

Oxidation of Iron(II) Porphyrins by Alkyl Halides

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Abstract: Iron(II) deuteroporphyrin IX is rapidly oxidized by alkyl halides in *N*-methylpyrrolidone-acetic acid at room temperature. Three kinds of transformations are observed: (i) coupling of benzylic, allylic, and propargylic halides; (ii) elimination of vicinal dihalides; (iii) hydrogenolysis to alkane. The reactivity, stoichiometry, stereochemistry, and kinetics of the reactions are consistent with an initial scission of the carbon-halogen bond to yield a radical and an iron(III) porphyrin. Iron(II) porphyrins can reduce alkyl radicals, but an alternate route from alkyl halide to alkane does occur with some halides.

Iron porphyrins in hemoproteins reflect a remarkable variety¹ of chemical reactivity that is not attained by these entities in solution.² An understanding of the forces that modulate the chemistry of such highly ordered organometallic active sites is important to both hemoprotein function and homogeneous catalysis. Our efforts have initially focused upon a mapping of the electron transfer capacities of hemes. The bond types capable of oxidizing iron(II) to iron(III) porphyrins have been noted.³ Thus, quinones, nitro and nitroso compounds, and alkyl halides along with oxygen and peroxides rapidly oxidize hemes to hemins at room temperature in dilute homogeneous solution. The swift oxidation by organic halides has been suggested as a possible means of intoxication of organisms by haloorganic biocides⁴ and a striking series of parallel biodehalogenations is presented in the Discussion.

The present work outlines the general character of the oxidation of hemes by alkyl halides. The results constitute a significant part of the basis of a recent theory of hemoprotein reactivity^{5a} and the accompanying paper^{5b} verifies the predicted reactivity for hemoproteins of defined geometry and axial bond type toward selected organic halides.

Results

Heme Solutions. We have employed a variety of reagents for the generation of Fe(II) porphyrins in solution. The most reliable and convenient system, that allows adequate solubility for product studies, is the reduction of the chloroiron(III) complex by iron powder in *N*-methylpyrrolidone-acetic acid. The preparation from chlorohemins under argon (eq 1) is detailed in



the Experimental Section. It is an adaptation of the procedure originally described by Corwin and co-workers.⁶ The visible spectrum of iron(II) deuteroporphyrin IX is sketched in Figure 1. The solutions

(1) R. Lemberg and J. W. Legge, "Hematin Compounds and Bile Pigments," Interscience, New York, N. Y., 1949.

(2) J. E. Falk, "Porphyrins and Metalloporphyrins," Elsevier, New York, N. Y., 1964.

(3) R. S. Wade, R. Havlin, and C. E. Castro, *J. Amer. Chem. Soc.*, **91**, 7530 (1969).

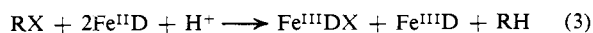
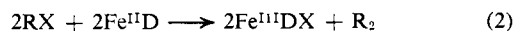
(4) C. E. Castro, *J. Amer. Chem. Soc.*, **86**, 2310 (1964); C. E. Castro and I. J. Thomason in "Plant Parasitic Nematodes," Vol. II, B. M. Zuckerman, W. F. Mai, and R. A. Rohde, Ed., Academic Press, New York, N. Y., 1971, Chapter 26.

(5) (a) C. E. Castro, *J. Theoret. Biol.*, **33**, 475 (1971); (b) R. S. Wade and C. E. Castro, *J. Amer. Chem. Soc.*, **95**, 231 (1973).

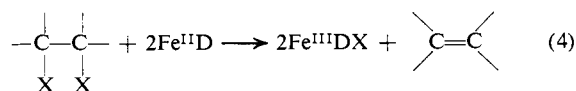
(6) D. G. Whitten, E. W. Baker, and A. H. Corwin, *J. Org. Chem.*, **28**, 2363 (1963).

are very difficult to transfer without some oxidation and consequently fresh solutions were prepared *in situ* for both product and kinetic work. Excess iron was removed magnetically from reactions before the addition of halide substrate.

