in Table 1. The  $\text{CO}/\text{Pd}_{\text{total}}$  ratio of 0.13 for the untreated 5% Pd/C catalyst is in good agreement with the dispersion of 0.10 obtained from hydrogen chemisorption on the pretreated catalyst; therefore, the irreversible CO uptake of 61.4  $\mu\text{mol}/\text{g cat}$  was used to calculate the TOF for all CNNDBA reduction reactions on the 5% Pd/C catalyst. The surface-weighted average crystallite size for the 5% Pd/C catalysts, based on CO adsorption and the relationship  $\bar{d}_s = 1.13/D$ , was  $\bar{d}_s = 8.7$  nm, whereas a volume-weighted average crystallite size of 17 nm was obtained from XRD line-broadening measurements.

#### 3.2. Effect of catalyst support

Reduction reactions of CNNDBA in hydrogen were carried out over the five catalysts under a standard set of reaction conditions, which are given in Table 2 along with initial activity and selectivity. The selectivity ( $S$ ) for debenzilation is defined as  $S = \text{rate of debenzilation}/(\text{rates of debenzilation} + \text{dechlorination})$ . To counter the effect of changing pH on the overall reaction rate due to the formation of HCl from the dechlorination reaction, this comparison was conducted within a narrow pH range ( $5.4 \pm 0.25$ ) using a triethylamine/acetic acid buffer. Table 2 shows the initial rates of CNNDBA con-

sumption along with the corresponding TOFs based on Pd<sub>s</sub> atoms obtained from the CO chemisorption data. Except for the 5% Pd/C catalyst, all catalysts used for the runs summarized in Table 2 were pretreated in H<sub>2</sub> at 573 K for 2 h, evacuated, and then passivated in air at 300 K to create a layer of chemisorbed oxygen before being used in the reactor. The low rates with the oxide-supported catalysts are not due to mass transport limitations, because the Weisz–Prater (W-P) numbers were much smaller than those for the Pd/C catalyst, as discussed later. It is more likely that the low activities are due to the absence of an in situ high-temperature reduction of the passivated catalysts before their use. At this pH, a low selectivity for debenzilation is expected, and the uncertainty limits in the pH control could account for much of the variations in selectivity because of the strong dependence on pH in this region (see Fig. 5).

#### 3.3. Effect of solvent

It has been established that the presence of acids promotes debenzilation, whereas the presence of bases favors dechlorination [9,11,12]. Indeed, Fig. 2 indicates that the reaction generates almost exclusively debenzilation products (CNBA and CA) when sulfuric acid is present, and this composition profile replicates the results reported for a Pd/C catalyst (experiment #19) very nicely [9], with the only difference in reaction conditions being a H<sub>2</sub> pressure of 156 kPa instead of 101 kPa. The solubility of CNNDBA depends significantly on the nature of the solvent, with the best solvents being polar nonprotic solvents like tetrahydrofuran (THF) and acetone, whereas polar protic solvents like methanol and acetic acid provide only limited solubility. The availability of transferable protons in the liquid reaction mixture clearly influences the product distribution during CNNDBA reduction, as shown in Figs. 2a–d, and an abundance of transferable protons also enhances the initial rates and TOFs, as shown in Table 3.

#### 3.4. Effect of pH

Studer and Blaser showed that acids promote the debenzilation pathway, whereas bases promote the dechlorination pathway [9]. When starting with a reaction mixture that contains neither acidic nor basic modifiers, the overall reaction rate and the selectivity can change continually because the slightly basic starting mixture (the amine functionality of CNNDBA has basic character) becomes acidic due to HCl produced by dechlorination; thus the product of the latter pathway becomes a “promoter” for the debenzilation reaction. To examine the effect of pH, runs were conducted with 100  $\mu\text{mol}$  CNNDBA/ml at 298 K and 156 kPa H<sub>2</sub> in THF at buffered pH levels of 0.1, 3.5, 4.7, 5.2, 6.0, and 12.0. Figs. 3a–f illustrate the changes in product distribution going from a reaction mixture at a pH of 0.1 to one at a pH of 12. It can be seen from Figs. 3a–f that at lower pH levels, the debenzilation pathway is predominant, whereas at higher pH levels, dechlorination is favored. Table 4 summarizes the initial rates of CNNDBA conversion for reaction mixtures

buffered at different pH values, based on CNNDDBA concentrations, and Fig. 4 illustrates the dependence of the initial rate of CNNDDBA reduction on the pH of the buffered reaction mixture.

