cantly different from that of the bath. In thermal reactions such as peroxide decomposition, a certain fraction of the peroxide will thus react at a temperature significantly different from the recorded bath temperature, the possible result being an ill-defined reaction system. From determinations of the temperature in the ampoule as a function of time and the rate constant for decomposition of the peroxide in question as a function of temperature (Table III) we found, for a bath temperature of 95°, that <1.6% of the peroxide decomposed before the reaction temperature reached 94°. This situation was deemed acceptable and reactions were run at 95°. Of course, a temperature low enough such that we need not have been concerned with the possibility of some nonisothermal decomposition could have been used. However, as will be discussed in a subsequent paper, we are also concerned with the mechanism of formation of cyclopropane, and its yield increases with increasing temperature. Since the present work is concerned with other aspects of the chemistry of the same transient intermediate as will be central to forthcoming discussions, we decided to maximize the overlap between the two studies and ran the present reactions under those conditions which were best for the production of cyclopropane but still permitted almost all of the reaction to occur under isothermal conditions.

Table I. Aliquots of a 250-ml solution of 1.1127 g (2.612 mmol) of 4-iodobutyryl peroxide in CCl_4 were placed in ampoules which were degassed and sealed at 0.1 mm and boiling nitrogen temperature. The ampoules were heated in the oil bath at 95.1 ± 0.05° for 15 hr (~12 half-lives) and then stored in a freezer until analyzed.

At the peroxide concentration deemed optimum for minimizing undesired side reactions in the study of iodine scrambling, the solutions were too dilute to be analyzed directly by use of vpc with thermal conductivity detection. Flame ionization detection had sufficient sensitivity to permit direct analysis, but the passage of the halides involved through the detector caused large and erratic changes in sensitivity. The method of vpc analysis, using toluene as an internal standard, was a two-step procedure. Cyclopropane was determined on a 0.5 in. × 10 ft SE-30 (30% on Chromosorb W) column (column temperature 80°, flow rate 60 ml/min). The solution was then concentrated by distillation to ~5% of its original volume and analyzed on a 0.25 in. × 5 ft SE-30 (20% on Chromosorb W) column (injector 220°, detector 260°, column programmed from ambient to 200°, helium flow rate 25 cc/min). Controls run on known mixtures indicated that our analytical procedure gave a recovery of >97% for all components except CCl_3CCl_3 (93%).

Table II. Decomposition of $(ICH_2CH_2CD_2CO_2-)_2$. Ampoules prepared as described earlier were kept at 95.0 ± 0.05° for 12 hr (~10 half-lives). Solvent and low boiling products were removed by distillation on a 60-cm platinum spinning band column and the residue was subjected to a bulb-to-bulb vacuum distillation. The distillate was subjected to preparative vpc on a 0.5-in. 30% SE-30 column and the products with retention times of 1,3-diiodopropane, 1-chloro-3-iodopropane, hexachloroethane, 1,6-diiodohexane, and 3-iodopropyl 4-iodobutyrate were collected and analyzed.

Table II. Treatment of Products with Ph_3SnH. 4-Iodobutyryl-*2,2,2',2'-d*$_4$ peroxide (2.1469 g, 4.992 mmol, 96.3 ± 1.3% deuterium α to the carbonyl group) was dissolved in 500 ml of carbon tetrachloride and the resulting solution divided into fifty 10-ml ampoules which were degassed, sealed, and heated for 15 hr at 95.0 ± 0.05°. Solvent was distilled from the combined solutions on a 60-cm platinum spinning band column. Benzene (250 ml) was added to the 10-ml residue and the resulting solution concentrated to ~2 ml. The residue was distilled under vacuum (ultimately 0.002 mm) into an ampoule at boiling nitrogen temperature containing 4.0 g (11.4 mmol) of triphenyltin hydride. The ampoule was sealed at boiling nitrogen temperature and then warmed to room temperature and shaken vigorously. The reaction started spontaneously, with considerable evolution of heat, and was moderated as needed by cooling under running water. When the evolution of heat ceased, the ampoule was tumbled mechanically overnight. The products of the reaction were subjected to bulb-to-bulb distillation and the distillate, ~2 ml of colorless liquid, was subjected to vpc on the preparative SE-30 column described previously. The products with retention times of 1-chloropropane, hexane, and *n*-propyl butyrate were collected and analyzed.

