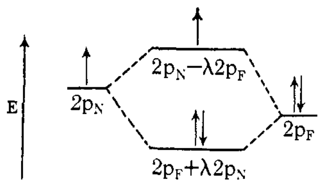
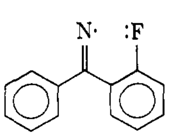


Figure 6. Orbital energies and occupancies for radical **7**, both in classical terms involving the one-center orbitals $2p_N$ and $2p_F$, and also in molecular orbital terms involving the two-center orbitals $2p_F + \lambda 2p_N$ and $2p_N - \lambda 2p_F$.

for such interactions,[16,23] and the F–F distance is too large for appreciable "through-space" interactions.

Finally, the same general approach that was used in the preceding discussion to treat "through-space" coupling between two fluorine nuclei as a two-orbital, four-electron problem can also be used to treat "through-space" coupling between an odd electron and a fluorine nucleus (or any other magnetic nucleus of an atom with an appropriately oriented lone-pair orbital) as a two-orbital, three-electron problem. Examples of this latter type of coupling are provided by radicals **7**[26] and **8**,[27] which are structurally related to the systems of types **1** and **2**, respectively, that were considered earlier. Classically, radical **7** is formulated with an odd electron in an in-plane $2p_N$ orbital on nitrogen and a lone pair of electrons in an in-plane $2p_F$ orbital on fluorine. An



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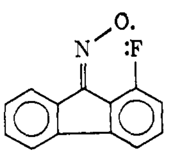

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approximate molecular orbital description of **7** is obtained by replacing these two spatially overlapping atomic orbitals by a pair of two-center molecular orbitals, $2p_F + \lambda 2p_N$ and $2p_N - \lambda 2p_F$ with $0 < \lambda < 1$, as indicated in Figure 6. The presence of an odd electron in the $2p_N - \lambda 2p_F$ orbital in **7** would place significant electron spin density around the fluorine, which would account for the large hyperfine splitting by the fluorine nucleus that has been reported for this radical.[26] The large hyperfine interactions found[27] for radical **8** can be accounted for by an entirely analogous molecular orbital treatment, using as the basis set the in-plane 2p orbital on oxygen and the in-plane 2p orbital on fluorine. Basically this same explanation, expressed in different terms, has been offered previously for hyperfine interactions of this type.[26–28]

Acknowledgment. The support of this work by the National Science Foundation through research grant GP-10640 and also through a Senior Postdoctoral Fellowship during 1970–1971 is gratefully acknowledged.

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(28) (a) P. J. Scheidler and J. R. Bolton, *J. Amer. Chem. Soc.*, **88**, 371 (1966); (b) B. C. Gilbert and R. O. C. Norman, *J. Chem. Soc. B*, 981 (1967); (c) R. O. C. Norman and B. C. Gilbert, *J. Phys. Chem.*, **71**, 14 (1967); (d) E. G. Janzen and J. L. Gerlock, *J. Amer. Chem. Soc.*, **89**, 4902 (1967); (e) F. A. Neugebauer, *Tetrahedron Lett.*, 2345 (1970); (f) M. Iwasaki, *Mol. Phys.*, **20**, 503 (1971).

On the Mechanism of Phenolic Oxidative Coupling Reactions. Ferricyanide Oxidation of 2,3′,4-Trihydroxybenzophenone, an Example of a Radical Aromatic Substitution Mechanism[1]

Patrick D. McDonald and Gordon A. Hamilton*

Contribution from the Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802. Received July 9, 1973

Abstract: A thorough uv spectrophotometric kinetic study of the oxidation of 2,3′,4-trihydroxybenzophenone (**1**) by alkaline ferricyanide has been performed under pseudo-first-order conditions. Experimental observations and conclusions concerning the kinetics and mechanism of this system include the following: (1) the reaction is first order in the benzophenone **1**; (2) a nearly quantitative yield of 2,6-dihydroxyxanthone is always formed under a variety of conditions; the yield of the isomeric 3,5-dihydroxyxanthone is always less than 5%; (3) values for the three pK_a's of **1** were determined, using a spectrophotometric technique, to be 12.20, 9.24, and 7.02, respectively; (4) a curious, unexplained "tailing in" phenomenon is observed on some first-order kinetic plots; added CN$^-$ and some other anions eliminate this unusual behavior, and all important experiments were run under conditions which minimized this initial deviation from linearity; (5) a large increase in reaction rate with increasing ionic strength is noted; (6) specific cations catalyze the reaction, increasing in effectiveness in the order $Na^+ < K^+ < Cs^+$; (7) the oxidation is strictly first order in ferricyanide under all conditions; (8) inhibition by ferrocyanide is always observed; (9) the rate increases markedly as the pH is increased. A radical aromatic substitution mechanism is proposed to be the only process consistent with all the experimental observations. These experiments constitute the first documented example of such a mechanism being involved in a phenolic oxidation coupling reaction.

Phenolic oxidative coupling is an important step in the biosynthesis of many naturally occurring compounds.[2] In the presence of a variety of chemical

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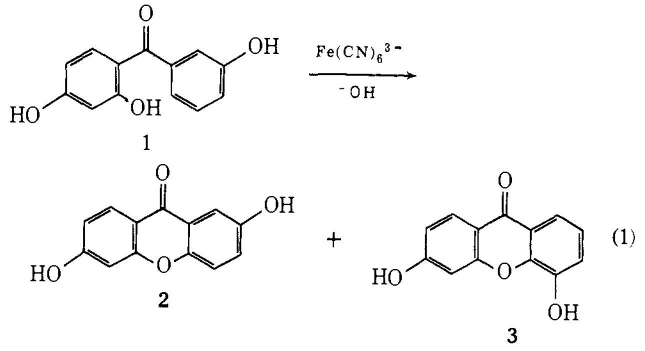
(1) Taken in part from the Ph.D. Thesis of P. D. McD., The Pennsylvania State University, 1970; Preliminary report: Fifth MARM, American Chemical Society, Newark, Del., April 2, 1970, Organic Abstract No. 29. This work was supported in part by a fellowship to P. D. McD., 1969-1970, from the donors of the Petroleum Research Fund, administered by the American Chemical Society, and in part by a research grant from the National Science Foundation.

(2) W. I. Taylor and A. R. Battersby, "Oxidative Coupling of Phenols," Marcel Dekker, New York, N. Y., 1967.

and biological oxidants, phenolic molecules combine to form many different products arising from carbon–carbon or carbon–oxygen coupling at positions ortho and/or para to the aromatic hydroxy groups. The multitude of coupling modes observed among simple phenols led early workers to suggest that the overall two-electron oxidation really occurs in two, successive, single-electron steps with the intermediate formation and subsequent coupling of two phenoxy radicals. This idea is strengthened by the facts that the majority of successful chemical reagents are known one-electron oxidizing agents and that certain stable, highly substituted phenoxy radicals can be isolated and easily characterized.