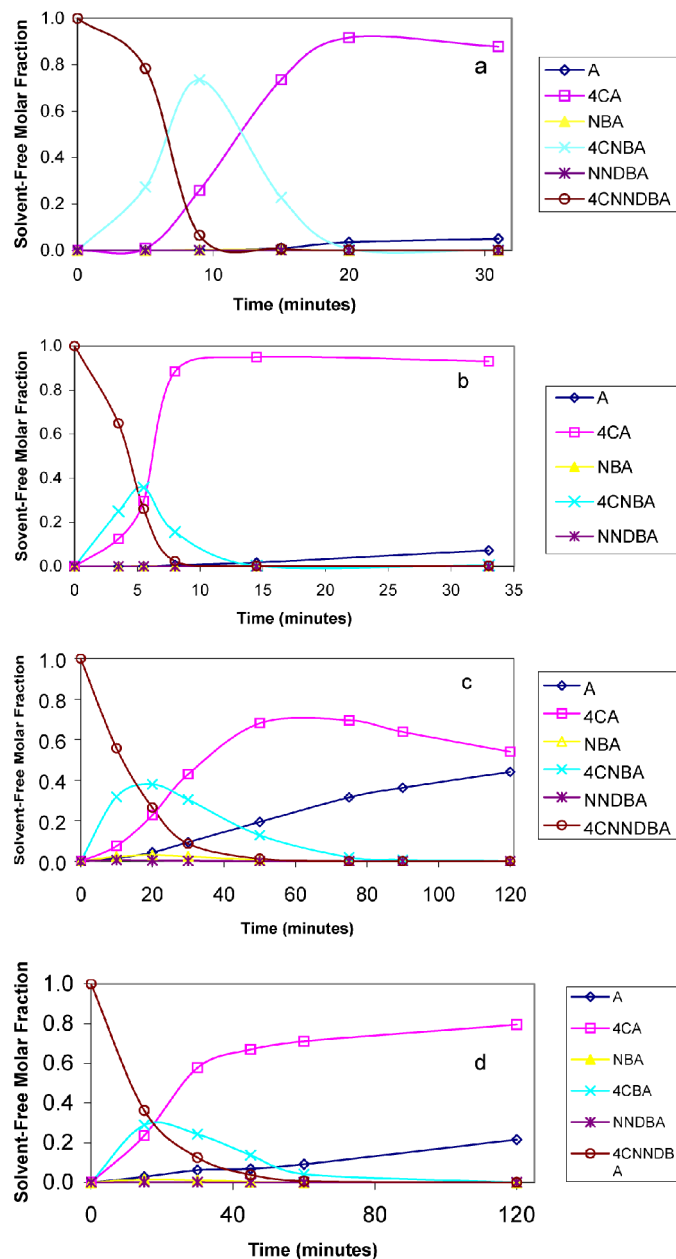


Fig. 2. Temporal composition profile during CNNDDBA reduction on 5% Pd/C at 298 K and 156 kPa H<sub>2</sub>: (a) in CH<sub>3</sub>OH with 120 μmol CNNDDBA/ml and 120 μmol H<sub>2</sub>SO<sub>4</sub>/ml; (b) in acetic acid with 33 μmol CNNDDBA/ml; (c) in THF + H<sub>2</sub>O (4:1 by wt) with 95 μmol CNNDDBA/ml; (d) in THF + CH<sub>3</sub>OH (7:3 by wt) with 95 μmol CNNDDBA/ml.

Table 3  
Initial reaction rates and TOFs for CNNDDBA reduction at 298 K Under 156 kPa H<sub>2</sub>

Solvent	Modifier	Starting CNNDDBA concentration (μmol/ml)	Initial rate of CNNDDBA disappearance (μmol/(s g <sub>cat</sub> ))	TOF for CNNDDBA (s <sup>-1</sup> )
Methanol	Sulfuric acid (120 μmol/ml)	120	499	8.12
Acetic acid	None	33	219	3.56
THF/water (4:1 by wt)	None	95	99.1	1.61
THF/methanol (7:3 by wt)	None	95	70.0	1.14

A significant change in slope is apparent at a pH just under 5, and increased acidity below this point markedly enhances the rate of debenzoylation. Table 5 gives the initial debenzoylation rate (to CNBA,  $r_B$ ) versus dechlorination rate (to NNDBA,  $r_C$ ) for reaction mixtures buffered at different pH levels, based on product concentrations. Fig. 5 shows that the pH controls the reaction pathway ( $r_B$  or  $r_C$ ) and, at a pH of around 4.5, the selectivity for debenzoylation equals that for dechlorination.

### 3.5. Effect of temperature, substrate concentration, and hydrogen pressure

The effects of temperature, initial CNNDDBA concentration, and hydrogen pressure on the initial rate of CNNDDBA disappearance and the debenzoylation selectivity were studied during CNNDDBA reduction over 5% Pd/C in THF solutions under hydrogen, with solutions buffered at a pH of 5.4 using triethylamine/acetic acid. Initial rates and TOFs for CNNDDBA reduction were determined at 278, 298, and 330 K, and the selectivity to debenzoylation was calculated, as given in Table 6. These rates give an activation energy of 34.2 kJ/mol [14]. The effect of the starting concentration (9.5–39.9 μmol/ml) of the organic substrate on the initial rate of CNNDDBA reduction and product selectivity was studied at 156 kPa H<sub>2</sub> and 298 K; the results are given in Table 7. A reaction order of 0.46 on CNNDDBA concentration is obtained from these rates [14]. Reduction reactions at 298 K, an initial CNNDDBA concentration of 28.3 μmol/ml, and a constant H<sub>2</sub> pressure of either 115, 156, 194, or 263 kPa were conducted to determine the effect of the latter on the initial rate of CNNDDBA disappearance and the debenzoylation selectivity. The results are given in Table 8, from which a reaction order on H<sub>2</sub> of 0.67 was determined [14].