The Heme Reductions. Reactions were carried out at room temperature in 1:1 *N*-methylpyrrolidone-acetic acid. Initial concentrations were in the range of 5×10^{-3} to 1×10^{-2} M iron(II) deuteroporphyrin (Fe^{IID}) and 2.5×10^{-3} to 0.1 M halide. Three general transformations are observed: coupling of benzylic, allylic, and propargylic halides (eq 2), hydrogenolysis (eq 3),



and elimination of vicinal halides (eq 4). The sub-



strates and products are given in Table I. The halides are listed qualitatively in a decreasing order of reactivity toward Fe^{IID}. All reactions were run at least three times and the yields reflect the adequacy of the work-up and product analyses. Except for the allyl halides, α -phenylethyl chloride, and methylene bromide all reactions presented are quantitative within experimental error. In addition to the substrates listed in the table we have scanned (*cf.* Experimental Section) a wide variety of carbon-halogen bond types. The material balance in some of these systems is incomplete and we shall report upon them later. In general, however, halides bearing no activating α substituents are slow to react, and aromatic and vinylic halides are inert. Thus, a qualitative reactivity sequence is benzhydryl > α -phenylethyl > allyl > alkyl, and for a given structure RI > RBr > RCl. For the allylic halides the relative rates of allyl iodide:allyl bromide:allyl chloride are in the order 130,000:200:1. Both vicinal and geminal halides are quite reactive and the general activating influence of α -halogen, nitrile, and carbonyl moieties is apparent. The even distribution of *meso*- and *d,l*-2,3-diphenylbutane obtained from the α -phenylethyl halides illustrates the stereochemistry of the coupling process.

Because of the lability of axial halo ligands of iron in this milieu, the product iron(III) spectrum corresponds to that of the initial iron(III) solvate spectrum before reduction with iron powder (Figure 1). The spectrum is slightly sharpened by saturation with potassium

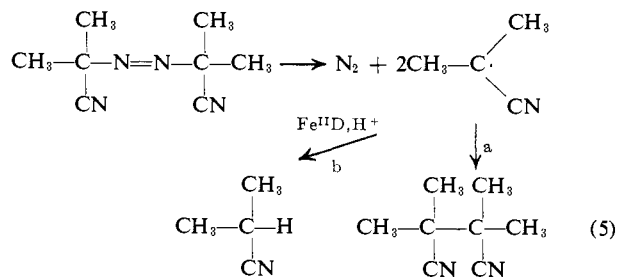
Table I. Product and Yields of the Reduction of Organic Halides by Iron(II) Deuteroporphyrin IX

Substrate	Product	Yield, ^a %	Rel reactivity ^b
Bromomalononitrile	Malononitrile	98	Instantaneous, complete in <1 min
Benzhydryl chloride	<i>sym</i> -Tetraphenylethane	97	
α -Bromoisobutyronitrile	Isobutyronitrile	101	
Hexachloroethane	Tetrachloroethylene	95	
Allyl iodide	Biallyl	26	
	Cyclohexene	35	Rapid, complete in 2-30 min
Propargyl bromide	1,5-Hexadiyne	97	
Phenacyl bromide	Acetophenone	98	
2,2-Bis(<i>p</i> -chlorophenyl)- 1,1,1-trichloroethane (DDT)	DDD ^d	85	
Allyl bromide	Biallyl	25	
	Cyclohexene	30	
α -Phenylethyl bromide	1:1 <i>meso</i> - and <i>d,l</i> -2,3-diphenylbutane	70	
Allyl chloride	Biallyl	25	Slow, complete in 5 hr to 3 days
	Cyclohexene	30	
α -Phenylethyl chloride	1:1 <i>meso</i> - and <i>d,l</i> -2,3-diphenylbutane	38	
Methylene dibromide	Methane	3	
	Ethylene	13	
Ethylene dibromide	Ethylene	95 ^c	