However, as indicated in a recent review,[3] homolytic coupling, although well-substantiated in many cases, is only one of three general types of free-radical mechanisms that can be envisioned for phenol coupling reactions. Furthermore, nonradical, two-electron transfer pathways are attractive alternates for enzymatic, as well as certain chemical, systems. The actual mechanism of a given oxidation largely depends upon the nature of the particular oxidant being used and may differ considerably if another reagent is employed.

Previous efforts to study the mechanism of oxidative coupling reactions were severely limited by the many experimental difficulties involved in the analysis and work-up of systems which rapidly give a variety of primary and secondary oxidation products.[3] It was felt that the mechanism of a phenol coupling reaction could be studied easily by standard physical organic techniques if the system chosen gives a high yield of a single, isolable product from a readily available or easily synthesized starting compound. One of the few systems (eq 1) which meets these criteria is the alkaline ferricyanide oxidation of 2,3′,4-trihydroxybenzophenone (**1**) which gives as the major product 2,6-dihydroxyxanthone (**2**) and a small amount of 3,5-dihydroxyxanthone (**3**). This reaction was first reported by Lewis and his coworkers in connection with their studies on xanthone biosynthesis.[4] The results of a kinetic study of this reaction are reported herein.



Experimental Section

All melting points (uncorrected) were determined on a Thomas-Hoover melting point apparatus. Elemental carbon and hydrogen analyses were performed by N-H-W Laboratories, Garden City, Mich. Mass spectral data were obtained with an AEI MS-902 spectrometer. Infrared spectra were recorded on Perkin-Elmer Model 237B and 257 spectrophotometers. Nmr spectra were run on a Varian A60A instrument. In most cases, TMS was used as an internal standard (0 ppm). The aromatic region of each spectrum was expanded to a 100-Hz sweep width, and the signal was amplified to permit detailed analysis of the aromatic substitution pattern. Spin–spin coupling constants (J values) were determined by measuring the actual peak separations on each spectrum. Routine uv and visible spectral were run on a Cary 14 spectrophotometer. More accurate absorbance measurements were made with a Zeiss PMQ II spectrophotometer whose wavelength and photometric scales were calibrated according to the manufacturer's recommendations. All the quartz cuvettes used had a 1-cm optical path length. They were kept scrupulously clean, their relative absorption characteristics were measured, and their identities were maintained throughout the course of this work. Care was taken to avoid all possible sources of experimental uncertainty, as described by Goldring, *et al.*,[5] in measuring uv and visible spectra. Samples in the milligram range were weighed on a Cahn Electrobalance Model M-10. Routine pH readings were taken from a Radiometer Model TTTlc Titragraph pH meter with scale expander, using a G202B or a G202C glass electrode and a K401 calomel electrode. More accurate measurements were made with a Radiometer Model 4c pH meter fitted with a G202B glass electrode and a K100 calomel electrode. Scale readings were calibrated using several standard buffer solutions in the appropriate pH ranges.

Materials. All chemicals and solvents were either of the highest purity commercially available or of a lesser grade purified by standard procedures prior to use. Solvents used in obtaining ir, uv, and nmr spectra were all spectroquality grade. A mixed adsorbent for tlc was prepared from two parts by weight of silica gel GF_{254} (Merck) and one part of Avicel microcrystalline cellulose, Technical S. F. Grade (Arthur H. Thomas Co.). All water used was purified by passing once-distilled water through consecutive Barnstead Standard Demineralizer and Organic Removal Cartridges and then redistilling it in a Kontes WS 2 continuous water still equipped with a redistillation kit. Only quartz, Teflon, and glass came into contact with this ultrapure water.

Syntheses of 1, 2, and 3. These were made by the reaction sequence described by Lewis.[4] After their isolation following modified work-up procedures, the compounds had some physical or spectral properties which differed from those reported by Lewis for the products which he had isolated. Therefore, a thorough analysis of each compound was carried out, and appropriate derivatives were made and characterized so as to establish the structures beyond doubt. The important data follow.[6]

2,3′,4-Trimethoxybenzophenone. Mp 80–82°; ir (CCl_4) 1270 ($ArOCH_3$) and 1663 cm^{-1} ($C{=}O$); uv_{max} (95% EtOH) 219 (ϵ 18,000), 240 (sh, 7800), 250 (sh, 6500), 280–290 (5000), and 307–308 nm (6000); nmr (CCl_4, TMS) δ 3.62 (s, 3, 3′-OCH_3), 3.78 (s, 6, 2-OCH_3 and 4-OCH_3), 6.33–6.62 (m, 2, H_3 and H_5, both ortho and/or para to -OCH_3 but meta to $C{=}O$), 6.82–7.48 ppm (m, 5, $H_{2'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$, and H_6); mass spectrum (70 eV) m/e (rel intensity) 272 (32, parent), 258 (34), 257 (39), 255 (34), 241 (11), 227 (29), 165 (100, base), 151 (64), 135 (29), 122 (18), 108 (13), 107 (21), 92 (24), 77 (32).

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.52; H, 5.98.

2,3′,4-Trihydroxybenzophenone (1). Mp 178–180°; pure by tlc analysis; ir (Nujol mull) 1628 (H-bonded $C{=}O$), 3240 (H-bonded -OH), and 3600 cm^{-1} (free -OH); uv_{max} (95% EtOH) 218–219 (ϵ 21,400), 239 (10,250), 292–292.5 (13,090), and 320–324 nm (11,640); mass spectrum (70 eV) m/e (rel intensity) 230 (87, parent), 229 (81), 213 (50), 138 (14), 137 (100, base), 121 (21), 93 (18), 81 (19), 69 (13), 65 (20), 58 (25).

Anal. Calcd for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38. Found: C, 68.13; H, 4.29.

2,3′,4-Tri(trimethylsilyloxy)benzophenone. Nmr (CCl_4, rel to trimethylsilyl peaks at about 0 ppm) δ 6.52–7.27 (m, 5, H_6, $H_{2'}$, $H_{4'}$, $H_{5'}$, and $H_{6'}$,), 6.26 (q, 1, H_5, $J_{\text{ortho}} = 8.3$ Hz, $J_{\text{meta}} = 2.3$ Hz), 6.04 ppm (d, 1.2, H_3, $J_{\text{meta}} = 2.3$ Hz).

2,6-Dihydroxyxanthone (2). Mp >360°; ir (Nujol mull) 1635 ($C{=}O$), 3188 and 3280 cm^{-1} (-OH); uv_{max} (95% EtOH) 237.4–238.2 (ϵ 36,740), 265–265.5 (sh, 9790), and 313.5–314 nm (14,600); mass spectrum (70 eV) m/e (weak spectrum) 228 (parent), 200, 168, 139, 128, 123, 80, 58 (base).