Decomposition of $(ICD_2CH_2CH_2CO_2-)_2$ in Chloroform. A solution of 1.0592 g (2.462 mmol) of the peroxide in 250 ml of chloroform was divided into 25 10-ml ampoules, which were degassed, sealed, and heated at 95.0 ± 0.05° for 15 hr as described for the similar reaction in CCl_4. The combined products were distilled through a 60-cm platinum spinning band column, with a reflux ratio of $\geqq 20$; each 25-ml fraction was monitored by use of vpc, under conditions such that 2% of the total amount of 1-iodopropane finally isolated could have been detected in any one fraction. When the volume of liquid in the pot had been reduced to ~3 ml, without any 1-iodopropane detected at the head, the pot residue was subjected to preparative vpc on the SE-30 column previously described. Material with the retention times of 1-iodopropane and 1,6-diiodohexane was collected and analyzed.

A Mechanistic Study of the Synthesis and Spectral Properties of *meso*-Tetraarylporphyrins[1]

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Abstract: We have prepared 11 new derivatives of *meso*-tetraphenylporphin which are substituted on the phenyl groups. Kinetic studies of the rate of porphyrin formation and of oxygen consumption lead us to conclude that oxygen oxidation is the rate-determining step under ordinary synthetic conditions. We have also determined the extinction coefficients and the relative fluorescence intensities of these compounds.

In recent years we have been involved in a mechanistic investigation of the Rothemund reaction,[3] which is the only high-yield synthesis known for porphyrins starting from simple precursors. Badger, Jones, and Laslett,[4] who were the first to consider the mechanism, proposed that the reaction proceeded through the formation of an α,γ-dihydroxyporphyrinogen (**1**) chiefly

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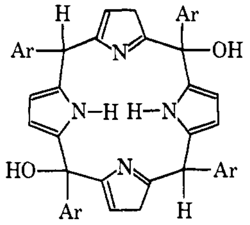
[1] Supported by the National Institutes of Health, General Medical Sciences, Grant No. GM 15019.

[2] National Institutes of Health Fellow, 1970–1971.

[3] (a) P. Rothemund, *J. Amer. Chem. Soc.*, 57, 2010 (1936); (b) P. Rothemund, *ibid.*, 61, 2912 (1939); (c) P. Rothemund and A. R. Menotti, *ibid.*, 63, 267 (1941); (d) P. Rothemund and A. R. Menotti, *ibid.*, 70, 1808 (1948).

[4] G. M. Badger, R. A. Jones, and R. L. Laslett, *Austr. J. Chem.*, 17, 1028 (1964).

on the basis of two observations: a small amount of chlorin always appeared concomitantly with the porphyrin, and, if zinc acetate, which has been used to increase the yield of porphyrin **3c**, is present, zinc dipyrromethene (**2**) can be isolated from the reaction mixture. Adler, *et al.*,[5,6] were able to increase the yield of the reaction from 5 to 40% under acidic, aerobic conditions. The role of atmospheric oxygen in the reaction was studied in some detail and it was established that oxygen is the sole oxidant. The effects of acidity, solvent, and concentration on both the rate and yield were studied. A general reaction scheme, which included possible intermediates and which accounted for most of the characteristics of the reaction, was devised. The intermediacy of the phlorin and the production of chlorin by reduction of the porphyrin were suggested.



