

for $C_{51}H_{61}N_3O_8S$: C, 73.44; H, 6.16; N, 5.04. Found: C, 73.51; H, 6.23; N, 5.08.

Conversion of 7a to (2R,3R,4R,5S)-(-)-8. Dry HCl was bubbled through a solution of 7a (0.158 g, 0.2 mmol) in CH_2Cl_2 (6 mL) and MeOH (10 mL) at 0 °C for 20 min. The solution was then stirred at room temperature for 30 min, then neutralized with aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (60 mL \times 3). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 2:1) to give (2R,3R,4R,5S)-(-)-8 (0.79 g, 80%): $[\alpha]_D^{20} -40.90^\circ$ (c 1.00, $CHCl_3$), [lit.^{4a} $[\alpha]_D^{20} -40.36^\circ$ (c 0.99, $CHCl_3$)].

Conversion of 7b to (2R,3R,4R,5S)-(-)-8. To a solution of 7b (0.115 g, 0.14 mmol), $CHCl_3$ (5 mL), and MeOH (5 mL) at room temperature was added concentrated H_2SO_4 (0.3 mL). The mixture was refluxed for 12 h, then neutralized with aqueous $NaHCO_3$, and extracted with Et_2O (30 mL \times 3). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 2:1) to give (2R,3R,4R,5S)-(-)-8 (0.055 g, 81%). Its absolute configuration and enantiomeric purity were determined by HPLC analysis. The retention time (t_R) was 21.21 min under the conditions employed. Column: Chiralcel OD; eluent: hexane/*i*-PrOH, 9/1; flow rate: 0.5 mL/min. The antipode, (+)-8, had $t_R = 18.48$ min.

Tosylation of (4R,5R)-6c' To Yield 10a. To a solution of (4R,5R)-6c' (0.2 g, 0.39 mmol), TsCl (0.082 g, 0.42 mmol), and $CHCl_3$ (10 mL) at room temperature was added NEt_3 (0.06 mL, 0.42 mmol). The mixture was refluxed for 1.5 h, then treated with saturated aqueous $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2 (20 mL \times 3). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was recrystallized (MeOH) to give 10a (0.242 g, 93%): colorless prisms (MeOH); mp 214–215 °C dec; IR (KBr) 1720, 1160, 1020, 760, 700 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.86, 2.20 (each s, each 3 H, NMe), 2.39 (s, 3 H, *p*-Me), 3.28 (s, 3 H, 4'-COOMe), 3.36 (dd, $J_{4'-3'} = 11.7$ and $J_{4'-5'} = 9.5$ Hz, 1 H, H-4'), 3.39 (d, $J_{2-3'} = 2.9$ Hz, 1 H, H-2), 3.68 (ddd, $J_{3-4'} = 11.7$, $J_{3-2'} = 9.2$, and $J_{3-2} = 2.9$ Hz, 1 H, H-3'), 3.71 (d, $J_{4-5} = 10.2$ Hz, 1 H, H-4), 3.80 (s, 3 H, 2'-COOMe), 4.21 (d, $J_{5-4} = 10.2$ Hz, 1 H, H-5), 4.53 (d, $J_{2-3'} = 9.2$ Hz, 1 H, H-2), 5.36 (d, $J_{5-4'} = 9.5$ Hz, 1 H, H-5'), 7.1–7.6 (m, 17 H, Ph and Ar), 7.71 (d, $J = 8.1$ Hz, 2 H, Ar); ^{13}C NMR ($CDCl_3$) δ 21.54 (*p*-Me), 38.66, 39.88 (each NMe), 47.17 (C-3'), 50.86 (C-4'), 51.68, 52.53 (each COOMe), 62.72 (C-2'),

65.87 (C-5'), 72.40, 73.14 (C-4 and C-5), 87.14 (C-2), 127.60, 127.66, 127.77, 127.89, 127.94, 128.07, 128.16, 129.43, 129.99, 134.83, 135.46, 138.34, 138.66, 143.80 (Ph and Ar), 169.51, 172.29 (each COOMe); MS m/z (rel intensity) 667 (M^+ , 1), 393 (5), 252 (41), 251 (base peak), 170 (8), 138 (19), 133 (21), 124 (10), 92 (10). Anal. Calcd for $C_{38}H_{41}N_3O_8S$: C, 68.27; H, 6.18; N, 6.29. Found: C, 68.16; H, 6.17; N, 6.26.

