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Preparation of Aniline Derivatives: An Advanced Undergraduate Laboratory Experiment Exploring Catalytic and Stoichiometric Reaction Methodologies

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This article describes a series of synthetic chemistry experiments, suitable for advanced undergraduate students, that will allow them to grasp the contrasts between stoichiometric and catalytic reactions. The experiments are also aimed at awakening and stimulating the student's mind with regard to the design of cost-effective and environmentally sound alternative synthetic routes, essential for sustainable global growth.

The use of transition metal complexes to activate oxygen or hydrogen peroxide for the catalytic oxidation of organic substrates is a topic of major interest from both a biological and an industrial point of view (*1*). In industry, the substitution of expensive, hazardous, and polluting stoichiometric oxidants such as CrO_3 and MnO_4^- by molecular oxygen or HOOH would be highly beneficial both economically and environmentally.

In this paper we describe a few experiments that exemplify the capability of $FeCl_2py_4^+$ to act as catalyst for the oxidation of aniline using HOOH as the oxidant and yielding their corresponding derivatives, namely, nitroso-, nitro-, aza-, and azoxy-benzene (*2*). Several system parameters are modified in order to illustrate the various tools available to control product distributions and efficiencies. Thus the experiments illustrate the customized optimization of a particular catalytic system.

In addition, nitro-aromatic derivatives are an important class of compounds synthetically, since they can be easily transformed, through multiple pathways, into their corresponding reduced products (*3*, pp 343–344). In contrast, the oxidative chemistry of aromatic amines is not as well established, since the reactions are more complicated (*3*, pp 165–169). Depending upon the oxidizing agent, different aniline derivatives can be generated. Therefore the catalytic processes described here are oxidation reactions using aniline as the starting material, whereas the stoichiometric reactions are reduction reactions using nitrobenzene as the starting material.

Product profiles and product characterization are achieved through the usual chromatographic (TLC, GC, GC–MS) and spectroscopic (IR, UV–vis, NMR) techniques.

Results and Discussion

Scheme I offers an integrated graphical summary of the stoichiometric and catalytic reactions described here.

Stoichiometric Reactions

Nitrosobenzene. Under acidic conditions at 65 °C, nitrobenzene is initially reduced by Zn powder to nitrosobenzene and subsequently to *N*-phenylhydroxylamine (*4*).

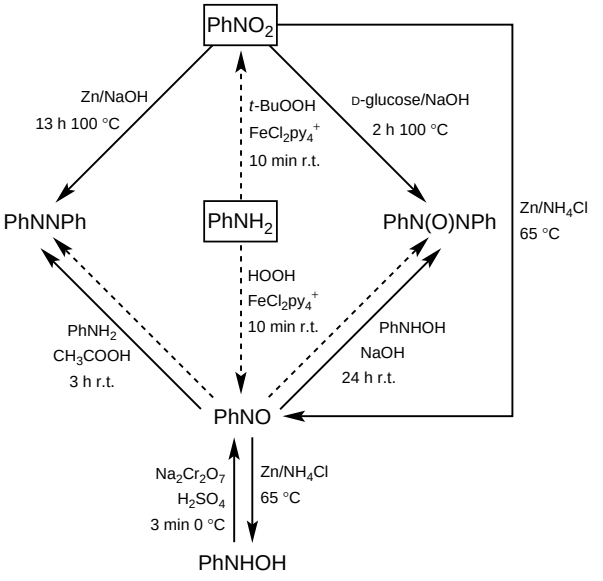
$$PhNO_2 \xrightarrow{Zn^0/NH_4Cl} PhNO \underset{Na_2Cr_2O_7}{\overset{Zn^0/NH_4Cl}{\rightleftharpoons}} PhNHOH \qquad (1)$$

It is difficult to control the reaction conditions so that only nitrosobenzene is obtained, because it is easily reduced to *N*-phenylhydroxylamine. Therefore we propose to prepare nitrosobenzene from the controlled oxidation of *N*-phenylhydroxylamine with sodium dichromate at 0 °C. This can be done either step by step with the isolation of *N*-phenylhydroxylamine, or in a one-pot reaction.