## 4. Discussion

With the exception of the article by Studer and Blaser [9], there are few detailed accounts of the removal of a benzyl group from an N atom (N-debenzoylation) in the presence of an acid; however, hydrochloride salts of protected amines have been reported to undergo debenzoylation [20]. In regard to dehalogenation, there are references that cite the presence of acids as either favorable [21] or unfavorable [22], whereas it is well referenced that bases catalyze dehalogenation [23,24]. Bases also help preserve benzyl protective groups when the reduction of other groups in the molecule is desired [25,26]. Although the effects of acids and bases on N-debenzoylation and dehalogenation reactions have been examined before, the effect of pH over a wide range has not been reported to

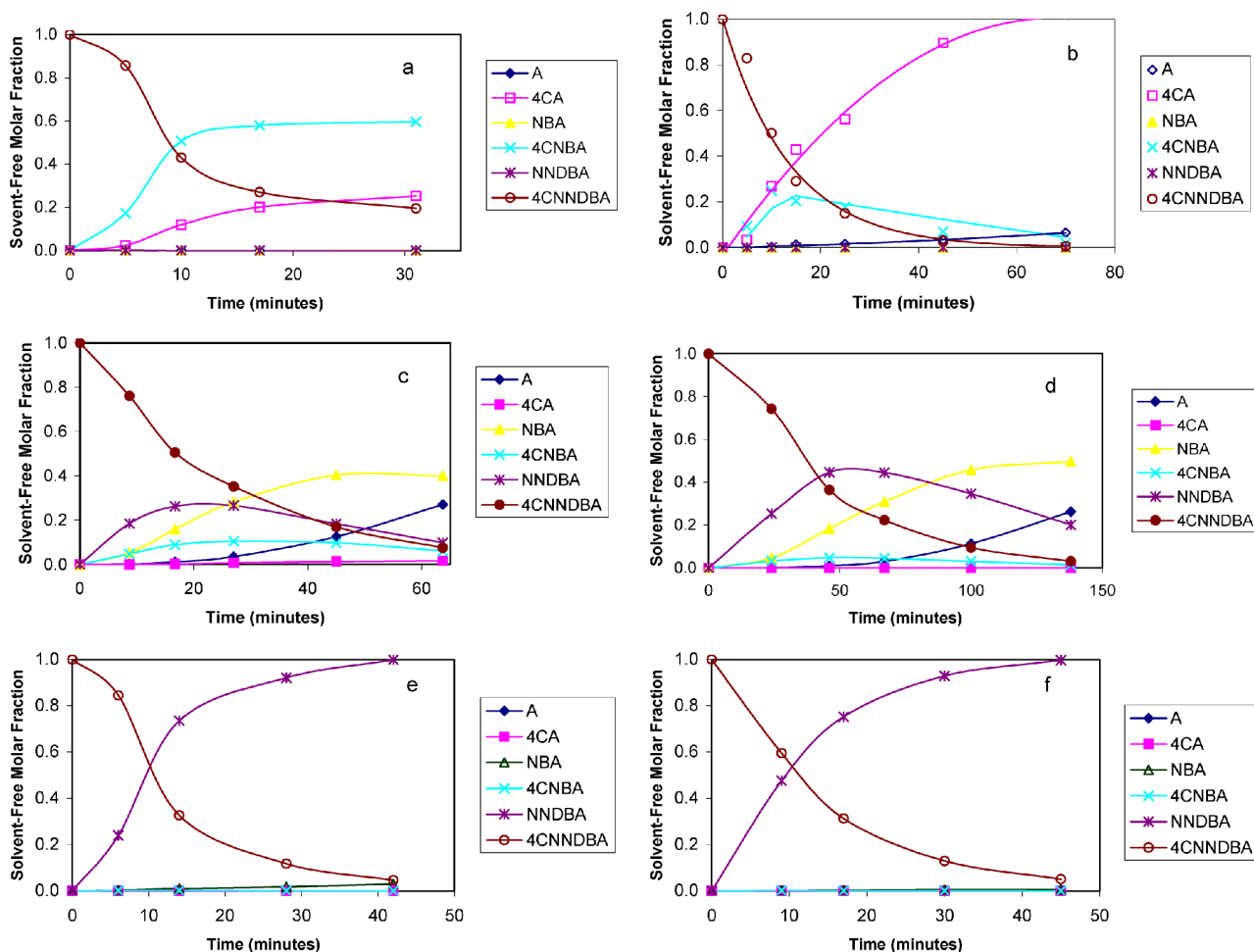


Fig. 3. Reduction of CNNDBA (100  $\mu\text{mol/ml}$ ) at 298 K on 5% Pd/C in THF solvent (156 kPa  $\text{H}_2$ ): (a) pH = 0.1; (b) pH = 3.5; (c) pH = 4.7; (d) pH = 5.2; (e) pH = 6.0; (f) pH = 12.