Tosylation of (4R,5R)-6d' To Yield 10b. In a similar manner, a mixture of (4R,5R)-6d' (0.261 g, 0.47 mmol), TsCl (0.178 g, 0.93 mmol), NEt_3 (0.13 mL, 0.93 mmol), and $CHCl_3$ (10 mL) was refluxed for 12 h. The usual hydrolytic workup and silica gel column chromatography (hexane/EtOAc, 3:1) gave 10b (0.291 g, 93%): colorless prisms (MeOH); mp 174.5–175.5 °C; IR (KBr) 1720, 1140, 740 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.61 (s, 9 H, COOBu-*t*), 1.85, 2.25 (each s, each 3 H, NMe), 2.41 (s, 3 H, *p*-Me), 3.23 (s, 3 H, COOMe), 3.28 (overlapping, 1 H, H-4'), 3.47 (d, $J_{2-3'} = 2.2$ Hz, 1 H, H-2), 3.59 (ddd, $J_{3-4'} = 10.7$, $J_{3-2'} = 9.5$, and $J_{3-2} = 2.2$ Hz, 1 H, H-3'), 3.66, 4.08 (each d, $J_{4-5} = 9.5$ Hz, each 1 H, H-4 and H-5), 4.26 ($J_{2-3'} = 9.5$ Hz, 1 H, H-2'), 5.27 (d, $J_{5-4'} = 9.5$ Hz, 1 H, H-5'), 7.1–7.6 (m, 17 H, Ph and Ar), 7.82 (d, $J = 8.0$ Hz, 2 H, Ar); ^{13}C NMR ($CDCl_3$) δ 21.55 (*p*-Me), 28.06 (COOBu-*t*), 38.93, 39.58 (each NMe), 46.28 (C-3'), 50.83 (C-4'), 51.58 (COOMe), 64.84 (C-2'), 65.93 (C-5'), 72.99, 73.19 (C-4 and C-5), 82.20 (COOBu-*t*), 86.62 (C-2), 127.51, 127.57, 127.63, 127.79, 127.93, 128.06, 128.12, 128.36, 128.56, 129.56, 129.56, 129.73, 134.29, 136.09, 138.43, 139.22, 143.78 (Ph and Ar), 169.56, 170.00 (each COOMe and COOBu-*t*); MS m/z (rel intensity) 709 (M^+ , 1), 289 (5), 252 (19), 251 (base peak). Anal. Calcd for $C_{41}H_{47}N_3O_8S$: C, 69.67; H, 6.67; N, 5.92. Found: C, 69.27; H, 6.48; N, 5.89.

Conversion of 10a to (2R,3R,4R,5S)-(-)-8. A procedure similar to that applied to 7a was used. Thus, a mixture of 10a (0.134 g, 0.2 mmol), concentrated H_2SO_4 (0.3 mL), MeOH (5 mL), and $CHCl_3$ (3 mL) was refluxed for 10 h. Workup and silica gel column chromatography ($CHCl_3$) gave (2R,3R,4R,5S)-(-)-8 (0.094 g, 95%). Its absolute configuration and enantiomeric purity were determined by HPLC analysis.

Conversion of 10b to (2R,3R,4R,5S)-(-)-8. A procedure similar to that applied to 7a was used. Thus, a mixture of 10b (0.1 g, 0.14 mmol), concentrated H_2SO_4 (0.3 mL), MeOH (5 mL), and $CHCl_3$ (3 mL) was refluxed for 15 h. Workup and silica gel column chromatography ($CHCl_3$) gave (2R,3R,4R,5S)-(-)-8 (0.066 g, 95%). Its absolute configuration and enantiomeric purity were determined as described above.

Studies on the Mechanism of Transfer Hydrogenation of Nitroarenes by Formate Salts Catalyzed by Pd/C

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Received January 23, 1991

The hydrogenation of nitroarenes to aminoarenes using formate salts as hydrogen donors and Pd/C as catalyst in a liquid/liquid/solid system was found to be a true hydrogen-transfer process. The mechanism of the reaction comprises successive adsorption of all three substrates to a single catalytic active site in the following order: nitroarene, formate anion, and water. Optimal concentrations of the substrates should be maintained to attain maximum reaction rate and overall yield. A general reaction mechanism is proposed.

Introduction

Numerous hydrogen donors were reported for the liquid-phase catalytic transfer hydrogenation of nitroarenes to the corresponding aminoarenes both under homogeneous and heterogeneous conditions.^{1–3} Typical examples are alcohols,⁴ formic acid and its derivatives,^{5–9} cyclic

amines,¹⁰ and hydroaromatic derivatives.¹¹ Of particular interest are the alkali metal formate salts, which are very

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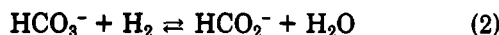
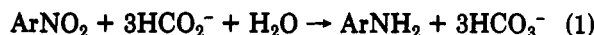
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mild in nature and conveniently available.^{12,13} In addition, formate salts are *recyclable* hydrogen donors since their dehydrogenated product, bicarbonate salts, are simply separated from the organic reaction mixtures and can be rehydrogenated to formate under exceptionally mild conditions.¹⁴ The typical catalytic transfer hydrogenation process of a nitroarene (eq 1) can be followed by hydro-



genation of the bicarbonate product back to formate (eq 2). On the basis of this cycle with addition of the fact that formate salts can, in the absence of an acceptor, decompose to hydrogen gas and bicarbonates, we proposed the utilization of formate salts as universal hydrogen carriers.¹⁵