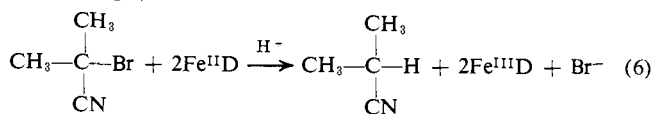
^a Calculated based upon the stoichiometry in eq 2-4 assuming complete conversion. ^b Initial concentration of Fe(II)D 8×10^{-3} and organic halide 4×10^{-3} to 8×10^{-2} . ^c Calculated at 60% conversion. ^d DDD = 2,2-(*p*-chlorophenyl)-1,1-dichloroethane.

bromide or chloride, but the change is less than 5% at any wavelength. Thus, we cannot discern the nature of the axial ligands on iron produced in these reactions at this time, but it may be possible with more precise instrumentation. The mass spectrum of iron(III) deuteroporphyrin isolated from reaction solutions (parent at 564) is identical with authentic hemin chloride. The parent ion containing the axial ligand is not detectable. However, with more volatile porphyrins in less polar media, ions corresponding to the solvate predominate the parent ion region. Thus, mass spectra of low-temperature stripped solutions of chloro iron(III) octaethylporphyrin in trichlorobenzene-acetic acid show a preponderance of the iron(III) acetate. Hence we believe that any porphyrin Fe(III)-halide bond produced in the better coordinating solvent employed in this study would be rapidly substituted.

In an effort to discern whether radicals could be intermediates in the hydrogenolysis process (eq 3), bisazoisobutyronitrile⁷ (4×10^{-3} M) was decomposed in the presence of Fe(II)D (8×10^{-3} M) at 90° for 2 hr. In addition to some recombination (30%) a good yield of isobutyronitrile (41%) was obtained. Runs in the ab-



sence of metalloporphyrin yielded only coupling product. Reaction 5b is to be compared with the quantitative reduction of the corresponding α -bromoisobutyronitrile (eq 6).



(7) The azo linkage does not oxidize hemes.⁸

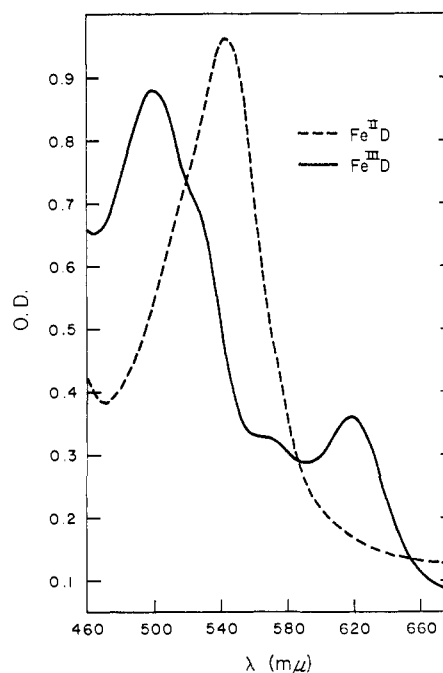


Figure 1. Visible spectra of iron(II) and iron(III) deuteroporphyrin IX, each at 10^{-4} M in 1:1 *N*-methylpyrrolidine-acetic acid.

Kinetics. The rate of appearance of Fe(III) deuteroporphyrin IX was monitored spectrophotometrically by following the increase in absorbance of the Fe(III) band at 620 m μ (Figure 1). Initial concentrations ranged from 1 to 2.5×10^{-4} M Fe(II)D and 10^{-4} to 2.5×10^{-4} M halide. Reaction orders were determined from initial slopes and verified by appropriate plots of the data. Good linearity was obtained. Usually an excess of halide was employed and rate constants were evaluated from pseudo-first- or -second-order plots. With very fast reactions stoichiometric ratios of initial concentrations were convenient. Some typical runs are presented in Figures 2, 3, and 4. The rate constants are given in Table II. While the coupling and elimination reactions (eq 2 and 4) obey clean second-order kinetics, rate = $k_2(\text{Fe}^{\text{II}}\text{Porp})(\text{RX})$. The