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(3) P. D. McDonald and G. A. Hamilton in "Oxidation in Organic Chemistry, Part B," W. S. Trahanovsky, Ed., Academic Press, New York, N. Y., 1973, Chapter 2, p 97.

(4) (a) J. R. Lewis, *J. Chem. Soc.*, 5074 (1964); (b) J. E. Atkinson and J. R. Lewis, *J. Chem. Soc. C*, 281 (1969).

(5) L. S. Goldring, R. C. Hawes, G. H. Hare, A. O. Beckman, and M. E. Stickney, *Anal. Chem.*, 25, 869 (1953).

(6) Details may be found in the Ph.D. thesis of P. D. McD.[1]

Anal. Calcd for $C_{13}H_8O_4$: C, 68.42; H, 3.53. Found: C, 68.22; H, 3.53.

2,6-Di(trimethylsilyloxy)xanthone. Nmr (CCl_4, rel to trimethylsilyl peaks at about 0 ppm) δ 7.82 (d, 1, H_8, $J_{\text{ortho}} = 9.2$ Hz), 7.26 (q, 1, H_1, $J_{\text{meta}} = 2.8$ Hz, $J_{\text{para}} = 0.7$ Hz), 6.97 (q, 1($^1/_2$ of 2), H_4, $J_{\text{ortho}} = 8.9$ Hz, $J_{\text{para}} = 0.7$ Hz), 6.75 (q, 1($^1/_2$ of 2), H_3, $J_{\text{ortho}} = 9.0$ Hz, $J_{\text{meta}} = 2.8$ Hz), 6.45 (q, 1($^1/_2$ of 2), H_7, $J_{\text{ortho}} = 9.2$ Hz, $J_{\text{meta}} = 2.2$ Hz), 6.43 ppm (d, 1($^1/_2$ of 2), H_5, $J_{\text{meta}} = 2.1$ Hz).

2,6-Dimethoxyxanthone. Mp 163.5–164.5°; nmr ($CDCl_3$, TMS) δ 3.93 (s, 6, 2-OCH_3 and 6-OCH_3), 6.87 (s, 1($^1/_2$ of 2), H_5), 6.95 (q, 1($^1/_2$ of 2), H_7, $J_{\text{ortho}} = 9.0$ Hz, $J_{\text{meta}} = 2.4$ Hz), 7.21 (q, 1($^1/_2$ of 2), H_3, $J_{\text{ortho}} = 9.2$ Hz, $J_{\text{meta}} = 1.6$ Hz), 7.43 (q, 1($^1/_2$ of 2), H_4, $J_{\text{ortho}} = 8.8$ Hz, $J_{\text{para}} = 1.0$ Hz), 7.72 (q, 1, H_1, $J_{\text{meta}} = 2.4$ Hz, $J_{\text{para}} = 1.2$ Hz), 8.25 ppm (q, 1, H_8, $J_{\text{ortho}} = 8.0$ Hz, $J_{\text{para}} = 1.4$ Hz); mass spectrum (70 eV) *m/e* (rel intensity) 257 (17), 256 (100, parent and base), 255 (52), 241 (18), 227 (13), 226 (24), 186 (8), 185 (19), 142 (6), 128 (8), 63 (11).

Anal. Calcd for $C_{15}H_{12}O_4$: C, 70.31; H, 4.72. Found: C, 70.49; H, 4.87.

3,5-Dihydroxyxanthone (3). $Uv_{\max}$ (95% EtOH) 235 (rel ϵ 4.45), 245 (sh, 4.28), 271 (2.10), 307 (1.91), and 330–335 nm (sh, 1.00). No other physical properties of **3** were measured since a sufficiently large sample was not obtained.

Kinetic Procedures. All reactions were followed spectrophotometrically and were run at 25 ± 0.05°; this temperature was maintained by means of a Haake Model F constant-temperature circulator which pumped water through a cell carriage (Zieler Instrument Co.) in the sample compartment of the Zeiss PMQ II spectrophotometer. At this temperature most reactions that were performed had half-lives of 3–30 min so the data were conveniently recorded manually. An analysis[6] of the spectra of reactants and products indicated that around pH 11 the largest change in absorbance during the reaction occurs at 265 nm so the reactions were followed at this wavelength. At pH 11.4 the following molar extinction coefficients (ϵ) at 265 nm were obtained: **1**, 7250; **2**, 27,700; $K_3Fe(CN)_6$, 1160; $Na_4Fe(CN)_6$, 2460; NaCN, 0.040. Unfortunately enough of **3** was not obtained to permit a quantitative measurement of its uv spectrum, but its ϵ at 265 nm was estimated to be 10,000. Under pseudo-first-order conditions, with all reagents in excess of **1**, the largest change in absorbance at 265 nm is due to the conversion of **1** into **2** with a smaller increase in absorbance (about one-tenth of the total) from the change of ferricyanide into ferrocyanide. No complications in the treatment of the kinetic data result from having an absorbance change due to more than one component during a pseudo-first-order reaction. For most experiments the total change in absorbance during the run was *ca.* 0.5 OD units. Typical reaction solutions had absorbances in the range of 0.7–2.5 OD units (measured *vs.* water). To utilize the most accurate portion (0.0–0.7) of the photometric scale on the spectrometer for obtaining the kinetic data, appropriate blank solutions were prepared and their absorbance set to zero by opening the slit on the monochromator. The blanks contained all reagents (except the organic components) at the concentrations estimated to be present at the end of a run.

Standard reagent solutions of the desired concentration and pH were prepared by dissolving precisely weighed amounts of the various reagents in exact volumes of water or a standardized aqueous sodium hydroxide solution (prepared carbonate free[7]). All the distilled water was deaerated to remove CO_2 prior to use, and the solutions were stored in amber polyethylene bottles under N_2. Ordinary aqueous solutions of $K_3Fe(CN)_6$ and basic solutions of phenols are subject to decomposition; however, it was found that solutions carefully prepared and stored in the dark under N_2 could be used for periods of 4–5 days before any significant decomposition occurred. Care was taken not to expose any of the $K_3Fe(CN)_6$ or $Na_4Fe(CN)_6$ solutions to unnecessary light or heat. For the preparation of reaction mixtures (total volume, 2.5 ml) solution volumes were usually measured precisely with Gilmont micrometer syringes (0.200 or 2.000 ml capacity) or Drummond Microtrol syringes (20 or 100 μl capacity). All transfer operations were performed under a N_2 blanket.