Early studies on the application of formate salts as hydrogen donors were concerned with the insolubility of these reagents in apolar organic solvents. Consequently, protic and polar aprotic solvents¹⁶ as well as phase-transfer techniques utilizing quaternary ammonium salts combined with homogeneous metal catalysts^{17,18} were applied. In a similar approach, Heck proposed the soluble triethylammonium formate as a hydrogen donor. We have, however, observed that the reaction will proceed smoothly even when solid sodium formate is reacted directly with dissolved organic substrate in the presence of Pd/C catalyst as a second solid phase. Similar observations were made by Spatola et al.¹⁹ and Kabalka and co-workers,²⁰ who have used ammonium formate as hydrogen donors in liquid/liquid/solid or liquid/solid/solid systems. Many of the procedures reported formerly suffered from lack of knowledge of the specific interaction of the substrates with the solid catalyst; this resulted in wasteful methods particularly with regard to the very large amounts of catalyst used (in certain instances stoichiometric excess of "catalyst" was actually used).^{10,21} We now present our kinetic and mechanistic studies on the reduction of nitroarenes by formate salts in presence of Pd/C catalyst, which resulted in a highly optimized procedure that is by far more efficient and economical in comparison to the previous art in terms of donor/substrate and donor/catalyst ratios as well as overall rate and selectivity.

Results and Discussion

When 10 mL of a 4 M solution of potassium formate is heated to 70 °C in the presence of 0.5 g of 10% Pd/C catalyst, complete decomposition to hydrogen and potassium bicarbonate is observed after 30 min.²⁴ The reaction was found to follow a first-order rate equation and exhibited an exceptionally high kinetic isotope effect when

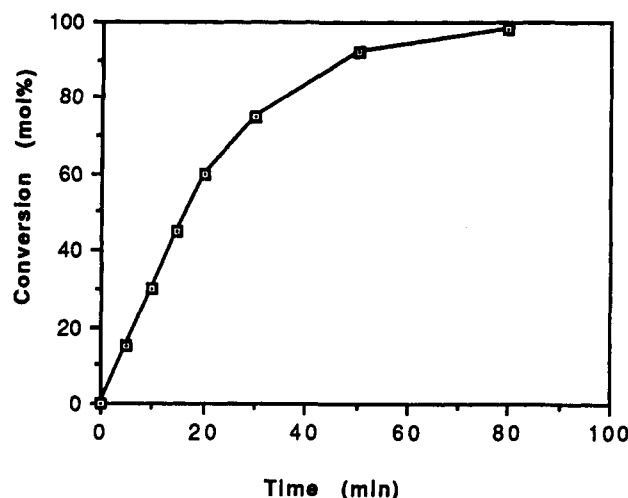
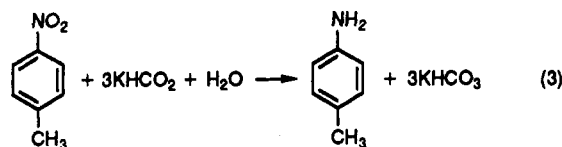


Figure 1. Hydrogenation of 4-nitrotoluene with potassium formate. Experimental conditions: 50 mmol of 4-nitrotoluene in 50 mL of toluene, 150 mmol of potassium formate in 400 mmol of water, 0.1 g of 10% Pd/C, 80 °C.

each of the following combinations was reacted: DCOOK/H₂O, HCOOK/D₂O, or DCOOK/D₂O. It was clearly demonstrated that the hydrogen molecule is formed by combination of a hydride originated from the formate and proton supplied by the water. Upon repetition of the previous experiment but with the addition of 13.3 mmol of 4-nitrotoluene to the system, the reaction took a totally different course: the decomposition process ceased completely and, instead, quantitative reduction of the nitrotoluene to 4-toluidine (eq 3) took place.



Using a highly sensitive hydrogen monitor, we confirmed that no elementary hydrogen was present in or above the reacting mixture as long as 4-nitrotoluene had not been completely consumed. Some carbon dioxide was monitored in the gas phase above the reaction due to bicarbonate decomposition. Gas chromatographic analysis of samples taken from the reaction, while in progress, indicated the present of starting nitroarene and the product, aminoarene, but no intermediate nitroso or hydroxylamine derivatives were detected. After 2 h, analysis of the organic phase by gas chromatography and of the aqueous phase by titration revealed complete conversion of the nitrotoluene to toluidine and of the formate to bicarbonate. No difference in the behavior of the reaction was noticed when either an open or a sealed flask was used. These observations indicate that the encountered process is a true hydrogen transfer rather than a consecutive dehydrogenation–hydrogenation reaction. There is evidently a clear difference between the behavior of ammonium formate as hydrogen donor as compared to this system.¹⁹ On the one hand, ammonium formate can supply a molecule of hydrogen even in the absence of water (decomposing to ammonia and carbon dioxide), but on the other hand it suffers from competing dehydrogenation even in the presence of acceptors.¹⁹ Consequently, ammonium formate is a less effective hydrogen donor particularly for larger scale syntheses.