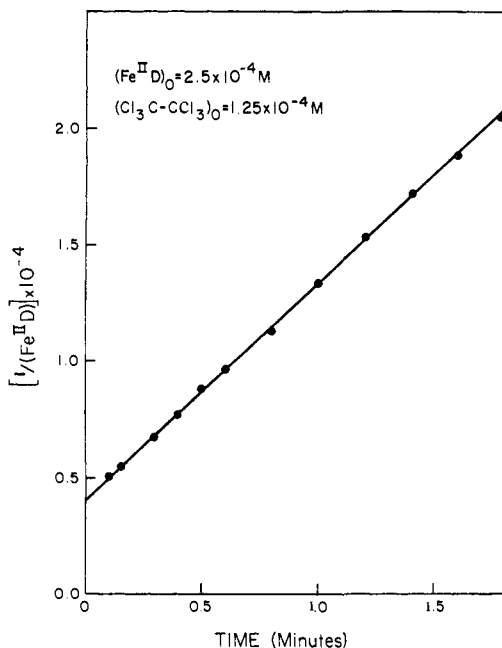


Figure 2. General second-order plot for the oxidation of deuteroheme by hexachloroethane with stoichiometric ratios of reactants.

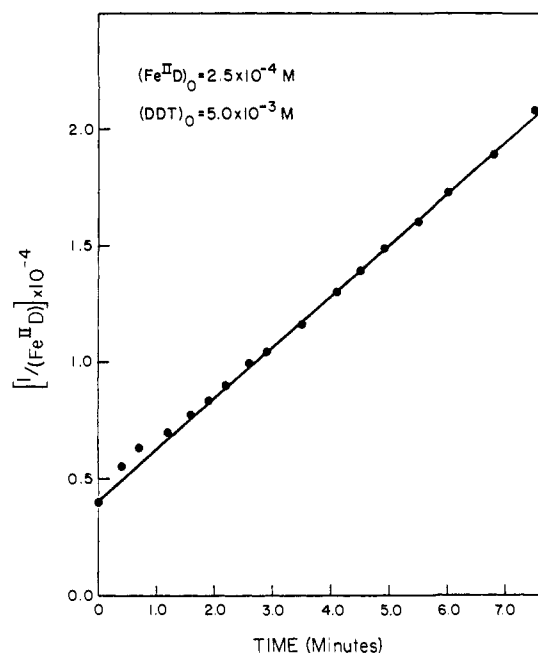


Figure 4. Pseudo-second-order plot for the oxidation of deuteroheme by DDT.

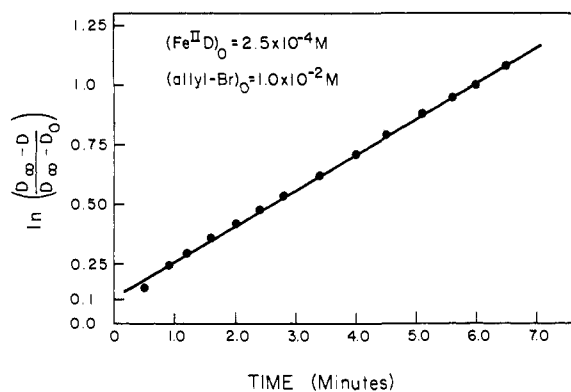


Figure 3. Pseudo-first-order plot for the oxidation of deuteroheme by allyl bromide.

Table II. Rate Constants for the Oxidation of Iron(II) Deuteroporphyrin IX by Organic Halides

Substrate	Stoichiometry	$k_2,^a$ l./ (mol sec)	$k_3,^a$ l. ² / (mol ² sec)
α -Bromoisobutyronitrile	Eq 3	5.9×10^2	
Hexachloroethane	Eq 4	3.0×10^2	
Allyl iodide ^b	Eq 16	1.6×10^3	
Propargyl bromide	Eq 2	1.9	
Phenacyl bromide	Eq 3		1.9×10^4
DDT ^c	Eq 3		8.0×10^3
Allyl bromide	Eq 16	0.25	
Allyl chloride	Eq 16	1.2×10^{-3}	