Table 4

Initial rates of CNNDBA reduction over 5% Pd/C as a function of the pH of the reaction mixture

pH	Initial rate ( $\mu\text{mol CNNDBA}/(\text{s g}_{\text{cat}})$ )
0.1	282
3.5	67.4
4.7	18.5
5.2	9.00
6.0	13.3
12.0	10.9

Reaction conditions: 298 K, 156 kPa  $\text{H}_2$ , 100  $\mu\text{mol CNNDBA/ml}$  initially, THF solvent with buffer.

date; consequently, one goal of the present study was to determine the variation in the reduction rate of CNNDBA and the selectivity to debenylation as a function of pH. If the reduction is carried out in the absence of an acid or base modifier, then the pH of the solvent will change over the course of the reaction as HCl is formed from the competitive parallel dechlorination reactions. The dechlorination of CNNDBA predominates initially (favored by the mild basicity of the tertiary amine group in the molecule), but as the HCl byproduct increases in the system, debenylation selectivity increases.

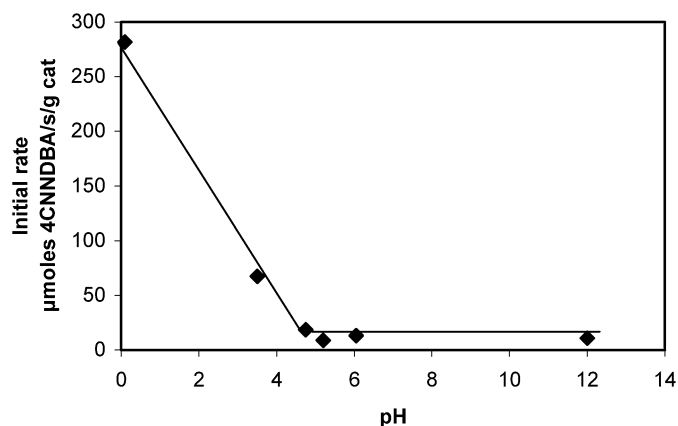


Fig. 4. Initial rate of CNNDBA reduction on 5% Pd vs. pH of the buffered reaction mixture. (Reaction conditions: 298 K, 156 kPa  $\text{H}_2$ , 100  $\mu\text{mol CNNDBA/ml}$  initially.)

For the reductive dehalogenation of a generic organic molecule, a base modifier acts favorably by neutralizing the HCl byproduct that otherwise could deactivate the catalyst and also by providing the additional polarity necessary for the cleavage of the C-halogen bond. In the case of derivatives of 4-chloroaniline (such as CNNDBA), a base modifier also keeps

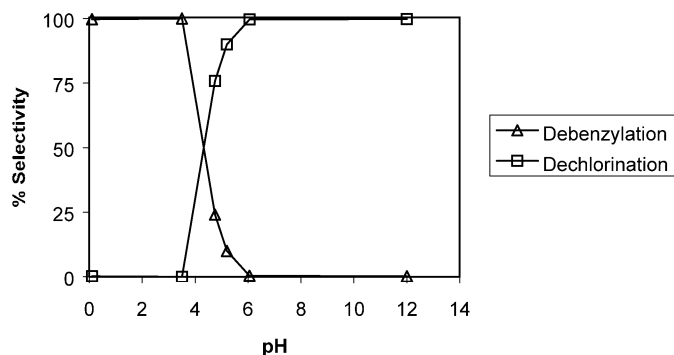


Fig. 5. Plot of selectivity to CNBA (debenzylation,  $r_B$ ) and to NNDBA (dechlorination,  $r_C$ ) over 5% Pd/C as a function of the measured pH of the buffered reaction mixture. (For reaction conditions, see Fig. 4.)

the nitrogen unprotonated over the course of the reaction. If a base were not present, then the amine group would become protonated as HCl formed, and thus would convert from an electron-donating group to an electron-withdrawing group, as indicated in Fig. 6. Having an electron-donating group (like a free amine) in the *ortho* or *para* position facilitates removal of the halogen anion, whereas an electron-withdrawing group (like a protonated amine) impedes displacement of the halogen. Nitrogen-containing bases have been shown to inhibit debenzoylation reactions [27,28], and CNNDDBA itself is a nitrogen-containing base with the potential to self-inhibit debenzoylation; however, the experimental results suggest that the protonated amine does not act as an inhibitor, thus allowing reductive debenzoylation to occur.