A typical kinetic profile for reaction 3 is shown in Figure 1. It is apparent from Figure 1 that the reaction proceeded as a zero-order process until approximately 60% conversion

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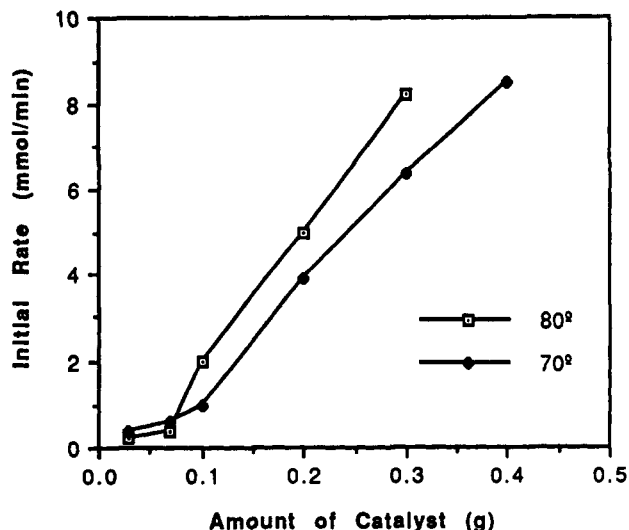


Figure 2. Effect of amount of catalyst on the rate. Experimental conditions: 50 mmol of 4-nitrotoluene in 50 mL of toluene, 150 mmol of potassium formate in 400 mmol of water.

is achieved where there is a shift to first-order kinetics. It has been observed that the transfer hydrogenation 3 is approximately 20 times faster than the decomposition process 1 under the same conditions.

In order to acquire insight to the reaction mechanism and to optimize the reduction procedure, we examined the effect of several chemical and physical parameters on the rate of reaction 3.

Effect of Stirring. In this three-phase system (liquid/liquid/solid) one can anticipate that the stirring rate will have significant effects. We measured the initial rate of reactions 3 under standard conditions as a function of the rate of stirring between 0–1000 rpm (mechanical direct drive stirrer with 3-cm crescent shaped Teflon blade in a 100-mL round-bottom flask). As expected, no reaction is observed if the mixture has not been stirred. Above a stirring rate of 400 rpm, the reaction rate is practically independent of the speed of agitation, and it can be assumed that in this region the reaction is chemically controlled. Thus, the rest of the work was conducted with a constant stirring of 500 rpm.

Amount of Catalyst. Figure 2 displays the initial rate of reaction 3 as a function of the amount of 10% Pd/C catalyst at 70 and 80 °C. It is apparent that no reaction is observed at all in the absence of a catalyst. Above 0.08 g of catalyst, the initial reaction rate increases linearly with the quantity of the catalyst applied. In the region below 0.08 g of catalyst we observed "critical mass" phenomenon where a minimum weight of a catalyst is required to initiate the process. We attribute this to the presence of minor impurities in the mixture that poison the catalyst. We were able to remove these impurities by pretreatment of the reactants with active carbon before adding the catalyst. Following this procedure, the poisoning phenomenon was eliminated and linear dependence on the catalyst amount is observed under the conditions of Figure 2. No difference in the reaction rate was observed when either 1, 5, or 10% Pd/C catalyst was applied (with the same amount of palladium in each run).

Dependence of Initial Rate on the Concentration of the Substrate. Figure 3 displays the initial rate of reaction 3 as a function of the concentration of 4-nitrotoluene in the organic phase.

Evidently, the rate is independent of the organic substrate concentration in the range 0.5–5 M. Higher initial concentrations result, however, in a lower rate. This

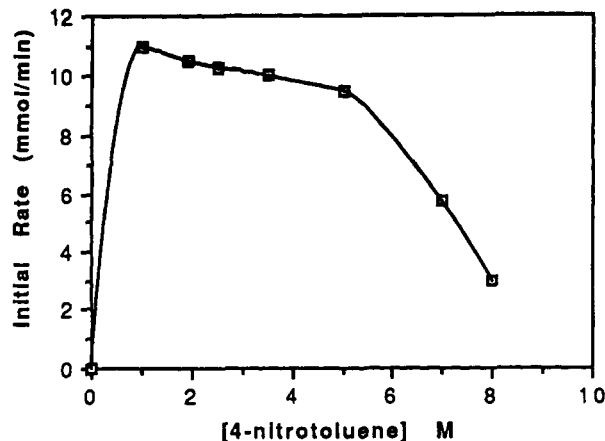


Figure 3. Dependence of initial rate of acceptor concentration. Experimental conditions: 50 mmol of 4-nitrotoluene in 50 mL of toluene, 150 mmol of potassium formate, 390 mmol of water, 0.5 g of Pd/C, 70 °C.