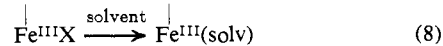
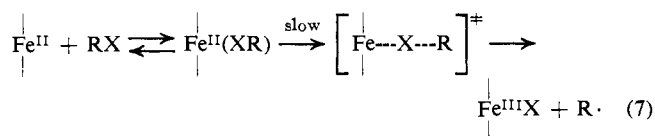
^a Average of three runs, reproducibility $\pm 10\%$. ^b Estimated from initial slopes. ^c An estimate from initial slopes for this reaction in 1:1 isopropyl alcohol-acetic acid was $k_3 \sim 5 \times 10^5$.

hydrogenolysis reaction (eq 3) is either third order or second depending upon the substrate (Table II); rate = $k_3(\text{Fe}^{\text{II}}\text{Porp})^2(\text{RX})$.

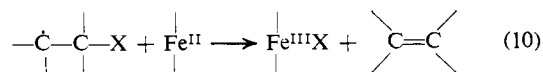
Discussion

Taken together, the stoichiometry reactivity sequence, kinetics, and stereochemistry of the coupling reactions

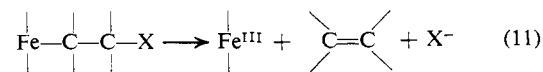
bespeak a mechanism in which a cleavage to radicals is rate determining (eq 7-9). Except for the rapid sol-



volysis of the hemin halide product (eq 8) the reaction is entirely analogous to that observed for the oxidation of Cr(II) by organic halides^{8a-c} and the reactions of Co^{II} dioximato⁹ complexes with these substrates. Indeed, the heightened reactivity of vicinal and geminal halides observed with Fe^{II} porphyrins parallels the enhanced reactivity of these substrates toward chromous sulfate^{8b,c} and other low-valent metal species containing Co(II)¹⁰ and Cr(II).¹¹ The formation of olefin from vicinal halides follows from either a second step analogous to eq 7 but occurring more rapidly because of a stabilization to the transition state imparted by the β -halo radical^{8b} (eq 10) or *via* the intermediacy of a β -



haloalkyl iron intermediate (eq 11).



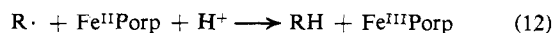
(8) (a) C. E. Castro and W. C. Kray, Jr., *J. Amer. Chem. Soc.*, **85**, 2768 (1963); (b) *ibid.*, **86**, 4603 (1964); (c) *ibid.*, **84**, 4447 (1966).

(9) J. Halpern and P. F. Phelan, *ibid.*, **94**, 1881 (1972); P. W. Schneider, P. F. Phelan, and J. Halpern, *ibid.*, **91**, 77 (1969), and references therein.

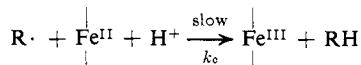
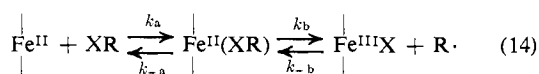
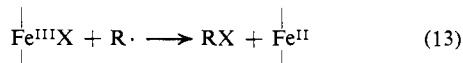
(10) J. Halpern and J. P. Maher, *ibid.*, **87**, 5361 (1965).

(11) J. K. Kochi, D. M. Singleton, and L. J. Andrews, *Tetrahedron*, **24**, 3503 (1968).

The kinetics of the third-order hydrogenolysis processes set them apart from these and other reductions by transition metal species. Thus, although we have demonstrated that the reduction of a radical to an alkane can occur, the general process¹² (eq 12) is fast.