In our study, the Pd dispersed on oxidic supports gave lower TOFs than Pd on carbon, as shown in Table 2. Studer and Blaser also found Pd/C to be the catalyst of choice for debenzoylation reactions [9], but it is unclear at this time why the carbon support allowed a higher specific activity. The selectivity to debenzoylation is low at a pH of 5.4 and shows a 2-fold variation among the oxide-supported Pd catalysts, but it is noticeably lower with the Pd/C catalyst. Different catalytic behavior of Pd/C compared to Pd/oxide has been previously observed for CO hydrogenation [29]. Studer and Blaser concluded that the selectivity to dehalogenation for CNNDDBA on Pd catalysts increases with the dielectric constant of the solvent, because polar protic solvents particularly favored the dechlorination reaction, a fact corroborated by Mukhopadhyay et al. [30]. Acetic acid was a notable exception, which favored the debenzoylation route,

Table 6

Effect of temperature on the initial rates of CNNDDBA disappearance and debenzoylation selectivity (to CNBA)

$T$ (K)	Initial rate of CNNDDBA disappearance ( $\mu\text{mol}/(\text{s g}_{\text{cat}})$ )	TOF ( $\text{s}^{-1}$ )	Debenzylation selectivity (%)
278	3.62	0.059	6.8
298	9.95	0.162	8.1
330	23.6	0.385	11.3

Reaction conditions: HF solvent buffered at pH = 5.4, 156 kPa  $\text{H}_2$  and 28.3  $\mu\text{mol}$  CNNDDBA/ml initially.

Table 7

Effect of CNNDDBA concentration on initial rate and debenzoylation selectivity (to CNBA)

CNNDDBA concentration ( $\mu\text{mol}/\text{ml}$ )	Initial rate of CNNDDBA disappearance ( $\mu\text{mol}/(\text{s g}_{\text{cat}})$ )	Debenzylation selectivity (%)
9.54	7.12	2.1
19.1	9.42	5.0
28.3	9.95	8.1
37.9	14.4	7.3

Reaction conditions: 298 K, 156 kPa  $\text{H}_2$ , THF solvent buffered at pH = 5.4.

Table 8

Effect of  $\text{H}_2$  pressure on initial rate and debenzoylation selectivity (to CNBA)

$p$ (kPa)	Initial rate of CNNDDBA disappearance ( $\mu\text{mol}/(\text{s g}_{\text{cat}})$ )	Debenzylation selectivity (%)
115	8.22	6.9
156	9.95	8.1
194	11.2	8.8
263	14.1	9.6

Reaction conditions: 298 K, 28.3  $\mu\text{mol}$  CNNDDBA/ml initially, THF solvent buffered at pH = 5.4.

as did other acid modifiers, and this pattern was confirmed in this study (see Fig. 2).

The modifier (acid or base) can interact not only with the organic reagent, but also with the catalyst surface. Activated carbon can contain surface groups that incorporate heteroatoms, and these groups can have acidic, neutral, or basic character, thus providing an overall amphoteric character to the carbon support [31]. Both negatively and positively charged surface sites can exist, depending on the pH. For example, at a basic pH, the sites containing deprotonated carboxylic groups will attract a layer of cations from the reaction medium, whereas at

Table 5

Initial rates of Debenzylation and Dechlorination and Selectivity during CNNDDBA Reduction over 5% Pd/C as a function of pH

pH	Initial rate of CNBA formation (debenzylation)		Initial rate of NNDBA formation (dechlorination)		Debenzylation selectivity (%)
	$r_B$ ( $\mu\text{mol}/(\text{s g}_{\text{cat}})$ )	TOF ( $\text{s}^{-1}$ )	$r_C$ ( $\mu\text{mol}/(\text{s g}_{\text{cat}})$ )	TOF ( $\text{s}^{-1}$ )	
0.1	287	4.7	1.0	0.016	99.6
3.5	63	0.98	0.4	0.007	99.4
4.7	3.5	0.057	16.1	0.25	17.9
5.2	0.70	0.011	8.9	0.14	7.3
6.0	0.05	0.0008	13.8	0.22	0.34
12.0	0.02	0.0003	12.5	0.20	0.16

Reaction conditions: 298 K, 156 kPa  $\text{H}_2$ , 100  $\mu\text{mol}$  CNNDDBA/ml initially, THF solvent with buffer.

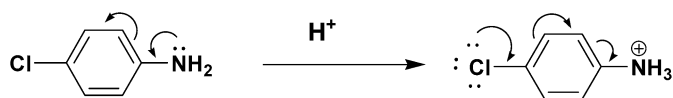


Fig. 6. Free amine groups are electron-donating, whereas protonated amine groups are electron-withdrawing groups.

an acidic pH, the oxygenated surface groups will attract anions from solution. During CNNDDBA reduction under acidic conditions, the positively charged amine should diffuse to Pd active sites with no significant interaction between carbon sites of opposite electrical charge.