Almost all aromatic C-nitroso compounds exist as blue or green monomers or as colorless bisnitroso dimers (*3, 5*). This is also the case of nitrosobenzene, which in the solid state is a colorless dimer that dissociates readily in solution ($CHCl_3$) to generate a green monomer (see eq 2).

$$\underset{\text{green monomer}}{PhNO} \rightleftharpoons \underset{\text{colorless dimer}}{Ph(O)NN(O)Ph} \qquad (2)$$

IR spectroscopy is particularly useful in this case because it permits differentiation between those two structures. For the monomeric species, the N=O stretching vibrational mode frequencies appear at 1506 cm^{-1}, whereas the N–O stretching for the dimeric species shifts to 1397 cm^{-1}.



Scheme I
solid lines: stoichiometric reactions
broken lines: catalytic reactions

Azoxybenzene. Azoxybenzene can be prepared by the direct reduction of nitrobenzene in an alkaline medium using D-glucose as the reducing agent (*4*).

$$2PhNO_2 \xrightarrow{\text{D-glucose/NaOH}} PhN(O)NPh \qquad (3)$$

The reaction requires 2 hours at 100 °C to be completed. Azoxybenzene can also be obtained when nitrosobenzene and *N*-phenylhydroxylamine are mixed together in basic solution (see Scheme I and eq 4).

$$PhNO + PhNHOH \xrightarrow[CH_3CN]{NaOH} PhN(O)NPh + H_2O \qquad (4)$$

Azobenzene. Reduction of nitrobenzene in a methanolic NaOH solution containing 4 equivalents of zinc powder at reflux for 13 h leads to the formation of azobenzene (*4*).

$$2PhNO_2 \xrightarrow[CH_3OH]{Zn^0/NaOH} PhNNPh \qquad (5)$$

It is crucial to control the amount of zinc, to avoid further reduction to hydrazobenzene, PhNHNHPh. An alternative route to the formation of azobenzene is to react nitrosobenzene and aniline in an acetic acid solution (*3*).

$$PhNO + PhNH_2 \xrightarrow{CH_3COOH} PhNNPh + H_2O \qquad (6)$$

Azoxybenzene and azobenzene are chromophores with conjugated double bonds that present distinctive features in their UV–vis spectra. The azobenzene compound presents two bands in the 210–400-nm region (λ_{max}[MeOH] = 228 nm, ε = 14,200; and 316 nm, ε = 19,186), whereas the azoxy presents three (λ_{max}[MeOH] = 231 nm, ε = 8795; 258 nm, ε = 7568); and 320 nm, ε = 14318).

Catalytic Reactions

In this section, we describe how aniline can be catalytically oxidized by $FeCl_2py_4^+$ (which is readily obtained when dissolving $[FeCl_2(H_2O)_4]Cl{\cdot}2H_2O$ in pyridine) (*2*) using mainly HOOH as the oxidative reagent. The product selectivities and efficiencies depend on the catalyst; solvent; temperature; oxidative reagent; relative concentrations of catalyst, oxidant, and substrate; and reaction times, as reflected in Table 1.

The system described in entry 1 yields almost exclusively PhNO after a 10-min reaction time

$$PhNH_2 + 2HOOH \xrightarrow{FeCl_2py_4^+} PhNO + 3H_2O \qquad (7)$$

with a reaction efficiency of 60.3% relative to the oxidative agent HOOH. Thus, HOOH is being used mainly to catalytically transform aniline into nitrosobenzene; the remaining equivalents are disproportionated into water and molecular oxygen:

$$2HOOH \xrightarrow{FeCl_2py_4^+} 2H_2O + O_2 \qquad (8)$$

After HOOH has been depleted, then azobenzene and azoxybenzene are formed catalytically at the expense of PhNO (entries 2–11 and Fig. 1) (*2*)