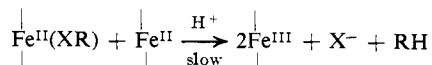
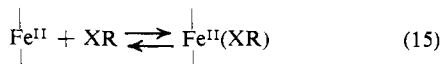
The reaction of 2-cyanopropyl radicals with Fe(II)D competes effectively with their dimerization in this and other milieu. Thus, a mechanism for alkane production consisting of reaction 7 followed by 12 should give only second-order kinetics as it does with α -bromoisobutyronitrile. It has also been established¹² that reaction 7 can be reversible (eq 13) but the sequence (14)



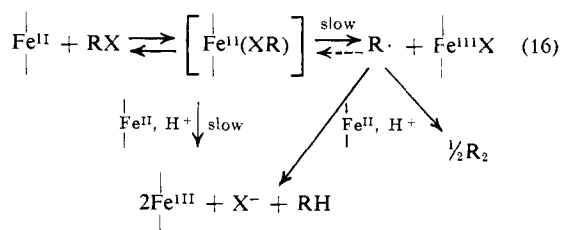
would demand a rate law inverse order in Fe^{III} porphyrin

$$rate = k_c(R\cdot)(Fe^{II}Porp) = \left(\frac{k_c k_b k_a}{k_{-b} k_{-a}}\right) \frac{(RX)(Fe^{II}Porp)^2}{(Fe^{III}Porp)}$$

and this is not observed. The state of aggregation of hemes in our solutions is not known, and porphyrin aggregates can exist.¹³ However, we eliminate the possibility that "heme dimers" are involved in these reactions because: (i) the solutions are dilute; (ii) the coupling, elimination, and some hydrogenolysis reactions clearly proceed through monomeric Fe(II) species; (iii) although the hydrogenolysis kinetics for DDT and phenacyl bromide can be explained by a selective reaction of these particular substrates with dimeric Fe(II) porphyrins, the selectivity itself is most unlikely. Based upon the evidence at hand, the most reasonable mechanism for hydrogenolysis in these cases entails the attack of a second heme upon a heme-alkyl halide complex (eq 15). In summary, all of the reactions in this



work can be described by the following general formulation

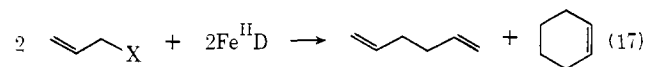


(12) A separate study of the oxidation and reduction of radicals by Fe(II) and Fe(III) porphyrins will be reported; C. Robertson, H. Davis, and C. E. Castro, unpublished results.

(13) R. R. Das, R. F. Pasternack, and R. S. Plane, *J. Amer. Chem. Soc.*, **92**, 3312 (1970), and references therein; R. J. Abraham, P. A. Dubridge, S. H. Jackson, and G. W. Kenner, *Proc. Chem. Soc.*, 134 (1963).

The path and mechanism of the reaction are primarily determined by the ease of the carbon-halogen bond scission. The dotted lines are meant to reflect reactions that do occur, but we have no evidence for their participation in this system.

The production of cyclohexene in addition to biallyl from the allylic halides is unusual (eq 17). Independen-



dent experiments demonstrate that neither iron(II) nor iron(III) deuteroporphyrin will isomerize biallyl to cyclohexene under reaction conditions. The consistent lack of a material balance with these substrates and the unusual nature of the products suggests the generation of a relatively stable iron-alkyl intermediate. However, we have no positive experimental evidence for these entities at this time.

Biodehalogenations. The reductive dehalogenations of many of the substrates examined in this work have been observed *in vivo*. They constitute a striking parallel to the reactions we have observed with hemes. Thus, DDT is converted to DDD in a variety of organisms.^{14,15} Dogs breathe carbon tetrachloride and exhale chloroform.¹⁶ Rabbits convert hexachloroethane to tetrachloroethylene.¹⁷ Similarly, mixed microbial cultures from whole soil transform¹⁸ ethylene dibromide to ethylene and 1,2-dibromo-3-chloropropane to allyl chloride.

