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Phase-Transfer Catalyzed and Two-Phase Reactions of Aromatic Nitro Compounds with Iron Carbonyls

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Abstract: The first examples of the application of phase-transfer catalysis to metal carbonyl chemistry are described. Anilines were formed in good to excellent yields by treatment of nitro arenes with triiron dodecacarbonyl, aqueous sodium hydroxide, benzene, and benzyltriethylammonium chloride as the catalyst (room temperature, 0.75–2.0 h). A mechanism is proposed involving $HFe_3(CO)_{11}^-$ as a key intermediate. The reduction of nitro compounds can also be effected using $Fe(CO)_5$ (or $Fe_2(CO)_9$) in place of $Fe_3(CO)_{12}$, but the catalyst is not required. Steric and electronic effects are significantly different in the $Fe_3(CO)_{12}$ and $Fe(CO)_5$ reactions.

There have been many important applications of phase-transfer catalysis in synthetic organic chemistry during the past few years (e.g., carbene reactions).[1] It seemed conceivable to us that the process should also be useful in transition metal organometallic chemistry, particularly for reactions involving anionic species. This paper describes the first application of phase-transfer catalysis to metal carbonyl chemistry.[2]

Iron carbonyl hydrides $[HFe(CO)_4^-, HFe_3(CO)_{11}^-]$ are useful reagents for effecting reductive amination,[3-5] alkylation,[6,7] hydroacylation,[8] dehalogenation,[9] and for reduction of nitroarenes,[10,11] Schiff bases,[12] diazines,[12] and α,β-unsaturated carbonyls.[13] As these hydrides can be generated by reaction of the appropriate iron carbonyl with hydroxide ion or methanol, they appeared to be excellent models for testing

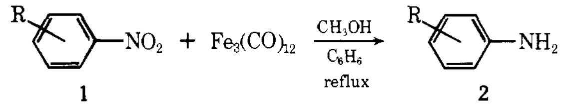
Table I. Yields of Anilines (**2**) Obtained from **1** and $Fe_3(CO)_{12}$ in the Presence or Absence of Benzyltriethylammonium Chloride

		Yield, %	
2, R =	Reaction time, h	With catalyst	Without catalyst
p-CH_3	2.0	85	6
p-OCH_3	2.0	92	3
p-Cl	0.75	88	<1
p-$COCH_3$	2.0	60[a]	

[a] 4,4-Azoxyacetophenone was formed as a by-product (16% yield).

the applicability of phase-transfer catalysis to metal carbonyl reactions.

The deoxygenation of nitrobenzenes to anilines by triiron dodecacarbonyl $[Fe_3(CO)_{12}]^{10}$ was chosen for our initial investigation in this area. Landesberg and co-workers[10] found that refluxing equimolar amounts of a nitrobenzene (**1**) and $Fe_3(CO)_{12}$, for 10-17 h, in benzene containing methanol (conditions by which the hydridoundecacarbonyltriferrate anion, $HFe_3(CO)_{11}^-$ is generated) afforded the corresponding aniline (**2**).



Results and Discussion

Treatment of **1** with half the molar quantity of $Fe_3(CO)_{12}$, aqueous sodium hydroxide, benzene, and benzyltriethylammonium chloride as the catalyst (room temperature) gave anilines (**2**) in yields comparable with, or superior to, those obtained using $Fe_3(CO)_{12}$ and methanol (Table I). In addition, this technique has the following advantages: the reaction is complete in no more than 2 h at room temperature; it requires half the amount of $Fe_3(CO)_{12}$; and it is readily worked up.

$$\mathbf{1} + Fe_3(CO)_{12} \xrightarrow[\substack{PhCH_2N(C_2H_5)_3^+Cl^- \\ 0.75\text{-}2.0\ \text{h} \\ \text{room temp}}]{\substack{\text{aqueous NaOH} \\ C_6H_6}} \mathbf{2}$$

The yields listed in Table I are optimal. Use of a 4:1 ratio of $\mathbf{1}/Fe_3(CO)_{12}$ gave **2** in lower yield (e.g., **2** (R = CH_3) 49%), while **2** (R = CH_3) was obtained in 78% yield by use of 1:1 $Fe_3(CO)_{12}/\mathbf{1}$. Anilines were formed in 0-6% yield when the reaction was effected without the catalyst. Nitro compound was recovered when the reaction was attempted using water instead of aqueous sodium hydroxide. Cetyltrimethylammonium bromide is a less effective catalyst than benzyltriethylammonium chloride.