Because of the pH dependence, any kinetic data for rates and selectivity of debenzilation versus dehalogenation should be determined in buffered systems. In this study, the choice of triethylamine/acetic acid provided a buffer that gave good control in the pH range of 3.5–12. To add one data point at a pH near 0, a mixture of acetic acid and sulfuric acid was used. Fig. 4 clearly shows that at a pH of 0–4.5, the initial rate of CNNDDBA consumption decreased markedly with increasing pH; however, for reactions taking place in buffers with a pH > 4.5, the reaction rate did not change. The selectivity to debenzilation was essentially 100% in the pH range of 0–3.5 (Fig. 5), but it dropped sharply at higher pH levels and was totally suppressed at a pH of 6. Fig. 5 shows that the two selectivity curves intersect at a pH near 4.5, the same pH at which there is an inflection point in the overall rate of reaction (see Fig. 4). This inflection point corresponds approximately to the  $pK_a$  of the organic reagent, where 50% of the CNNDDBA is protonated and 50% is in free-base form [32]. Fig. 5 also illustrates that dechlorination can be the predominant reaction, even under acidic conditions, as long as the pH of the buffer is higher than the  $pK_a$  of the amine group (i.e., in a pH range of 4.5–7). The finding that dehalogenation reactions can be catalyzed under acidic conditions is significant for three reasons: (i) It dispels previous conclusions that the presence of a base modifier is require for a dehalogenation reaction to occur; (ii) it shows that debenzilation reactions can be selectively carried out at higher pH levels than previously suggested; and (iii) it offers a guideline for obtaining high selectivity for either dehalogenation or debenzilation under mild conditions, which may help preserve functionalities in the molecule that might otherwise be affected by strong acidic or basic conditions.

The selectivity to debenzilation was low (2–11%) in THF at a buffered pH of 5.4, but it increased with an increase in the hydrogen pressure, the reaction temperature, or the concentration of the organic substrate (see Tables 6–8). The apparent activation energy of 34.2 kJ/mol for the rate of CNNDDBA disappearance related primarily to the hydrodechlorination reaction, which is the dominant reaction at this pH. No comparable values for an aromatic could be found for comparison, but C–Cl bond energies for aromatics are similar to, or 20–25% higher than, those for aliphatics, and apparent activation energies for the vapor-phase hydrodechlorination of  $CF_3CFCl_2$  have been reported to be 52 kJ/mol on Pd/Al<sub>2</sub>O<sub>3</sub> [33] and 75–130 kJ/mol on Pd/C for removal of the initial Cl atom [34,35]. The initial rate data obtained at 298 K and a pH of 5.4 under different reactant concentrations were first fitted to a power rate law; these

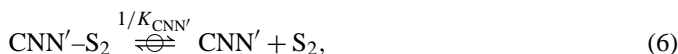
correlations gave a reaction order of 0.45 for CNNDDBA and a reaction order of 0.67 on H<sub>2</sub> pressure.

The kinetic data in Tables 4–8 were verified to be free of mass transfer effects in the following manner. Rates of H<sub>2</sub> uptake did not change above 500 rpm; therefore, all reactions were conducted at 700 rpm to guarantee the absence of interphase (external) mass transport limitations [36]. To ascertain that pore diffusion had no significant effect on rates, the W-P criterion was applied to this liquid-phase reaction over the most active 5% Pd/C catalyst [14]. The bulk diffusivity of H<sub>2</sub> in THF was calculated to be  $5.5 \times 10^{-5}$  cm<sup>2</sup>/s at 298 K [37], and a Henry's law calculation gave a solubility of 5.7 μmol H<sub>2</sub>/cm<sup>3</sup> THF at 156 kPa [14]. A different equation was used to calculate a bulk diffusivity of  $2.0 \times 10^{-5}$  cm<sup>2</sup>/s for CNNDDBA in THF [36,38]. The chemisorption and XRD line-broadening measurements indicated 9- to 17-nm Pd crystallites, so it is reasonable that these Pd particles reside in pores that are ca. 10 nm in diameter or larger. Using 10-nm pores and Ternan's equation [36,39], an effective diffusivity in the pores of  $6 \times 10^{-6}$  cm<sup>2</sup>/s is estimated. With these parameters, the dimensionless W-P criterion ( $N_{W-P}$ ),

$$N_{W-P} = \frac{\mathfrak{R} R_p^2}{C_s D_{eff}}, \quad (1)$$

where  $\mathfrak{R}$  is the observed rate for reactant  $i$  per volume of catalyst,  $R_p$  is the average catalyst particle radius (15 μm),  $C_s$  is the concentration of reactant  $i$  at the catalyst surface, and  $D_{eff}$  is the effective diffusivity of reactant  $i$  in the liquid solvent within the pores, gave values of 0.04 for CNNDDBA and 0.02 for H<sub>2</sub> at the highest rate in Tables 7 and 8 of 14.4 μmol/(s g). These values are well below 0.3, indicating no significant intraphase (internal) mass transfer limitations [36]. Even the highest rate in Table 4 gave W-P numbers of 0.2–0.3.

In regard to modeling, two forms of a classical Langmuir–Hinshelwood (L-H) mechanism were found to fit the data; one sequence assumed a single type of active site, whereas the second sequence used a similar L-H catalytic cycle but invoked two types of active sites, one site to adsorb and dissociate H<sub>2</sub> and the other to adsorb the organic reactant. The former type would correspond to 3-fold and 4-fold hollow sites for H atoms, and the latter type would represent on-top sites comprised of an ensemble of one or more Pd atoms. Because the latter model provided a slightly better fit of the data, only it is discussed herein. In either case, quasi-equilibrated adsorption of H<sub>2</sub> and CNNDDBA was assumed with the rate-determining step (RDS) being the addition of the second H atom. The proposed catalytic cycle is shown below, where  $L_i$  represents the leaving group (i.e., L<sub>B</sub> for benzyl and L<sub>C</sub> for Cl) and C<sub>NN'</sub> is either N,N-dibenzylaniline (NNDBA) or chloro-N-benzylaniline (CNBA):







where  $S_1$  and  $S_2$  are the two types of active sites.