Experimental Section

Materials. All available or purchased halide substrates were purified before use and had physical constants that checked the literature. Freshly distilled liquids showed only one peak upon gas chromatography. Solids were recrystallized to sharp melting points. Details have been given elsewhere.⁹ Bromomalononitrile was prepared by the procedure of Ferris and Orgel.¹⁹ The substance had mp 63–64°. *N*-Methylpyrrolidone was freshly distilled, bp 80° (5 mm), and passed through a Fisher A-540 alumina column before use. Deuterohemin IX was prepared *via* the resorcinol melt with protohemin IX obtained from Mann Biochemicals. The procedure is described by Falk.²⁰ Slow crystallization from acetic acid saturated with NaCl and containing some HCl afforded a low yield (35%) of a clean crop of deuterohemin IX. Our experience with this crystallization is that a waiting period of longer than 10–12 hr brings down a product composed of 8% of a monovinyl deuteroporphyrin as determined by mass spectrometry.

Scanning. A typical scanning procedure is outlined. A cuvette containing 2.5 ml of 2.5×10^{-4} M deuterohemin (λ_{max} 620, 526, 500), ~10 mg of iron powder, and a small stirring bar is fitted with a tight serum cap and flushed with argon (*via* hypodermic needles) for 10 min. Stirring is commenced and reduction to the heme (λ_{max} 536) is complete in ~0.5 hr. Excess substrate is injected neat or in solution during the argon sweep. The spectrum is monitored for appearance of the hemin. Other solvents (methanol, ethanol) and other reductants ($H_2/Pd-BaSO_4$) can be employed. The catalytic reduction requires filtering through a Celite pad. A cuvette to cuvette transfer is accomplished under argon through a long hypodermic needle.

Reactions. A specific procedure for the reduction of phenacyl bromide is given to illustrate the general method.

Deuterohemin IX (1.68 g, 2.8×10^{-3} mol) (Fe(III)D-Cl) was

(14) B. J. Kallman and A. K. Andrews, *Science*, **13**, 141, 1050 (1963).

(15) P. J. Bunyan, M. M. J. Page, and A. Taylor, *Nature (London)*, **210**, 5040 (1966).

(16) T. C. Butler, *J. Pharmacol.*, **134**, 311 (1961).

(17) R. T. Williams, "Detoxication Mechanisms," Wiley, New York, N. Y., 1959, p 31.

(18) C. E. Castro and N. O. Belser, *Environ. Sci. Technol.*, **2**, 779 (1968).

(19) J. P. Ferris and L. E. Orgel, *J. Org. Chem.*, **30**, 2365 (1965).

(20) Reference 2, p 79.

Table III. Product Characterization and Quantitation

Product (derivative)	Characterization		Quantitation ^b
	Vpc column ^a	Other	
Malononitrile (Malonamide)	3-ft Porapak P		3-ft Porapak P
<i>sym</i> -Tetraphenylethane	5-ft 3% deg on Porapak P 1% 5 ft × 1/8 in. SE Gum on Chromosorb W	Mmp 212-212.5°	1% 5 ft × 1/8 in. SE Gum Chromosorb W
Isobutyronitrile	6-ft 20% Carbowax on Firebrick	Ir	6-ft 20% Carbowax on Firebrick
Tetrachloroethylene	6-ft DC-710	Ir	1% 5-ft SE Gum 30 on Chromosorb W
Biallyl	6-ft 20% Carbowax on Firebrick		6-ft 20% Carbowax on Firebrick
(1,2,5,6-Tetrabromohexane)	2-ft 2% SF-96 on Chromosorb W		
Cyclohexene	6-ft 20% Carbowax on Firebrick		6-ft 20% Carbowax on Firebrick
(1,2-Dibromocyclohexane)	5-ft 5% SE Gum 30 on Chromosorb W		
1,5-Hexadiyne	6-ft Carbowax AgNO ₃ on Firebrick	Ir	6-ft Porapak P
Acetophenone	6-ft Carbowax AgNO ₃ on Firebrick	Ir	5-ft 5% SE Gum 30 on Chromosorb W
2,2-Bis(<i>p</i> -chlorophenyl)-1,1-dichloroethane	1. 5-ft 1% SE Gum on Chromosorb W, mp 126-127.5°	Mmp 111.5-112.5°	Gravimetric
<i>meso</i> -2,3-Diphenylbutane	1% 5-ft SE Gum on Chromosorb W	Ir	6-ft DC-710
<i>d,l</i> -2,3-Diphenylbutane	1% 5-ft SE Gum on Chromosorb W	Ir	6-ft DC-710
Methane	6-ft Porapak P 4-ft Porapak Q		6-ft Porapak P
Ethylene (Dibromoethane)	4-ft Porapak Q 5-ft 5% deg on Chromosorb W		4-ft Porapak Q