After the cuvettes containing the reaction mixture (with all components except **1**) and blank were temperature equilibrated for 20–30 min, the reactions were initiated by adding rapidly an aliquot (usually 20 μl) of an alkaline solution of **1** which had been placed on a "golf club" stirring rod. Rapid mixing of the solutions by vigorous up-and-down agitation of the rod allowed readings to be obtained 5–20 sec after initiation. Readings were taken for at least 3 half-times and the infinity absorbance measured after 10 half-times had elapsed. Frequently a complete uv-visible spectrum of the completed reaction *vs.* the blank was recorded using the Cary 14 spectrometer, and the final pH was measured under N_2. Selected reaction mixtures were stored in polyethylene vials if the product studies were to be performed.

Since all reactions were run under pseudo-first-order conditions with **1** the limiting reagent, the rate is given by

$$\text{rate} = k_{\text{obsd}}[\mathbf{1_T}]$$

where $[\mathbf{1_T}]$ is the total concentration of all the forms of **1** (ionized and un-ionized), and k_{obsd} is the observed first-order rate constant given by the slope of a line resulting from a plot of $-\ln (A_\infty - A_t)$ *vs.* t (where A_∞ is the absorbance at infinite time and A_t the absorbance at time t). The results were analyzed in this way utilizing a computer program[6] which performed an error analysis and gave three values of the rate constant: the first calculated from data obtained during the first half-time, the second from data obtained during the first two half-times, and the third from data obtained during the first three half-times. In this way any deviations from linearity could be observed. This was also frequently checked visually utilizing another program[6] and an IBM 1401/CalComp 564 plotter to automatically produce a first-order kinetics graph.

In most cases, the k_{obsd} used in further calculations was that for the first two half-lives of each reaction, although the kinetics were almost always linear for at least three half-lives. The root-mean-square error (rmse) of the ordinate on the first-order plot usually ranged from 0.0020 to 0.0100. This corresponds to an average deviation of 0.001–0.005 in the absorbance data recorded from the spectrophotometer, or 0.2–1.0% of the normal total absorbance change during a run. For fast reactions or reactions run with low initial ferrocyanide concentrations (in which the ferrocyanide concentration changes significantly during the reaction), the rmse was somewhat larger, being as high as 3.5% of the total absorbance change in the latter case. The reported rate constants had a precision of ±5%, and usually the limit of error was even smaller, about ±1 or 2%.

Product Analyses.[6] Two methods (tlc and uv) were used to identify qualitatively and quantitatively the amounts of **1**, **2**, and **3** present at the end of a reaction. By these techniques yields could be estimated to the nearest 5–10%. The best combination of adsorbent and solvent found for separating *via* tlc all the organic components in any given reaction mixture is silica gel–Avicel SF (2:1 weight ratio) and *n*-butyl alcohol saturated with ammonium hydroxide. In this system, the R_F values of **1**, **2**, and **3** are 0.40, 0.33, and 0.17, respectively. The entire volume (2.5 ml) of selected reaction mixtures (after neutralization to pH 6.5) was applied directly to a 20 × 20 cm tlc plate, developed, and visualized with uv light.

In the uv method the spectrum of selected reactions (at infinity) was measured *vs.* a blank containing all the nonorganic components at the concentrations predicted to be present at the end of a reaction. Thus, knowing the detailed spectra of **1**, **2**, and **3** it was possible to estimate the amounts of each present at infinite time.

pK_a Determinations.[6] The absorbance–pH data from a spectrophotometric titration of **1** with NaOH in aqueous solution at 25° and constant ionic strength of 8.33×10^{-2} were used to calculate the values for the K_a's and pK_a's of the three hydroxy groups in **1** *via* a computerized nonlinear least-squares analysis of the relation

$$K_a = [H^+](A - A_N)/(A_I - A)$$

where A is the absorbance of the sample at a given hydrogen ion concentration, A_I is the absorbance of the ionized or deprotonated species, and A_N is the absorbance of the neutral or protonated species at the analytical wavelength. Using analytical wavelengths of 346 nm for the first and third ionizations of **1** (probably mainly the 4- and 2-OH's, respectively) and 246 nm for the second ionization (probably mainly the 3′-OH), the following values were determined: $K_1 = 9.54 \times 10^{-8} \pm 6.7\%$, $pK_1 = 7.02 \pm 0.029$; $K_2 = 5.76 \times 10^{-10} \pm 1.9\%$, $pK_2 = 9.24 \pm 0.009$; $K_3 = 6.35 \times 10^{-13} \pm 0.9\%$, $pK_3 = 12.20 \pm 0.007$.

Results and Discussion

Some General Characteristics. A number of kinetic reaction mixtures from experiments under various conditions of pH, ionic strength, reagent concentrations, etc., were analyzed for products by the tlc and uv methods,

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[7] H. A. Laitinen, "Chemical Analysis," McGraw-Hill, New York, N. Y., 1960, pp 90–92.

and the results were always the same. The only detectable organic product present at the end of a reaction is **2** and it is formed in 90–100% yield; none of the starting material **1** or the other possible product **3** could be detected (limit of detection, 5%). Also, no other uv-absorbing organic products were observed. Thus, under the conditions of the kinetic experiments the conversion of **1** to **2** is essentially quantitative.

In preliminary kinetic runs it was found that the following had no effect on the observed rate: the presence or absence of O_2, initiation of the reaction by adding ferricyanide rather than **1**, using samples of ferricyanide and ferrocyanide from several different manufacturers. The first-order plots of data from preliminary experiments were fairly linear, but reproducibly there appeared to be a slight increase in slope during the first half-time; the plots, however, seemed perfectly linear during the second and third half-times. Generally this change in slope amounted to a 5–10% increase in k_{obsd} but its magnitude varied from run to run, depending upon the reaction conditions. In experiments designed mainly to find conditions where this "tailing in" phenomenon is minimized, the following observations were made: (1) added CN^- salts eliminate the "tailing in" when their concentrations reach about 0.01 *M* (Figure 1; the slopes of the lines in Figure 1 differ due to the ionic strength effect discussed below); (2) added I^- causes a significant reduction in the "tailing in," Br^- has a lesser effect, Cl^- still less, and ClO_4^- has no effect (all salts at 0.01 *M*); (3) light from a sunlamp causes an almost complete disappearance of the "tailing in" but the ultimately obtained k_{obsd} is not changed significantly; (4) the effect is not observed below pH 10; (5) the magnitude of the effect increases as the initial ferrocyanide concentration is decreased.

No complete explanation for the observed "tailing in" phenomenon could be deduced. The effects of CN^- suggested that perhaps some feature of the chemistry of complex iron cyanides is involved, but a review of the literature on complex cyanide chemistry[8] indicates that there should be no competing reactions of the hexacyanoferrate complexes. In any event, all important experiments discussed below were run under conditions such that this deviation from linearity was kept at a minimum (less than 5%).