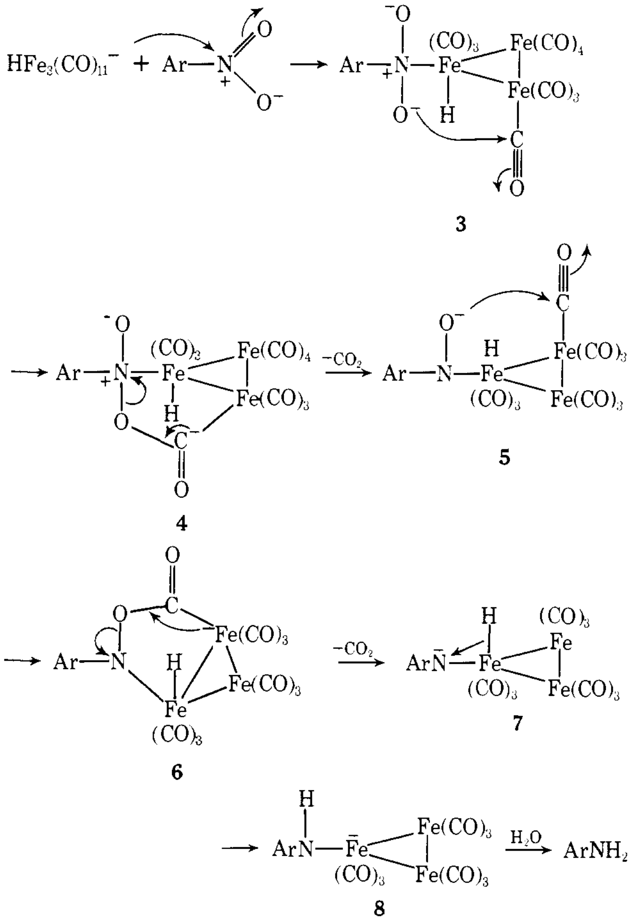
Several competitive reactions were run, using phase-transfer catalysis, in order to determine the sensitivity of the reaction to electronic and steric effects. When an equimolar mixture of **1** (R = p-Cl, H, p-CH_3) was reacted with excess $Fe_3(CO)_{12}$ for 20 min, the percent of nitro compounds remaining was 9, 26, and 65%, respectively (gas chromatographic analysis—also analyzed for anilines, which were fully consistent). These results are in accord with Hammett σ values. Treatment of an equimolar mixture of **1** (R = p-CH_3, o-CH_3, 2,6-dimethyl) with excess $Fe_3(CO)_{12}$ for 10 min gave recovered nitro compounds in 28, 22, and 50%, respectively. Steric effects are therefore anomalous.

Scheme I

$$PhCH_2N(C_2H_5)_3^+Cl^- + OH^- \longrightarrow PhCH_2N(C_2H_5)_3^+OH^- + Cl^- \quad \text{aqueous}$$

$$4PhCH_2N(C_2H_5)_3^+OH^- + Fe_3(CO)_{12} \longrightarrow [PhCH_2N(C_2H_5)_3^+]_2[Fe_3(CO)_{11}^{2-}] + [PhCH_2N(C_2H_5)_3^+]_2[CO_3^{2-}] + 2H_2O \quad \text{organic}$$

$$Fe_3(CO)_{11}^{2-} + H_2O \longrightarrow HFe_3(CO)_{11}^- + OH^- \quad \text{aqueous}$$



The reaction likely occurs by initial anion exchange in aqueous solution to form benzyltriethylammonium hydroxide (Scheme I). The latter is then transferred to the organic phase, where the highly reactive anion attacks $Fe_3(CO)_{12}$ to give $Fe_3(CO)_{11}^{2-}$.[14] The dianion may be transferred to the aqueous phase, where it is converted to $HFe_3(CO)_{11}^-$, and then migrated to the organic phase. Hydroxide ion is also regenerated in the latter reaction, thus completing a catalytic cycle.

Nucleophilic attack of $HFe_3(CO)_{11}^-$ on a nitro arene would give **3**. Attack by the nitro compound on $HFe_3(CO)_{11}^-$ has been previously proposed,[10] but $HFe_3(CO)_{11}^-$ is the more nucleophilic of the two species (one would expect attack by **1** on a *neutral* metal carbonyl). Complex **3** can now undergo intramolecular cyclization at a carbonyl carbon to give **4** [i.e., attack by O^- takes place at an essentially neutral metal carbonyl—$Fe_n(CO)_m$ portion of **3**], which on subsequent elimination of carbon dioxide affords **5**. Repetition of this process would give **7** (via **6**), which on hydrogen migration (**8**) and iron-nitrogen bond cleavage would afford the aniline. It is conceivable that the anionic iron carbonyl by-product could attack another molecule of a nitrobenzene in the above-described manner. Bis(arylnitrino)enneacarbonyltriiron complexes are not involved in the reaction, since $(C_6H_5N)_2Fe_3(CO)_9{}^{10}$ was convertible to aniline in only trace amounts, using phase-transfer catalysis conditions.