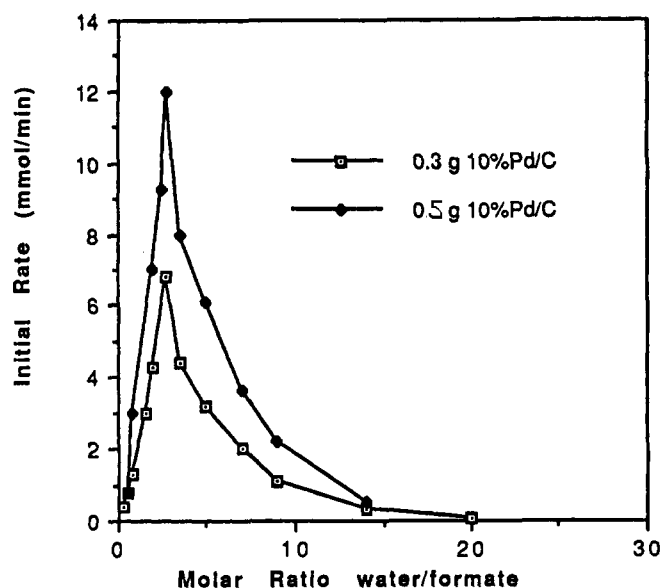


Figure 4. Dependence of rate on aqueous-phase concentration. Experimental conditions: 50 mmol of 4-nitrotoluene in 50 mL of toluene, 150 mmol of potassium formate in varying amounts of water, 70 °C.

zero-order dependence indicates that the adsorption of the nitro substrate to the active sites of the catalyst is a fast step and is definitely not the rate-determining step in the overall process. The rate decrease at higher concentrations suggests that the adsorption of the aqueous substrates (water and formate) to the catalyst is weaker than that of nitrotoluene; with excess of the latter the sites become saturated and unavailable for activation of the other reactants. This observation also indicates that the catalytic sites responsible for the activation of the acceptor are similar in nature to the site activating the two donors.

Effect of Formate Concentration in the Aqueous Phase. Since the system actually incorporates two donors (water and formate) whose concentration cannot be independently changed, we found it convenient to measure the dependence of the initial reaction rate on the initial water/formate molar ratio. The results with two sets of experiments using 0.3 and 0.5 g of catalyst, respectively, are shown in Figure 4.

These surprising results indicate that a very sharp optimum initial rate is obtained when the water/formate molar ratio is 2.7. This ratio corresponds to an 11 M solution of potassium formate in water. Using either

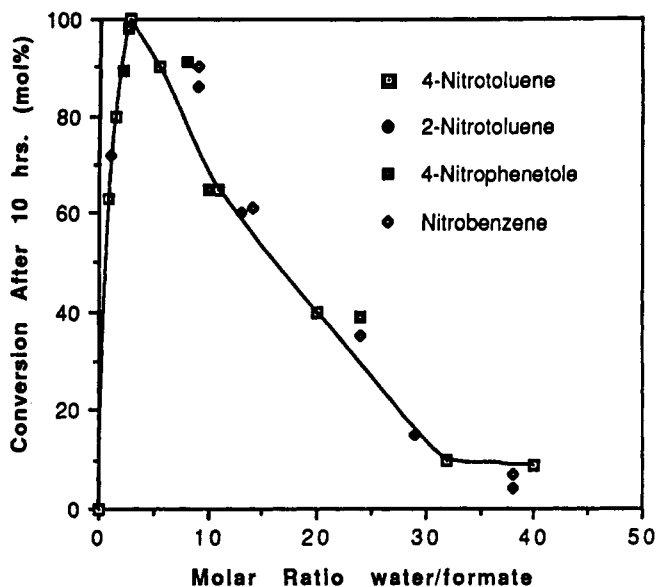


Figure 5. Effect of formate concentration on the yield of reduction of nitroarenes. Experimental conditions: as in Figure 5.

Table I. Effect of the Solvent on the Initial Rate

| solvent | rate ^a | solvent | rate ^a |
|----------|-------------------|----------|-------------------|
| ethanol | 7.1 | methanol | 0.0 |
| butanol | 3.5 | toluene | 2.1 |
| propanol | 2.5 | benzene | 2.0 |
| octanol | 1.0 | | |

^aIn mmol/min. Experimental conditions: 50 mmol of 4-nitrotoluene in 50 mL of solvent, 165 mmol of potassium formate in 500 mmol of water, 0.1 g of 10% Pd/C, 70 °C.

higher or lower initial aqueous phase concentrations results in significantly lower initial rates. The same optimal concentration is derived when the conversion after 10 h is examined as a function of the initial water/formate molar ratio. This is shown in Figure 5. This maximum at 11 M concentration is independent of the amount of catalyst employed (Figure 4). Interestingly, it is also not dependent on the nature of the nitroarene substrate. Thus, nitrobenzene, 2-nitrotoluene, and 4-ethoxynitrobenzene all gave identical behavior under the conditions of Figure 5 with maximum (100%) conversion obtained with initial 11 M potassium formate concentration.

These results suggest that the reaction proceeds via a competitive adsorption of water and formate to identical active sites on the catalyst surface. Excess of either of the donors would result in blocking the access of the other to the catalyst surface and impair the overall reduction process. This critical dependence of the reaction rate on the amount of water in the system is, in our opinion, the main feature of this study. Understanding this phenomenon is essential for the design of optimal procedures in reduction processes using formate salts as hydrogen donors.