The observation that good first-order plots can be obtained with all reactants except **1** in excess indicates that the reaction is first-order in **1**. This was further checked by varying the initial concentration of **1** while keeping all other reaction conditions constant. Under the conditions pH 11.4 (6.81×10^{-3} *M* NaOH), $[K_3Fe(CN)_6] = 1.50 \times 10^{-3}$ *M*, $[Na_4Fe(CN)_6] = 2.50 \times 10^{-4}$ *M*, $[NaCN] = 1.00 \times 10^{-2}$ *M*, ionic strength $= 2.84 \times 10^{-2}$, and the initial concentrations ($\times 10^5$ *M*) of **1** being 1.25, 1.88, 2.50, and 3.75 the observed first-order rate constants ($\times 10^3$ sec^{-1}) were found to be 2.86, 3.06, 3.13, and 3.30 respectively. In all cases good first-order plots were obtained. This apparent 15% increase in rate is small compared with the threefold difference in the initial concentration of **1**. Thus, the reaction appears to be first-order in **1**.

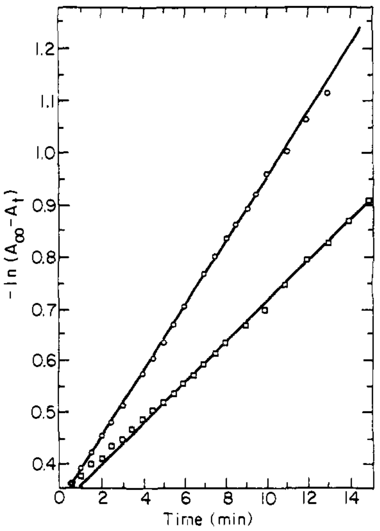

Figure 1. First-order kinetic plots showing the "tailing in" phenomenon and its elimination by CN^-. Reaction conditions: 25.0°, pH 11.4 (6.81×10^{-3} *M* NaOH), $[K_3Fe(CN)_6] = 1.25 \times 10^{-3}$ *M*, $[K_4Fe(CN)_6] = 2.50 \times 10^{-4}$ *M*; □, no KCN, ionic strength = 1.70×10^{-2}; ○, 0.01 *M* KCN, ionic strength = 2.70×10^{-2}.

Ionic Strength and Specific Cation Effects. There is a large increase in the observed first-order rate constant when increasing amounts of salts are added to the reaction solution with all other conditions remaining the same. Some representative data at two pH's are given in Table I (runs 1–8). At either pH a plot of k_{obsd} *vs.* the square root of the ionic strength is linear, but the slopes at the two pH's differ considerably due to the large pH effect on k_{obsd}.

Such a large ionic strength effect is to be expected in the reaction under investigation because two highly charged negative ions must come together to bring about the initial oxidation. Olson and Simonson have postulated that the rate of a reaction between ions of like sign is not dependent upon ionic strength but rather almost exclusively on the concentration and character of salt ions of charge sign opposite to that of the reactants.[9] That this is essentially the case in the present reaction is shown by the rate constants obtained for runs 9–11 in Table I. Thus, although the ionic strength of runs 9 and 10 is the same the rate constants differ considerably; when identical cation concentrations are used (runs 9 and 11) the rate constants are similar. However, the k_{obsd} from run 11, being slightly less than that from run 9, indicates that the nature of the general ion atmosphere has a small effect on the reaction rate, but nonetheless one which cannot be entirely ignored.[10]

During the course of the ionic strength studies, it was found that the ferricyanide oxidation of **1** is subject to specific cation catalysis. As shown by runs 12–14 (Table I), at constant ionic strength K^+ is slightly more effective in catalyzing the reaction than Na^+ but Cs^+ is

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[8] (a) B. M. Chadwick and A. G. Sharpe, *Advan. Inorg. Chem. Radiochem.*, **8**, 83 (1966); (b) M. H. Ford-Smith, "The Chemistry of Complex Cyanides," Her Majesty's Stationery Office, London, 1964, p 15; (c) W. P. Griffith, *Quart. Rev., Chem. Soc.*, **16**, 188 (1962); (d) "The Chemistry of the Ferrocyanides," Cyanamid's Nitrogen Chemicals Digest, Vol. VII, American Cyanamid Co., 1953; (e) S. Aperger, I. Murati, and D. Pavlovic, *J. Chem. Soc.*, 730 (1960); (f) I. M. Kolthoff and E. A. Pearson, *Ind. Eng. Chem. Anal. Ed.*, **3**, 381 (1931); (g) A. W. Adamson, J. P. Welker, and M. Volpe, *J. Amer. Chem. Soc.*, **72**, 4030 (1950); (h) A. C. MacDiarmid and N. F. Hall, *ibid.*, **76**, 4222 (1954); (i) D. R Stranks and R. G. Wilkins, *Chem. Rev.*, **57**, 743 (1957); (j) A. W. Adamson, *J. Phys. Chem.*, **56**, 858 (1952).

[9] A. R. Olson and T. R. Simonson, *J. Chem. Phys.*, **17**, 1167 (1949).

[10] H. Taube, *Advan. Inorg. Chem. Radiochem.*, **1**, 1 (1959).

Table I. Effect of Ionic Strength and Specific Cations on the Oxidation of **1** by Ferricyanide[a]

Run no.	Added salts ($M \times 10^2$)	pH[b]	Ionic strength ($\times 10^2$)	k_{obsd}, sec^{-1} $\times 10^3$
1	None	11.39	1.70	1.45
2	KCN (1.00)	11.46	2.76	2.52
3	KCN (1.00), KCl (2.00)	11.43	4.76	4.26
4	KCN (1.00), KCl (7.00)	11.37	9.76	6.86
5	KCN (1.00), KCl (12.0)	11.42	14.76	9.01
6	NaCl (4.53)	9.4	8.66	0.138
7	NaCl (13.2)	9.4	17.3	0.301
8	NaCl (21.8)	9.4	25.9	0.366
9	NaCl (7.02)	11.03	8.35	5.76
10	Na_2SO_4 (2.34)	11.12	8.35	3.83
11	Na_2SO_4 (3.51)	11.14	11.85	5.34
12	NaCl (1.00)[c]	11.4	2.84	3.00
13	KCl (1.00)[c]	11.4	2.84	3.38
14	CsCl (1.00)[c]	11.4	2.84	5.83
15	NaCl (0.90)[d]	11.4	2.84	2.74
16	NaCl (0.70), CsCl (0.20)[d]	11.4	2.84	3.29
17	NaCl (0.50), CsCl (0.40)[d]	11.4	2.84	3.67
18	NaCl (0.30), CsCl (0.60)[d]	11.4	2.84	4.23
19	NaCl (0.10), CsCl (0.80)[d]	11.4	2.84	4.69
20	CsCl (0.90)[d]	11.4	2.84	5.01