The other two iron carbonyls, $Fe(CO)_5$ or $Fe_2(CO)_9$, also

Table II. Yields of Anilines (**2**) Obtained from **1**, $Fe(CO)_5$, and 1 N NaOH

2, R =	Reaction time, h	Yield, %
p-CH_3	2	85[a]
p-OCH_3	4	80
p-Cl	2	80
p-$COCH_3$	2	15[b]

[a] Use of 1 M $NaOD/D_2O$ resulted in deuteration at nitrogen and not at an aromatic carbon. [b] The major product was 4,4′-azoxyacetophenone (57% yield).

reduce nitro compounds to anilines in a two-phase system, but a catalyst is not necessary. For example, **2** (R = p-CH_3) was obtained in 70% yield by reaction of **1** (R = p-CH_3) with an equimolar amount of $Fe_2(CO)_9$/benzene and 1 N NaOH. The yield was reduced to 59% when the reaction was effected in the presence of benzyltriethylammonium chloride. A 34% yield of p-toluidine resulted using a 4:1 mole ratio of **1** (R = CH_3)/$Fe_2(CO)_9$, but without a catalyst.

p-Toluidine was formed in 59% yield by benzyltriethylammonium chloride catalyzed reaction of **1** (R = p-CH_3) with an equimolar amount of $Fe(CO)_5$/benzene and 1 N NaOH for 2 h at room temperature. However, the yield increased to 85% when the reaction was conducted in the absence of a catalyst. This two-phase reaction is a useful one for the synthesis of aromatic amines (Table II). Use of a 2:1 or 1:2 mole ratio of $Fe(CO)_5$/**1** gave reduced product yields (e.g., 74 and 48%, respectively, for R = CH_3). Less than 1% reduction occurred when water was used instead of 1 M NaOH for the aqueous phase. Interestingly, the product distribution of 4,4′-azoxyacetophenone and **2** (R = $COCH_3$) obtained from **1** (R = $COCH_3$) and $Fe_3(CO)_{12}$ [phase-transfer catalysis] is the reverse of that observed with $Fe(CO)_5$ [without catalyst].

Another interesting aspect of the iron pentacarbonyl system is that the nitro compound is *required* to induce attack of hydroxide ion on $Fe(CO)_5$ using a two-phase system. When a benzene solution of $Fe(CO)_5$ was treated with 1 N NaOH for 2 h in the absence of **1**, the metal carbonyl was recovered in 87% yield. The nitro compound was not affected by OH^- in the absence of $Fe(CO)_5$ [two-phase system].

Experiments relating to steric and electronic effects gave completely different results for $Fe(CO)_5$ as compared to $Fe_3(CO)_{12}$. Treatment of an equimolar mixture of **1** (R = p-Cl, H, p-CH_3) with an excess of $Fe(CO)_5/C_6H_6$ and 1 N NaOH for 20 min gave the following respective per cents of recovered nitro compounds: 34, 24, and 42%. Similar reaction of **1** (R = p-CH_3, o-CH_3, 2,6-dimethyl) for 10 min resulted in 21, 31, and 48% recovery of the nitro compounds. Clearly, these results show no pattern with regards to electronic effects, but steric effects are important.

The mechanism of the $Fe(CO)_5$ reaction appears to be quite complex, based on the above results. It is conceivable that the reaction proceeds by an electron transfer pathway.

In summary, this work has demonstrated the application of phase-transfer catalysis to metal carbonyl chemistry. Furthermore, there is a remarkable difference in the behavior of $Fe(CO)_5$ and $Fe_3(CO)_{12}$ toward OH^-, as well as in reaction with nitro compounds and possibly other substrates,[12] points which have not been realized prior to this study. We are currently investigating other uses of phase-transfer catalysis in organometallic chemistry.

Experimental Section

General. Infrared (IR) spectra were obtained on a Beckman IR20A spectrometer. Proton magnetic resonance spectra were determined on Varian T-60 and/or HA-100 spectrometers (tetramethylsilane as internal standard). Mass spectra were determined using a Varian MS 902 spectrometer. Analytical vapor-phase chromatography was performed on a Varian Aerograph 700 gas chromatograph [Carbowax 20 (6 or 12 ft long), 150–170 °C].