$$PhNH_2 + PhNO \xrightarrow{FeCl_2py_4^+} PhNNPh + H_2O \qquad (9)$$

$$PhNH_2 + 3PhNO \xrightarrow{FeCl_2py_4^+} 2PhN(O)NPh + H_2O \qquad (10)$$

Entry 12 shows the effect of increasing the ratio of catalyst to oxidizing agent from the original 5/100 to 5/400. This generates substantial amounts of $PhNO_2$ and PhN(O)NPh at the very beginning of the reaction in addition to PhNO,

Table 1. $FeCl_2py_4^+$-Catalyzed Transformation of 1 M Aniline in Pyridine

Entry	System Conditions[w]				Product Concn/(mM ± 5%)				Eff (%)[a]
	Time/min	Cat Concn/mM	Oxidant Compound	Oxidant Concn/mM	PhNO	$PhNO_2$	PhNNPh	PhN(O)–NPh	
1	10	5	HOOH	100	29.1	ND[b]	0.3	0.5	60.3
2	40	5	HOOH	100	30.7	ND	0.4	0.7	64.3
3	60	5	HOOH	100	29.5	ND	0.5	0.9	62.7
4	120	5	HOOH	100	29.0	ND	0.7	1.2	63.0
5	180	5	HOOH	100	27.5	ND	1.4	1.6	62.6
6	210	5	HOOH	100	26.3	ND	1.7	1.8	61.4
7	240	5	HOOH	100	25.1	ND	2.1	1.9	60.1
8	600	5	HOOH	100	23.2	ND	4.0	1.9	60.1
9	2,880	5	HOOH	100	21.3	ND	5.2	2.1	59.3
10	4,320	5	HOOH	100	18.3	ND	5.7	2.3	54.9
11	10,080	5	HOOH	100	10.6	ND	5.9	2.5	40.5
12	10	5	HOOH	400	43.3	9.8	2.5	15.8	42.1
13	10	5	HOOH PhNO	100 100	123.8	2.3	0.7	5.1	71.2
14	10	5	*t*-BuOOH	100	ND	7.5	ND	ND	22.5
15	180	0	HOOH	100	ND	ND	ND	ND	0.0
16	180	5	HOOH	0	ND	ND	ND	ND	0.0

[a]Efficiency is calculated with respect to HOOH. It is assumed that the formation of PhNO and PhNNPh from $PhNH_2$ requires 2 molecules of HOOH, whereas $PhNO_2$ and PhN(O)NPh require 3. [b]ND means not detected.

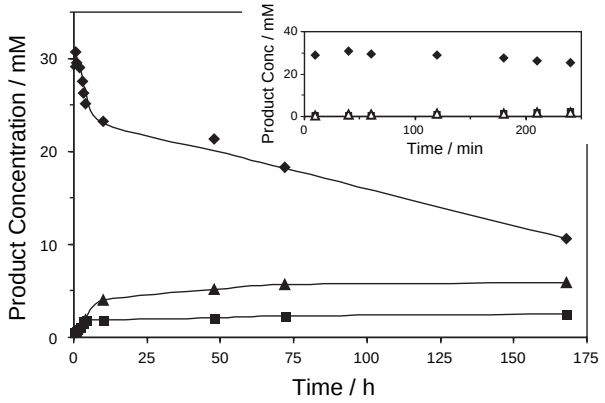


Figure 1. Product profile vs time for the system $FeCl_2py_4^+$, 5 mM/HOOH, 100 mM/$PhNH_2$, 1 M/pyridine. The inset shows the first four hours of the reaction (◆, PhNO; ▲, PhNNPh; ■, PhN(O)NPh).

clearly indicating the presence of alternative reaction pathways favored under this particular reaction condition. A similar effect is produced using a combination of PhNO and HOOH as oxidative reagents as outlined in entry 13. Finally, the use of *t*-BuOOH as the oxidative reagent (entry 14) produces exclusively $PhNO_2$

$$PhNH_2 + 3t\text{-BuOOH} \xrightarrow{FeCl_2py_4^+} PhNO_2 + 3t\text{-BuOH} + H_2O \quad (11)$$

indicating the high selectivity of the system, but with a significant decrease in the reaction efficiency compared to the HOOH cases.