[a] Temperature, 25.0°; initial reactant concentrations: $[\mathbf{1}_T]$ = 2.50×10^{-5} M, $[K_3Fe(CN)_6]$ = 1.25×10^{-3} M (except where noted), $[Fe(CN)_6^{-4}]$ = 2.50×10^{-4} M (the potassium salt was used for the first five listed runs and the sodium salt for all others); the pH 11.4 reactions were prepared to be 6.81×10^{-3} M in NaOH; those at pH 11.0–11.1, 3.15×10^{-3} M in NaOH; and those at pH 9.4 were carbonate buffered, $[HCO_3^- + CO_3^{2-}]$ = 0.025 M; $[Na^+]$ = 0.0281 M was used in preparing the carbonate buffer. [b] pH's measured at infinite time are given with two significant figures to the right of the decimal point; calculated or estimated values are given to only one decimal point. [c] $[K_3Fe(CN)_6]$ = 1.50×10^{-3} M. [d] Solutions also contained 2.5×10^{-3} M NaCN.

a considerably better catalyst. Runs 15–20 of Table I show results obtained when Na^+ is replaced by varying amounts of Cs^+ at constant ionic strength. A plot of k_{obsd} *vs.* $[Cs^+]$ gives a straight line suggesting that the catalysis is first order in each cation concentration, *i.e.*, $k_{obsd} = k_0 + \Sigma k_i[M_i^+]$ where M_i^+ = Na^+, K^+, Cs^+, etc. However, insufficient data were obtained to determine the various catalytic constants (k_i).

Similar cation catalysis has been observed in studies of the kinetics of electron transfer between ferricyanide and ferrocyanide ions.[11] There it was proposed that cations serve to reduce the Coulombic repulsion between the highly charged reactant ions in some sort of bridged complex and perhaps may even participate directly in the electron transfer. Such notions are consistent with the results of the present experiments.

Reaction Order in Ferricyanide. Results from two sets of experiments, in which the ferricyanide concentration is varied while other conditions (pH, ionic strength, ferrocyanide concentration, etc.) are held constant, are given in Table II. As shown by the constancy of k' (last column) at each pH, the rate of the reaction depends on the first power of the ferricyanide concentration, *i.e.*, $k_{obsd} = k'$[ferricyanide]. Other groups of experiments at various pH's, ionic strength, and initial ferrocyanide concentrations were also performed,[6] and in all cases the reaction was found to be first order in ferricyanide.

Table II. Effect of Ferricyanide Concentration on the Rate of Oxidation of **1**

pH	[Ferricyanide], $M \times 10^3$	k_{obsd}, $sec^{-1} \times 10^3$	$k' = k_{obsd}/$[ferricyanide], l. mol^{-1} sec^{-1}
11.4	1.50[a]	3.13	2.09
	1.25[b]	2.66	2.13
	1.25[c]	2.68	2.14
	1.00[b]	2.27	2.27
	1.00[c]	2.37	2.37
	0.50[b]	1.09	2.18
	0.50[c]	1.13	2.26
	0.25[b]	0.56	2.24
	0.25[c]	0.60	2.40
9.4[d]	1.50	0.206	0.137
	1.25	0.138	0.111
	1.00	0.119	0.119
	0.50	0.058	0.116

[a] Temperature, 25.0°; initial concentrations: $[Na_4Fe(CN)_6]$ = 2.50×10^{-4} M, $[\mathbf{1}_T]$ = 2.50×10^{-5} M, [NaOH] = 6.81×10^{-3} M, [NaCN] = 1.00×10^{-2} M; ionic strength 2.84×10^{-2}; ferricyanide added as $K_3Fe(CN)_6$. [b] Same as in *a* except more NaCN was added to maintain constant ionic strength at 2.84×10^{-2}. [c] Same as in *a* except KCl added to maintain constant ionic strength at 2.84×10^{-2}. [d] Temperature, 25.0°; initial concentrations: $[Na_4Fe(CN)_6]$ = 2.50×10^{-4} M, $[\mathbf{1}_T]$ = 2.50×10^{-5} M, $[NaHCO_3]$ = 2.50×10^{-2} M, [NaOH] = 3.12×10^{-3} M, [NaCl] = 4.45 to 4.75×10^{-2} M to maintain constant ionic strength of 8.66×10^{-2}; ferricyanide added as $K_3Fe(CN)_6$.

Inhibition by Ferrocyanide. As indicated by the representative results given in Table III, ferrocyanide

Table III. Effect of Ferrocyanide Concentration on the Rate of Oxidation of **1** by Ferricyanide

pH	[Ferricyanide],[a] $M \times 10^3$	[Ferrocyanide],[b] $M \times 10^4$	k_{obsd}, $sec^{-1} \times 10^3$
11.1[c]	1.25	0.00	6.4[e]
	1.25	0.125	5.8[e]
	1.25	0.625	4.24
	1.25	1.25	3.58
	1.25	2.50	3.04
	1.25	4.00	2.54
	0.625	0.00	3.0[e]
	0.625	0.125	2.7[e]
	0.625	0.625	1.98
	0.625	1.25	1.66
	0.625	2.50	1.42
	0.625	4.00	1.27
9.4[d]	1.25	0.00	0.87[e]
	1.25	0.125	0.69[e]
	1.25	0.625	0.331
	1.25	1.25	0.247
	1.25	2.50	0.138
	1.00	2.50	0.119
	0.50	2.50	0.058
	1.25	3.125	0.137

[a] Added as $K_3Fe(CN)_6$. [b] Initial concentration of $Na_4Fe(CN)_6$. [c] Initial concentrations: $[\mathbf{1}_T]$ = 2.50×10^{-5} M, [NaOH] = 4.88×10^{-3} M, [NaCl] = 1.82 to 2.17×10^{-2} to maintain constant cation concentration at 2.85×10^{-2} M; ferricyanide added as $K_3Fe(CN)_6$. [d] Initial concentrations: $[\mathbf{1}_T]$ = 2.50×10^{-5} M, $[NaHCO_3]$ = 2.50×10^{-2} M, [NaOH] = 3.12×10^{-3} M, [NaCl] = 4.50 to 4.75×10^{-2} M to maintain constant cation concentration at 7.82×10^{-2} M. [e] Only approximate values since poor first-order kinetics are obtained (see text).

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(11) (a) M. Shporer, G. Ron, A. Loewenstein, and G. Naoen, *Inorg. Chem.*, 4, 361 (1965); (b) R. J. Campion, C. F. Deck, P. King, Jr., and A. C. Wahl, *ibid.*, 6, 672 (1967).

markedly inhibits the reaction at all pH's and conditions studied. However, it is also evident from the results that the rate is not directly proportional to the reciprocal of the ferrocyanide concentration. A more complicated dependence is indicated and this will be considered later.