The fractional surface coverages for the species involved in the quasi-equilibrated steps preceding the RDS are

$$\Theta_{1(H)} = K_{H_2}^{1/2} P_{H_2}^{1/2} \Theta_{1(S)} \quad (8)$$

and

$$\Theta_{2(CNNDBA)} = K_{CNNDBA} C_{CNNDBA} \Theta_{(S)}, \quad (9)$$

where the adsorbed species is in parentheses, and the subscript S indicates a vacant site. From the RDS [Eq. (5)], the rate for either CNNDBA debenzoylation ( $i = B$ ) or dechlorination ( $i = C$ ) is given by:

$$r_i = L_1 L_2 k_i K_i K_{CNNDBA} K_{H_2} C_{CNNDBA} P_{H_2} \Theta_{1(S)} \Theta_{2(S)}, \quad (10)$$

where  $k_i$  is the rate constant for the respective RDS and  $L_1$  and  $L_2$  are the concentrations of the two types of active sites,  $S_1$  and  $S_2$ , respectively. Assuming that the most abundant surface intermediate on the type 1 or type 2 sites is a H atom or a CNNDBA molecule, respectively, the site balances for the two types of sites are then

$$\Theta_{1(S)} + \Theta_{1(H)} = 1 \quad (11)$$

and

$$\Theta_{2(S)} + \Theta_{2(CNNDBA)} = 1. \quad (12)$$

The absence of any form of adsorbed HCl in the site balance is justified by the presence of the buffer; that is, the triethylamine removes HCl by forming a chloride salt, which essentially will not dissociate in the absence of water. A combination of Eqs. (8)–(12) yields the final rate expression for CNNDBA disappearance,

$$r = r_B + r_C = \frac{k'_i K_{CNNDBA} K_{H_2} C_{CNNDBA} P_{H_2}}{(1 + K_{CNNDBA} C_{CNNDBA})(1 + K_{H_2}^{1/2} P_{H_2}^{1/2})}, \quad (13)$$

where  $k'_i = L_1 L_2 (k_B K_B + k_C K_C)$ . However, it is readily apparent in Tables 6–8 that  $k_C \gg k_B$ ; therefore, Eq. (13) is primarily a representation of the dechlorination rate. Fig. 7 illustrates the fit of the two-site L-H model to the initial rate data for CNNDBA reduction using the nonlinear regression software package *Scientist* (Micromath Scientific Software) for optimization. The optimum parameter values at 298 K are listed in Table 9. Compared with the one-site L-H model, the two-site L-H model provides reaction orders for CNNDBA and  $H_2$  slightly closer to those values obtained from the regression of the experimental data (Table 9), which gave a regression coefficient of  $R = 0.995$  [14].

Little literature exists on the mechanistic aspects of reductive debenzoylation reactions, and, although dehalogenation reactions are more frequently referenced, no generally accepted mechanism has yet emerged. Most proposed mechanisms have involved dissociated hydrogen in either hydride or radical form reacting with the adsorbed organic species [34,35, 40–43]. Some interpretations involve the addition of a H atom (or a hydride) to the C– $L_i$  bond in an aromatic molecule to facilitate its rupture [40,41]. This would correspond to the model

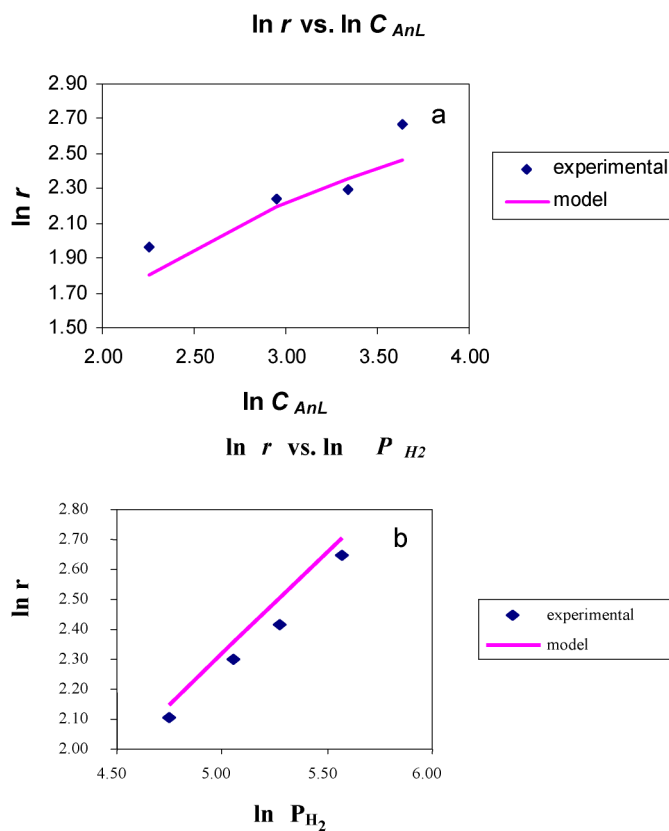


Fig. 7. Fit of the 2-site LH model to the initial rate dependencies for CNNDBA reduction at 298 K: (a) rate vs. CNNDBA concentration,  $P_{H_2} = 156$  kPa; (b) rate vs.  $H_2$  pressure,  $C_{CNNDBA} = 28.3$   $\mu\text{mol/ml}$  initially.