Triiron dodecacarbonyl was purchased from Pressure Chemical Co., and dried in vacuo prior to use. Iron pentacarbonyl and diiron enneacarbonyl were purchased from Alfa Inorganics, Inc. and were used as received. All nitro compounds, aromatic amines, and phase-transfer catalysts were commercial products and were used as received. Solvents were purified by standard techniques. All reactions were run under an atmosphere of prepurified nitrogen.

General Procedure for Reaction of Nitro Compounds with $Fe_3(CO)_{12}$. Benzene (10 ml), $Fe_3(CO)_{12}$ (0.25 g, 0.50 mmol), nitro compound (1.00 mmol), benzyltriethylammonium chloride (0.022 g, 0.100 mmol), and 1 N NaOH (10 ml) were placed in a 50-ml filtering flask containing a stirring bar. The solution was stirred at room temperature for 0.75–2.0 h. The organic layer was separated by centrifugation, and then filtered through silica gel to give pure aromatic amine, and/or analyzed by vapor-phase chromatography. The amines (**2**) and 4,4′-azoxyacetophenone were identified by comparison of spectral data (IR, NMR, MS), retention times, and R_f values with those for authentic samples. The reaction times and yields are listed in Table I. The uncatalyzed reaction was effected in an identical manner, except that no benzyltriethylammonium chloride was present (Table I). Substitution of water for 1 N NaOH in these reactions gave recovered **1**.

For competitive reactions, 0.50 mmol of each of three nitro compounds (see Results and Discussion—e.g., **1** (R = p-Cl, H, p-CH_3)) was treated with $Fe_3(CO)_{12}$ (2.50 mmol), catalyst (0.10 mmol), 1 N NaOH (10 ml), and C_6H_6 (10 ml) following the procedure outlined above. The mixtures of recovered nitro compounds and of anilines were each analyzed by vapor-phase chromatography.

Reaction of p-Nitrotoluene (1, R = p-CH_3) with $Fe_2(CO)_9$. A mixture of **1** (R = p-CH_3)(1.0 mmol), $Fe_2(CO)_9$ (1.0 mmol), 1 N NaOH (10 ml), and benzene (10 ml) was stirred for 2 h at room temperature. Standard work-up conditions (above) gave p-toluidine in 70% yield. When the reaction was repeated in the presence of benzyltriethylammonium chloride (0.10 mmol), the yield was reduced to 59%.

General Procedure for Two-Phase Reaction of 1 with $Fe(CO)_5$. An equimolar mixture of **1** (R = p-CH_3, p-OCH_3, p-Cl, p-$COCH_3$) and $Fe(CO)_5$ (1.0 mmol) in benzene (10 ml) was treated with 1 N NaOH (10 ml). After stirring for 2–4 h, the reaction was worked up as described for $Fe_3(CO)_{12}$. The yields and reaction times are listed in Table II. Lower product yields resulted in the presence of benzyltriethylammonium chloride (see text). When the reaction was run in the absence of both **1** and catalyst (2 h), $Fe(CO)_5$ was recovered in 87% yield.

For competitive reactions, 0.5 mmol of three nitro compounds (results and discussion) was reacted with $Fe(CO)_5$ (5.0 mmol), benzene (10 ml), and 1 N NaOH (10 ml) following the above general procedure. Vapor-phase chromatography and NMR spectroscopy (nitrobenzene as solvent) were used to analyze the mixtures of recovered nitro compounds and of anilines.

Acknowledgment. We are grateful to the National Research Council of Canada for financial support of this research, to D. Des Roches for experimental assistance, and to R. Capoor for recording spectra on the HA-100 NMR spectrometer. Dr. H. des Abbayes is a participant in the France–Canada scientific exchange program.

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Model for the Binding of D-Penicillamine to Metal Ions in Living Systems: Synthesis and Structure of L-Histidinyl-D-penicillaminatocobalt(III) Monohydrate, [Co(L-His)(D-Pen)]·H_2O