The concentration of ferrocyanide increases during any reaction. When no ferrocyanide is initially present, this increase becomes very significant and may cause the reaction to slow down considerably faster over its entire course than would be expected for a typical pseudo-first-order process. The existence of such a situation was verified by the poorer kinetics that were observed at low ferrocyanide concentrations. Therefore, most experiments were performed at a ferrocyanide concentration of 2.50×10^{-4} *M*. At this concentration, there is a 20% increase in the amount of ferrocyanide present during a complete reaction at the usual concentration of **1** (2.50×10^{-5} *M*). As can be deduced from the data in Table III, the change in k_{obsd} due to the gradual formation of ferrocyanide at this concentration is very small.

pH Dependence. Results from experiments performed between pH 8.0 and 11.8 at constant cation and reactant concentrations are given in Table IV. Below pH 11 the reactions had to be run in buffered solutions since an unbuffered reaction mixture shows a significant decrease in pH during the course of the run if the initial pH is less than 11. Some experiments run using other buffers and at other pH's[6] showed buffer effects, and thus they are not included in Table IV. Under the conditions of the experiments reported in Table IV, there are no significant buffer effects. A large uncertainty exists in k_{obsd} for the run at pH 8 since this reaction is extremely slow; only a few points taken over several days were recorded, and the infinity absorbance was estimated.

Table IV. Effects of pH on the Rate of Oxidation of **1** by Ferricyanide[a]

pH	k_{obsd}, $\mathrm{sec}^{-1} \times 10^2$	pH	k_{obsd}, $\mathrm{sec}^{-1} \times 10^4$
11.80[b]	3.30	10.0[c]	6.30
11.79[b]	2.94	9.8[c]	4.15
11.65[b]	2.79	9.6[c]	2.49
11.58[b]	2.35	9.4[c]	1.38
11.30[b]	1.86	9.2[c]	0.92
11.25[b]	1.42	9.0[c]	0.574
11.07[b]	1.06	8.0[d]	0.041

[a] Temperature, 25.0°; initial concentrations: $[\mathbf{1}_{\mathrm{T}}] = 2.50 \times 10^{-5}$ *M*, $[\mathrm{K_3Fe(CN)_6}] = 1.25 \times 10^{-3}$ *M*, $[\mathrm{Na_4Fe(CN)_6}] = 2.50 \times 10^{-4}$ *M*; all runs at constant cation concentration of 7.82×10^{-2} *M*, ionic strength 8.35 to 9.42×10^{-2}. [b] Contained appropriate amounts of NaOH to give desired pH and NaCl to keep cation concentration constant; pH recorded is that measured at end of reaction. [c] Buffered with carbonate, $[\mathrm{HCO_3^-}] + [\mathrm{CO_3^{2-}}] = 2.50 \times 10^{-2}$ *M*; appropriate amounts of $\mathrm{NaHCO_3}$, NaOH, and NaCl added to give desired pH and maintain constant cation concentration; pH recorded is pH of buffer. [d] Buffered with phosphate; $[\mathrm{NaH_2PO_4}] = 1.40 \times 10^{-3}$ *M*, $[\mathrm{Na_2HPO_4}] = 1.62 \times 10^{-2}$ *M*, $[\mathrm{NaCl}] = 2.34 \times 10^{-2}$ *M*; pH recorded is pH of buffer

As indicated by the results, the observed rate constant is markedly affected by pH. There is an approximate first-order dependence on the hydroxide ion concentration over the range investigated but the kinetic dependence is probably considerably more complex (see later discussion).

Mechanism. Any mechanism written to explain the ferricyanide oxidation of **1** at a given pH and cation concentration must be consistent with the following experimentally verified features: (1) a high yield of a single product **2** is formed, (2) the reaction is first-order in the total concentration of the phenol **1**, (3) the reaction is first order in the ferricyanide concentration, (4) the reaction is inhibited by ferrocyanide. Since the overall conversion of **1** to **2** is a two-electron oxidation, two molecules of ferricyanide (a one-electron oxidant) must be converted to ferrocyanide in the process. The first-order kinetic dependence on ferricyanide concentration implies that a free radical is an intermediate in the reaction and that the second molecule of ferricyanide reacts in a rapid step after the rate-determining step. Furthermore, the inhibition by ferrocyanide suggests that the kinetically significant step involving the ferricyanide is reversible. The simplest general scheme consistent with these conclusions, and also consistent with the other results listed above, is that shown in eq 2. In this and the following discussion

$$\mathbf{1}_{\mathrm{T}} \xrightarrow[k_{-1}[\mathrm{Fe(II)}]]{k_1[\mathrm{Fe(III)}]} X_{\mathrm{T}} \xrightarrow{k_2} \mathrm{Y} \xrightarrow[\mathrm{Fe(III)}]{\text{fast}} \mathbf{2}_{\mathrm{T}} \tag{2}$$

Fe(III) is used to signify ferricyanide; Fe(II), ferrocyanide; $\mathbf{1}_{\mathrm{T}}$ and $\mathbf{2}_{\mathrm{T}}$, all forms (ionized and un-ionized) or **1** and **2**, respectively; $\mathrm{X_T}$, all forms (ionized and un-ionized) of an initial intermediate, X; and Y, another intermediate which reacts rapidly an any number of steps (one involving Fe(III)) to give **2**. The rate expression for this mechanism is shown in eq 3. It is

$$\frac{\mathrm{d}[\mathbf{2}_{\mathrm{T}}]}{\mathrm{d}t} = \frac{k_1 k_2[\mathrm{Fe(III)}][\mathbf{1}_{\mathrm{T}}]}{k_{-1}[\mathrm{Fe(II)}] + k_2} \tag{3}$$

thus readily seen that the mechanism of eq 2 is consistent with the first-order dependence on the ferricyanide and phenol concentrations and also with the inhibition by ferrocyanide. In fact the observed kinetic dependence on ferrocyanide concentration can be shown to fit quantitatively with that predicted by eq 3. Under the pseudo-first-order conditions used in the present study the rate = $k_{\mathrm{obsd}}[\mathbf{1}_{\mathrm{T}}]$, and thus assuming the mechanism of eq 2 k_{obsd} is given by eq 4. On rearranging and taking the reciprocals of eq 4 one obtains eq 5. This predicts that a plot of $[\mathrm{Fe(III)}]/k_{\mathrm{obsd}}$ *vs.* [Fe(II)] should give a straight line for data obtained under a given set of pH and ionic strength conditions.

$$k_{\mathrm{obsd}} = \frac{k_1 k_2[\mathrm{Fe(III)}]}{k_{-1}[\mathrm{Fe(II)}] + k_2} \tag{4}$$

$$\frac{[\mathrm{Fe(III)}]}{k_{\mathrm{obsd}}} = \frac{k_{-1}[\mathrm{Fe(II)}]}{k_1 k_2} + \frac{1}{k_1} \tag{5}$$

In Figure 2 are shown such plots of the data contained in Table III (the inaccurate results obtained at low ferrocyanide concentrations are not included in the figure). The general linearity of the plots under the two sets of conditions is thus further evidence for the mechanism of eq 2. The slopes and intercepts of the lines are different due to the effects of pH and cation concentrations on the various rate constants.