^a On the gas chromatographic columns indicated the noted substance coemerged with an authentic sample at all temperatures. ^b An Aerograph A-600C with flame ionization detector was employed for vpc quantitation.

dissolved in 280 ml of 1:1 HoAc-*N*-methylpyrrolidone in a 500-ml three-necked flask. The flask was equipped with an argon inlet through a 10-ml addition funnel in one neck and an argon outlet to a mercury trap in the second neck. The third neck of the flask was sealed with a drooping T-shaped (inverted U) glass device containing a clean magnetic stirring bar in one of the arms.

After flushing the Fe(III)D-Cl solution with stirring under argon for 1 hr, 0.15 g of washed Fe⁰ powder (acetic acid, ether) was added. The system was sealed, and the Fe(III)D-Cl was left to reduce to deuteroheme (Fe(II)D) under argon.

Within 3-4 hr the reaction solution was the deep-red color characteristic of Fe(II)D. At this time 1.4×10^{-3} mol (0.279 g) of phenacyl bromide dissolved in 1 ml of the solvent mixture was added to the addition funnel under argon. The system was again sealed and allowed to deoxygenate for 1 hr. At this time the stir bar from the reaction mixture, with the remaining iron powder attached, was removed to one arm of the T-shaped device and the clean stir bar from the other arm was returned to the solution. The solution of phenacyl bromide was added all at once. The deep-red Fe(II)D solution began to change color immediately. Within 5 min the solution was the brown-black color characteristic of Fe(III)D-Cl. After 30 min the reaction was opened to the air.

Ether (500 ml) was added, followed by 1250 ml of H₂O. The ether phase and emulsion were saved. The water phase was washed two times with 100 ml each of ether. Approximately 1 mol of KOH pellets was dissolved in 1500 ml of H₂O. This was added to the combined ether-emulsion extracts and a clean separation was obtained. The ether phase was washed two-three times with H₂O, dried over K₂CO₃, and evaporated to near dryness. Analysis of the concentrate by vpc (A90-P) on a 6-ft Carbowax AgNO₃ column at several temperatures and flow rates showed one peak

which coemerged with an authentic sample of acetophenone. This major peak was trapped and an ir spectrum was identical with authentic acetophenone. The reaction product was quantitated directly from the reaction solution by vpc analyses; calcd yield, 98.5%.

Organic Products. Table III lists the organic products and their means of characterization. Most reactions were quantitated by direct flame ionization gas chromatographic analysis. In some cases reaction extracts were worked up in the manner described above. An external standard of authentic product was used for this purpose.

Kinetics. The rate of production of iron(III) porphyrin was monitored at 620 m μ . Kinetics were conducted in the manner described for scanning except that a variety of initial concentrations were employed. Iron(II) concentrations were calculated from the expression

$$\left(\frac{D_{\infty} - D}{D_{\infty} - D_0} \right) (\text{Fe}^{\text{III}})_0' = (\text{Fe}^{\text{II}})$$

wherein $(\text{Fe}^{\text{III}})_0'$ = the initial concentration of Fe^{III}D before reduction with iron powder. This expression implies an apparent extinction coefficient for iron(III) experimentally defined as

$$\frac{D_{\infty} - D_0}{(\text{Fe}^{\text{III}})_0'} = \epsilon_{\text{Fe}^{\text{III}}} = 2080 \pm 80$$

Although the base line for iron(II) was not identical for each cuvette the $D_{\infty} - D_0$ values obeyed Beer's law and were reproducible to within 4%. This is within the error limits of our spectrometer.