Nature of the Organic Solvent. The initial rates for reaction 3 have been recorded in several solvents. The results are given in Table I. These results indicate that ethanol and 1-propanol are the preferred solvents with toluene or benzene as second choice. To our surprise, no reaction was observed when methanol was applied as a solvent. This observation can be attributed to the fact that methanol dissolves all the reaction components into one phase (with the exception of the catalyst). We also verified that the higher activity of ethanol and propanol is not due to their own hydrogen donor capacity. This activity can probably be assigned to better stabilization of the tran-

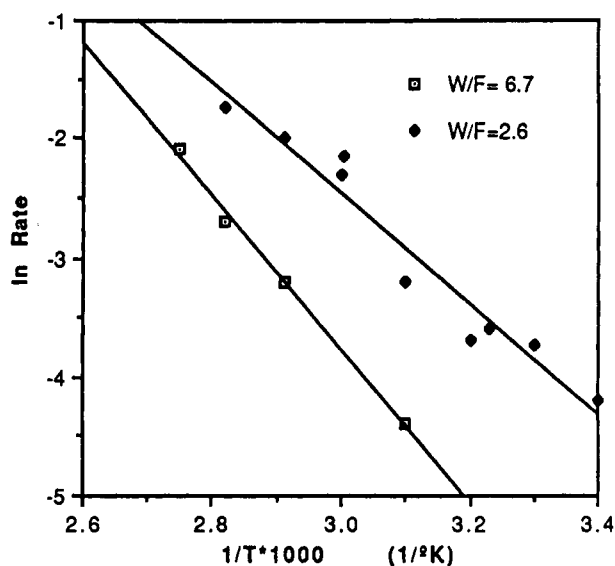


Figure 6. Effect of temperature on reaction 3. Experimental conditions: as in Figure 5; W, [water], F, [formate].

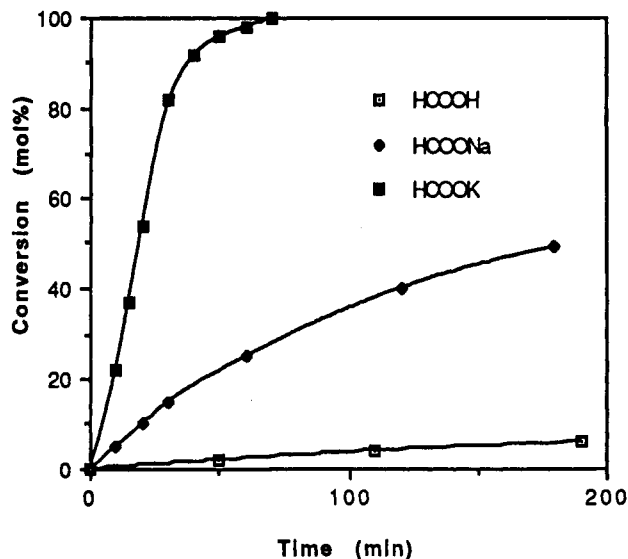


Figure 7. Effect of the donor on reaction rate. Experimental conditions: 50 mmol of 4-nitrotoluene in 50 mL of ethanol, 165 mmol of formate (or formic acid), 500 mmol of water, 0.1 g of 10% Pd/C catalyst, 70 °C.

sition states involved in the reduction process.

Effect of Temperature. The initial rates of reaction 3 for different temperatures have been measured in the range 50–90 °C in two sets of runs, one applying a water/formate ratio of 2.6 and one where this ratio was 6.7. The results are plotted in Figure 6. The activation energies calculated for the two sets are 10.6 and 19.8 kcal/mol, respectively. This clearly suggests a shift in the reaction mechanism when the formate concentration is modified.

Nature of the Formate Salt. As can be seen in Figure 7, potassium formate is a significantly more active donor than sodium formate while the free acid is practically inactive. This difference between the two salts is explained by higher solubility of potassium bicarbonate as compared with sodium bicarbonate (4 vs 1 M at 35 °C). When sodium formate was applied in reaction 3, solid sodium bicarbonate precipitated even at low conversion and partially impregnated the catalyst surface. Consequently, the observed rate decreased.

Kinetic Isotope Effect. When reaction 3 was carried out with D₂O and/or DCOOK as the hydrogen source

instead of H₂O/HCOOK under otherwise identical conditions, no change was observed in the reaction rate. These findings reveal that the scission of the formate H-C bond and the water H-O bond is not part of the rate-determining step in the overall process.

Structure of the Donor. No difference in the hydrogenation rate was observed when various substituted nitrobenzenes were reacted under the conditions of reaction 3. Thus, nitrobenzene, 2-, 3-, and 4-nitrotoluenes and -nitroethylbenzenes, 2- and 4-nitroanisoles, 4-nitrophenetole, 4-fluoronitrobenzene, and 4-nitrobenzaldehyde all reacted at essentially the same rate. On the other hand, 4-iodonitrobenzene and 4-nitrobenzotrile were reduced at an extremely slow rate. Chloronitrobenzenes and bromonitrobenzenes yielded anilines. Interestingly, the hydrogen-transfer process (3) was completely inhibited when a small amount of either benzonitrile or iodobenzene was added to the system. Addition of styrene or bromobenzene was found to suppress the reduction of nitrotoluene until these substrates had been consumed by hydrogenation to ethylbenzene and benzene, respectively.