Attempts to fit the experimental data to mechanisms other than that of eq 2 were unsuccessful. The simplest

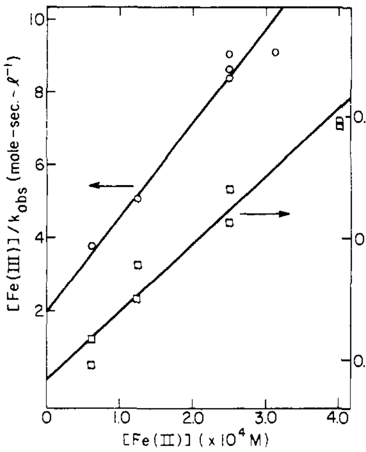


Figure 2. Ferrocyanide effects. For detailed reaction conditions see Table III: ○, pH 9.4, scale on left coordinte; □, pH 11.1, scale on right coordinate.

scheme for the usually suggested mechanism for oxidative coupling, namely, the homolytic coupling of a diradical, is shown by eq 6. The rate expression for

$$\mathbf{1}_T \underset{k_{-1}[\mathrm{Fe(II)}]}{\overset{k_1[\mathrm{Fe(III)}]}{\rightleftarrows}} X_T \xrightarrow{k_2'[\mathrm{Fe(III)}]} Y' \xrightarrow{\text{fast}} \longrightarrow \mathbf{2}_T \quad (6)$$

this mechanism is given in eq 7. Thus, this reaction

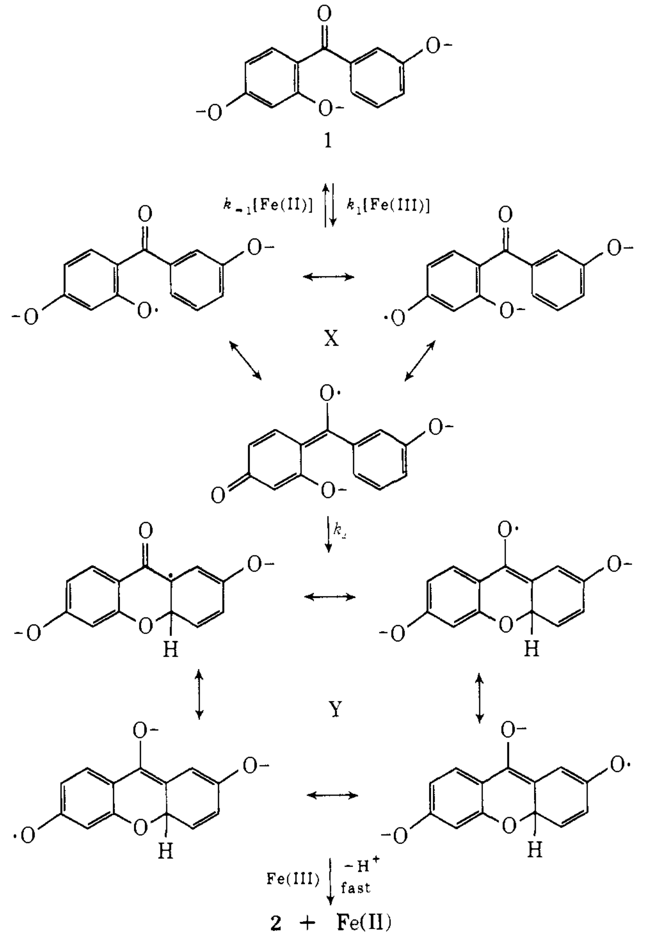
$$\frac{d[\mathbf{2}_T]}{dt} = \frac{k_1k_2'[\mathrm{Fe(III)}]^2[\mathbf{1}_T]}{k_{-1}[\mathrm{Fe(II)}] + k_2'[\mathrm{Fe(III)}]} \quad (7)$$

can only be first order in ferricyanide if the rate is independent of the ferrocyanide concentration; any inhibition by ferrocyanide requires the kinetic dependence in ferricyanide to be greater than one. More complex variants of the mechanism of eq 6 are also inconsistent with the experimental data (especially the kinetic dependence on ferricyanide), and thus mechanisms of this type can be eliminated.

Taking into account the separately determined three pK_a's of **1**, *i.e.*, 7.02, 9.24, and 12.20, the pH dependence of k_{obsd} indicates that most of the reaction occurs between the trianion of **1** and ferricyanide at pH's above 10. However, below pH 10 the reaction occurs more rapidly than predicted on that basis; the dianion must also be able to react with ferricyanide but at a slower rate. The observed pH effects over the entire pH range studied can be explained quantitatively[6] by an elaboration of the mechanism of eq 2 involving the two forms of **1** reacting with ferricyanide and the dianion of X reacting to give Y. As discussed earlier, the large ionic strength and cation effects are consistent with two highly charged negative ions coming together in the initial oxidation step.

Both X and Y of eq 2 must be radicals at the same oxidation level. The only reasonable explanation which would allow the conversion of X into Y to be partially rate determining is that a σ bond is formed (or broken) in the process; simple electron transfers within the extended π system of a radical from **1** would be too rapid to be kinetically significant. Considering the bonds which must be formed and broken in converting **1** into **2** the most likely step involved in the conversion of X into Y is that shown in the complete mechanism given in Scheme I. Some resonance forms of X and Y are given in Scheme I to indicate that they should be relatively stable radicals and thus are reasonable intermediates.

Scheme I



Thus, the overall conversion of **1** into **2** occurs by a radical aromatic substitution mechanism. The present work is the first documented example of such a mechanism in an oxidative coupling reaction. It should not be concluded that all oxidative couplings proceed by this mechanism. The particular system studied here may be somewhat unique because such a stable radical (Y) results when the σ bond is formed. However, the present work does illustrate the fact that overall oxidative coupling can be achieved by a mechanism other than the homolytic coupling of two free radicals. It is not known whether this type of mechanism is involved in biological oxidative couplings because no enzyme specific for a particular coupling in a biosynthetic pathway has ever been isolated and characterized. Until this situation is rectified several different types of mechanisms including that found here seem like reasonable possibilities for the biological reactions.[3]