Table 9

Optimized parameters for Eq. (13) and reaction orders provided by the two-site L-H model (298 K and pH = 5.4)

Equation	$k'$ (mol/(s g <sub>cat</sub> ))	$K_{H_2}$ (1/kPa)	$K_{CNNDBA}$ (L/mol)	Reaction order in $H_2$	Reaction order in CNNDBA
Two-site LH model	$1.45 \times 10^{-5}$	0.021	58.4	0.67	0.48
Power-law	—	—	—	0.67	0.45

proposed by Eqs. (2)–(7). However, dissociated adsorption of halogenated organic compounds, particularly halogenated paraffins, has also been proposed, with the hydrogen then reacting with the halide to remove it from the surface [42,43]. If steps 3–5 were altered to represent this change, then the resulting rate expression would be the same as Eq. (13), except that it would contain a concentration term for the hydrogenated leaving group, such as HCl. However, because of the buffer, this term would remain constant (and very small), and the resulting rate equation would be indistinguishable from Eq. (13) as this term became incorporated into  $k'$ . Consequently, we can draw no detailed conclusions regarding the reaction mechanism from our kinetic results. For reductive dehalogenation of aliphatic chlorofluorocarbons on Pd/C, the reaction orders observed by Ribeiro and coworkers [34,35] were 0.15–1 for the organic substrate and 0.4–0.6 for hydrogen, values similar to those obtained here for dehalogenation of an aromatic compound. These latter two studies, which were in unbuffered vapor-phase systems,

also reported a near first-order negative dependence on the HCl byproduct, and the authors made an effort to correct their TOF values for the varying HCl concentrations [34]. Their rate expression would also be consistent with the alternative reaction model discussed above.

## 5. Summary

The activity and selectivity for debenzilation versus dechlorination for the reduction of CNNDDBA in H<sub>2</sub> over Pd dispersed on various supports was investigated. During the reduction of CNNDDBA dissolved in a THF/water solvent, the debenzilation selectivity increased over time because the dechlorination reaction, which was initially predominant, produced HCl, a modifier that suppresses the latter reaction and enhances debenzilation. Consequently, reduction experiments were carried out in buffered solvents to control and examine the effect of pH on activity and selectivity. The results clearly indicated that dechlorination reactions were completely suppressed at a pH < 3, debenzilation reactions were suppressed at a pH > 6, and the selectivity for debenzilation equaled that for dechlorination at a pH of ~4.5, which corresponds to the pK<sub>a</sub> of the CNNDDBA substrate. This behavior is interpreted as follows. At a pH equal to its pK<sub>a</sub>, 50% of the CNNDDBA is protonated and 50% is unprotonated at the tertiary amine group; thus, at a pH lower than the pK<sub>a</sub>, CNNDDBA exists primarily in a protonated form, whereas at a pH higher than the pK<sub>a</sub>, CNNDDBA exists primarily in an unprotonated form. The protonated amine is an electron-withdrawing group that inhibits, via resonance, the cleavage of the halogen group during the dechlorination reaction, whereas the unprotonated amine, which is an electron-donating group, facilitates dechlorination under H<sub>2</sub>. Thus, it was determined that the selectivity to debenzilation depends primarily on the pH of the reaction mixture; however, the presence of a base is not required for the dechlorination reaction to proceed. In fact, with CNNDDBA, dechlorination occurs at a high rate even under acidic conditions as long as the pH of the reaction mixture is greater than the pK<sub>a</sub> of the protected amine.

In systems buffered at a pH of 5.4, the selectivity to debenzilation was low and only modestly enhanced by increases in temperature, hydrogen pressure, or initial CNNDDBA concentration. The effect of the catalyst support on selectivity was not pronounced, but a much higher TOF was observed for reactions catalyzed by Pd dispersed on carbon compared with Pd dispersed on oxidic supports such as Al<sub>2</sub>O<sub>3</sub>, TiO<sub>2</sub>, and SiO<sub>2</sub>. The initial rates of organic substrate reduction at a pH of 5.4 were modeled using a L–H sequence invoking two types of active sites, one site that dissociatively adsorbs H<sub>2</sub> and another that adsorbs the organic substrate. This model fit the data well and could provide the observed reaction orders of ~1/2 for H<sub>2</sub> and ~2/3 for CNNDDBA. The W–P criterion was applied to this liquid-phase reaction to verify that the kinetic data used for modeling were obtained in the kinetic regime.

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