Proposed Mechanism. Our experimental observations suggest that all the three substrates, namely the water, the formate salt, and the nitro acceptor, are adsorbed in a competitive manner onto a single active site on the catalyst surface. This is supported by the fact that the presence of the acceptor completely stops the decomposition of formate to molecular hydrogen. In addition, the insensitivity of the reaction to the surface concentration of the palladium catalyst also indicates that a dual or multisite mechanism is not playing a role in the transfer process.

It is apparent that the affinity of the catalyst to the substrates is decreasing in the order nitroarene > formate salt > water. Maximum reaction rate is obtained when the relative concentration of the three substrates is kept at such a level as to allow access of all the three components to the active sites.

The catalytic cycle therefore is supposedly composed of the following elementary steps (C, catalyst's active site; S, hydrogen acceptor; F, formate anion; W, water molecule; and B, bicarbonate anion).

Adsorption of the substrate:



Adsorption of formate anion:



Adsorption of water:



Hydrogen-transfer step on the catalyst active site:



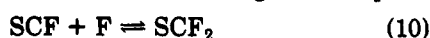
Desorption of the products:



Under conditions where an excess of either substrate or formate is present, inhibition is observed due to adsorption of more than one molecule per active site; e.g., in the presence of high acceptor concentration we might observe



or when the concentration of formate is high (on the expense of water concentration) the following will take place



The two species S₂C and SCF₂ are not part of the productive catalytic cycle and their presence reduces the

number of active intermediates, resulting in a lower overall rate. In the presence of substrates with very high affinity to the catalyst (e.g., iodobenzene or benzonitrile), steps 4 and 9 become significant and, consequently, the whole cycle stalls. The previous mechanism has naturally to be repeated three times in order to complete the reduction of nitroarene to aminoarene.

The lack of the kinetic isotope effect suggests that the rate-determining step precedes step 8 in which the formate C-H and the water O-H bonds are broken. Also, the 20-fold increase in the rate of reaction 3 as compared to reaction 1 indicates a different transition state and rate-determining step. The absence of an apparent effect of various ring substituents on the nitro substrates shows that step 4 is definitively not rate determining. We conclude that steps 5 or 6 are rate controlling for the overall reaction with the relative contribution of each step depending on the aqueous-phase concentration. This is also supported by the different activation energies measured at different formate/water ratios.

Conclusions

The true catalytic hydrogen-transfer process from formate salts to nitroarenes in a liquid/liquid/solid system provides a convenient and simple alternative to catalytic hydrogenation. On the basis of our mechanistic studies, an optimal reaction procedure was developed that is more effective and economical than methods previously reported.

Experimental Section

Formate salts and nitroarenes were purchased from Aldrich (analytical grade). Formate salts were carefully dried at 80 °C under vacuum (1 mmHg) for 24 h; nitroarenes were used without further purifications. Palladium catalysts were supplied by Engelhard. Sodium formate ²H was prepared by hydrolysis of sodium cyanide in D₂O.²²

Gas chromatographic analyses were performed on a Hewlett-Packard 5790A instrument equipped with a 3390A integrator using diphenylmethane as internal or external standard. The capillary column employed 5% phenyl methyl silicone 25 m × 0.31 mm with 0.52-mm film. GCMS analyses were carried out using the previous column with a Hewlett-Packard 5970A mass selective detector.

Formate assay was performed by enzymatic analysis using formate dehydrogenase²³ purchased from Sigma and also by ¹H NMR (Bruker WH-300) using 2-propanol as standard.

Water analyses were carried out by Karl Fischer titration using a Mettler KF titrator. Kinetic runs were carried in a 100-mL round-bottom flask equipped with a reflux condenser, a Heidolph RS-2 mechanical stirrer, and a digital thermometer. The speed of revolution was monitored by a Jacquet tachometer. The flask was placed in a thermostatic bath and charged with the solvent, nitroarene, formate, and water. Stirring was started, and after the desired temperature was achieved, the catalyst was added in one portion. Aliquots were taken at certain intervals from both the organic and the aqueous phases. The organic phase was analyzed by gas chromatography, and the formate in the aqueous phase was assayed by ¹H NMR and by formate dehydrogenase titration.

Representative Reduction of 4-Nitrotoluene. To a 100-mL three-necked round-bottom flask equipped with a mechanical stirrer, reflux condenser, and a thermometer and placed in a thermostatic bath were introduced the following: 12.60 g (150 mmol) of potassium formate, 8.10 g (450 mmol) of water, 6.85 g (50 mmol) of 4-nitrotoluene, and 50 mL of ethanol. The mixture was stirred and heated to 70 °C, 0.2 g of 10% Pd/C catalyst (50% water, 0.09 mmol Pd) was added, and the heterogeneous system was mixed for 1 h at the above temperature. Throughout the reaction, some carbon dioxide was evolved from the mixture and the pH 11-12 was measured in the aqueous phase. After being cooled, the aqueous phase was separated, the solvent was evaporated under vacuum, and the crude product was washed with

water and recrystallized from methanol: yield 4.86 g of pure 4-toluidine (90% yield), mp 47 °C.