Blank experiments show that in the absence of either $FeCl_2py_4^+$ or HOOH no observable reactions take place (entries 15 and 16, Table 1).

Figure 2 shows the proposed reaction mechanism for the catalytic oxidation reactions. When metal complexes interact with hydrogen peroxide in organic solvents the main reaction is nucleophilic addition/substitution (*6*). Thus in our particular case the Fe(III) complex reacts with HOOH to generate mainly species A. The coordinated hydroperoxide ligand in A is now capable of abstracting a hydrogen atom from aniline, forming species B, formally with bonded anilide and hydroxide ligands. Intermediate B now interacts with another molecule of HOOH forming intermediate species C. Again the coordinated hydroperoxide can abstract a hydrogen atom from the coordinated anilide ligand, ejecting a water molecule with concomitant formation of $FeCl_2py_4^+$ and nitrosobenzene.

Hazards

Material safety data sheets (MSDSs) for the products and reagents are available at several Web sites (see for instance: *http://hazard.com*; *http://siri.org/msds/*). These data indicate that students must wear regular protective gloves and safety glasses. It is also mandatory to handle all reagents in an appropriate fume hood.

Summary

Scheme I provides a graphical outline of all the reactions described above.

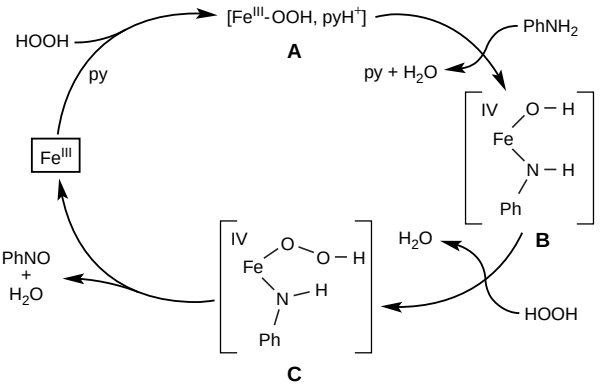


Figure 2. Proposed reaction mechanism.

For the stoichiometric reactions in basic solution, the reduction of nitrobenzene leads to the formation of the azo-(PhNNPh) and azoxy-(PhN(O)NPh) derivatives. In contrast, in acidic solution the reduction of nitrobenzene produces *N*-phenylhydroxylamine via nitrosobenzene. The former can be oxidized with sodium dichromate to nitrosobenzene in acidic medium. Under these conditions the formation of azoxy-, azo-, and hydrazobenzene (PhNHNHPh) is inhibited. For the stoichiometric reactions, PhNO undergoes condensation reactions with aniline in acidic solution and with PhNHOH in basic solution to generate the corresponding aza and azoxy derivatives, respectively. For the catalytic reactions it is illustrated that $FeCl_2py_4^+$ can activate HOOH to directly transform aniline into nitrosobenzene. The same catalyst is also able to drive the condensation reactions between aniline and nitrosobenzene to generate azabenzene and azoxybenzene. Under similar conditions, the replacement of HOOH by *t*-BuOOH yields exclusively nitrobenzene.

Reagents and Equipment

A detailed description of all experiments described in this work is provided online.[W] All reagents utilized were of the highest purity commercially available and were used without further purification. The instrumentation needed for these experiments includes a GC equipped with a capillary column and GC–MS, IR, UV–vis, and NMR spectrometers.

Acknowledgments

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[W]Supplemental Material

A complete description of laboratory experiments and procedures is provided in this issue of *JCE Online*.

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