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Abstract: The complex L-histidinyl-D-penicillaminatocobalt(III) monohydrate, $C_{11}H_{19}N_4O_5SCo$, has been synthesized and its crystal structure has been determined from three-dimensional x-ray diffractometer data. The crystals are monoclinic, space group $P2_1$, with two molecules in a cell of dimensions a = 7.078 (2), b = 12.263 (4), c = 8.856 (3) Å, and β = 96.06 (2)°. Full-matrix least-squares refinement using 2185 independent intensities (Mo Kα radiation) has yielded a conventional R factor of 0.032. The structure consists of monomeric Co(L-His)(D-Pen) units and water molecules. The penicillamine ligand coordinates to the metal as the dianion, with Co–S, Co–N, and Co–O bonds of length 2.281 (1), 1.973 (4), and 1.921 (1) Å, respectively. The histidine monoanion coordinates through Co–N(amino), Co–N(imidazole), and Co–O bonds of length 1.933 (3), 1.925 (3), and 1.989 (3) Å, respectively. The geometry at cobalt is distorted octahedral, with cis bond angles in the range 82.6 (1)–98.3 (2)°. It is noteworthy that the diastereomeric complex Co(L-His)(L-Pen) cannot be isolated using the same synthetic technique, and that addition of D,L-histidine and D,L-penicillamine to solutions of cobalt(II) salts lead only to the title complex and its enantiomer.

Metal poisoning, produced largely by industrial pollution[1] but also by the widespread use of metal and organometallic complexes in appliances and agriculture,[2] has become a focus of general concern in both industrialized and advanced agricultural societies.[3] It is well established that the administration of some organic chelating agents is of therapeutic value. Two of the more commonly employed agents contain sulfur atoms, these being BAL (2,3-dimercaptopropanol) and D-penicillamine (β,β-dimethyl-D-cysteine), while some (e.g., EDTA and its analogues) do not. While BAL has been found to be useful,[4] its administration to patients must be carefully monitored since BAL is itself toxic; such problems do not arise if D-penicillamine is used, although it is noteworthy that its enantiomer is toxic.

Largely as a consequence of this biological significance, but also in part as a result of a general interest in metal–peptide complexes as models for metalloenzymes, the structural chemistry of metal complexes of cysteine and penicillamine has received recent attention in a number of laboratories.[5-17] It is apparent from this work that, while tridentate coordination by cysteine and its derivatives is possible, it is not universal.

Since in the living system the toxic metal ions bind to peptide residues of proteins, we felt that complexes which contain metal ions coordinated to both an L-amino acid and D-Pen may be better models for the therapeutic action of D-Pen than are its complexes of the free metal ions. Since metal ions in a variety of metalloenzymes coordinate to histidyl residues, we chose L-histidine as our L-amino acid residue. We here report the synthesis and structure of the first fully characterized complex of the general type M(AA)(D-Pen) [where AA is an amino acid], the complex studied being [Co(L-His)(D-Pen)].

Experimental Section

Synthesis. L-Histidine (0.002 mol in 15 ml of water) was added to 0.001 mol of cobalt(II) chloride dissolved in 5 ml of water. To this solution was added 0.001 mol of D-penicillamine. The solution becomes progressively darker in color, changing from its original pale orange to deep brown over a period of 24 h; this color change is associated with the oxidation of cobalt(II) to cobalt(III). After several hours, dark prismatic crystals of the title compound formed. Substitution of D,L-penicillamine for D-penicillamine also produces the color change, but yields only crystals of the title complex, and substitution of D-histidine for L-histidine yields no isolable penicillamine containing complex, despite changing color from orange to brown. It is noteworthy, however, that electronic spectra of the reaction mixtures demonstrate that the complex Co(D-His)(D-Pen) [or its enantiomer Co(L-His)(L-Pen)] is formed in aqueous solution using either of these techniques; apparently, it is much more soluble than the diastereomeric material Co(L-His)(D-Pen).

Collection and Reduction of the X-Ray Data. On the basis of Weissenberg and precession photographs, the crystals were assigned to the monoclinic system. The observed systematic absences are $0k0$ for k odd, which suggests that the space group is $P2_1$ ($C_{2h}{}^5$). The cell constants, obtained by least-squares methods,[18] are a = 7.078 (2), b = 12.263 (4), c = 8.856 (3) Å, and β = 96.06 (2)°. The observations were made at 20.5° with the wavelength assumed as λ(Mo Kα_1) = 0.7093 Å. A density of 1.643 g cm^{-3} calculated for two formula units in the cell compares well with a value of 1.60 (2) g cm^{-3} observed by flotation in bromoform/carbon tetrachloride solution. Hence, in space group $P2_1$, no crystallographic symmetry is imposed on the molecules.

Diffraction data were collected on a Picker Facs-I diffractometer from a crystal with faces (010), ($0\bar{1}\bar{1}$), ($0\bar{1}1$), ($\bar{1}00$), (100), and ($11\bar{1}$), which represents one of the two typical morphologies of this complex which we have observed.

Many crystals which were examined were found to be twinned, but