Registry No. Pd, 7440-05-3; D₂, 7782-39-0; HCOOH, 64-18-6; HCOONa, 141-53-7; HCOOK, 590-29-4; hydrogen, 1333-74-0; 4-toluidine, 106-49-0; 3-nitrotoluidine, 99-08-1; 1-ethyl-3-nitrobenzene, 7369-50-8; 2-nitroanisole, 91-23-6; 4-nitroanisole, 100-17-4;

4-fluoronitrobenzene, 350-46-9; 4-nitrobenzaldehyde, 555-16-8; 4-iodonitrobenzene, 636-98-6; 4-nitrobenzotrile, 619-72-7; chloronitrobenzene, 25167-93-5; bromonitrobenzene, 61878-56-6; benzonitrile, 100-47-0; iodobenzene, 591-50-4; styrene, 100-42-5; bromobenzene, 108-86-1; 4-nitrotoluene, 99-99-0; 2-nitrotoluene, 88-72-2; 4-nitrophenetole, 100-29-8; nitrobenzene, 98-95-3; 1-ethyl-4-nitrobenzene, 100-12-9; 1-ethyl-2-nitrobenzene, 612-22-6.

Aromatic Radical Nucleophilic Substitution Reactions Initiated by Sodium Amalgam in Liquid Ammonia

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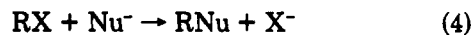
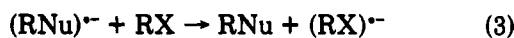
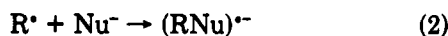
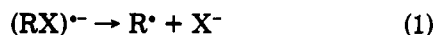
Received August 13, 1990

Neither 1-chloronaphthalene nor 2-chloroquinoline reacted with Ph₂P⁻ ions in liquid ammonia. However, in the presence of sodium amalgam [Na(Hg)], reaction did occur, and the substitution products 1-naphthylidiphenylphosphine and 2-quinolyldiphenylphosphine (isolated as the *P*-oxides), respectively, were obtained in good yield. *p*-Bromoanisole reacted with Na(Hg) amalgam in the presence of Ph₂P⁻ ions in liquid ammonia to give anisole as the only product, but when benzonitrile was used as a redox catalyst, a good yield of the substitution product *p*-anisylidiphenylphosphine (isolated as the *P*-oxide) was obtained. It is believed that Na(Hg) amalgam initiated these S_{RN}1 reactions. Preparative-scale reactions gave good yields of the substitution products.

First-order radical nucleophilic substitution (S_{RN}1) has been shown to be an excellent means of effecting the nucleophilic substitution of unactivated aromatic compounds possessing suitable leaving groups. Many different types of nucleophiles can be employed.¹

The mechanism of the reaction is a chain process. The propagation steps are shown in Scheme I,¹ in which eq 4 summarizes eqs 1-3.

Scheme I



Overall, Scheme I depicts a nucleophilic substitution in which radicals and radical anions are intermediates. However, this chain process requires an initiation step. In a few systems, spontaneous electron transfer (ET) from the nucleophile to the substrate has been observed and the radical anion (RX)^{·-} that is formed initiates the chain propagation steps.² When electron transfer does not occur spontaneously, it can be induced by light,³ by solvated electrons in liquid ammonia,⁴ by cathodically generated electrons,⁵ or by certain inorganic salts.⁶

All these methods of initiation have some disadvantages from a preparative point of view. For instance, light-initiated or electrochemically initiated reactions can be performed only in dilute solutions. Solvated electrons are very strong reducing agents, and in certain systems, reduction of the substitution products can take place.⁷

We believed it would be of interest to find an alternative method for initiating aromatic S_{RN}1 reactions, one that could be used on a preparative scale, and one in which the disadvantages of the other methods of initiation were absent.

We recently reported⁸ that sodium amalgam [Na(Hg)] selectively dehalogenated haloarenes in liquid ammonia. We believed that Na(Hg) amalgam could also be used as a catalyst in synthetic-scale S_{RN}1 reactions. We used the diphenylphosphide (Ph₂P⁻) ion as the model nucleophile because it is especially reactive in aromatic S_{RN}1 reactions.⁹

Results and Discussion

When 3% Na(Hg) amalgam was added to dry liquid ammonia, a heterogeneous mixture was formed. The supernatant liquid remained colorless, which suggested that no solvated electrons were present. Moreover, that *p*-chloroanisole (*p*-ClAn) and naphthalene did not react under these conditions⁸ also suggested that no electrons were present in the solution. Because *p*-ClAn and naphthalene did not react with the amalgam, their reduction potentials must be more negative than that of Na(Hg) amalgam in liquid ammonia. (The reduction potential of Na(Hg) amalgam in DMF is $E_{1/2} = -2.0$ vs SCE.¹⁰)

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