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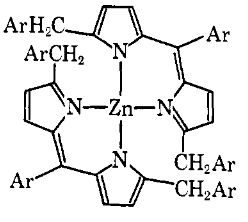

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Dolphin[7] took advantage of the fact that the initial condensation steps are faster and the subsequent oxidation steps are slower in the reaction of 3,4-dimethylpyrrole and benzaldehyde than in the reaction of pyrrole and benzaldehyde; thus, he was able to isolate and study intermediates of the condensation reaction. He suggested that the main reaction pathway involved the formation of porphyrinogen which is oxidized through the porphomethene and the porphodimethene to the porphyrin. He clearly proved that the chlorin can be derived from the porphyrin under the acidic, aerobic reaction conditions. Treibs[8] synthesized a number of porphyrins under acidic, aerobic conditions and postulated two pathways for the reaction, one of which involved the porphyrinogen.

The purpose of the present study is twofold: to gain a better understanding of the reaction mechanism by comparing the rates of the reactions of substituted benzaldehydes with pyrrole, and to deduce the cause of the spectral anomalies which we observed for the highly halogenated phenyl-*meso*-tetraphenylporphins.[9] We have prepared a series of *meso*-tetraphenylporphins in which the various positions of the phenyl groups are substituted. Because of the awkwardness of the correct nomenclature of these compounds, we will use names based on the position of the substituent on the phenyl group. For instance, we refer to tetra(*m*-chlorophenyl)porphin as the *m*-chloro compound and to tetra(2,6-dichlorophenyl)porphin as the di-*o*-chloro compound.

Experimental Section

A. Synthesis. Materials. Substituted benzaldehydes, pyrrole, and propionic acid were all obtained from Aldrich Chemical Co. and were used for the syntheses as supplied. For kinetic determinations, the pyrrole was chromatographed on neutral alumina immediately before use.

General Procedure. Numbers were assigned to the compounds as follows: *o*-fluoro, **3**; *o*-chloro, **4**; *o*-bromo, **5**; *m*-chloro, **6**; 2,6-dichloro, **7**; *o*-nitro, **8**; *o*-methyl, **9**; *o*-methoxy, **10**; *p*-chloro, **11**; *p*-fluoro, **12**; *p*-bromo, **13**. The procedure of Adler, *et al.*,[10] was used for the synthesis of compounds **3–6**, **9**, and **11–13**. The gravimetric yields for these compounds were: **3**, 10.2%; **4**, 3.26%; **5**, 2.1%; **6**, 18.2%; **9**, 14.9%; **11**, 23.3%; **12**, 5.2%; and **13**, 12.0%. The tetra(*o*-methylphenyl)porphin (**9**) reaction mixture was refrigerated for a week before it was filtered.

Anal. Calcd for **3** ($C_{44}H_{26}N_4F_4$): C, 76.958; H, 3.816; N, 8.158; F, 11.064. Found: C, 76.99; H, 3.79; N, 8.11; F, 11.07. Calcd for **5** ($C_{44}H_{26}N_4Br_4$): C, 56.804; H, 2.816; N, 6.022; Br, 34.356. Found: C, 56.85, H, 2.86; N, 5.98; Br, 34.49. Calcd for **6** ($C_{44}H_{26}N_4Cl_4$): C, 70.227; H, 3.482; N, 7.445; Cl, 18.844. Found: C, 70.36; H, 3.42; N, 7.44; Cl, 18.98. Calcd for **9** ($C_{48}H_{38}N_4$): C, 85.938; H, 5.709; N, 8.351. Found: C, 85.94; H, 5.71; N, 8.32. Calcd for **12**, same as **3**. Found: C, 76.91; H, 3.78; N, 8.18; F, 11.09. Calcd for **13**, same as **5**. Found: C, 56.83; H, 2.83; N, 5.98; Br, 34.56.

Since *o*-bromobenzaldehyde undergoes a slow chemical change on standing we employed the Varian HA-100D nmr spectrometer to obtain a high-resolution nmr analysis on **5** to ensure that the product had the expected structure. We found the following δ values: 7.9 (m with three prominent peaks), 8.2 (m with two prominent peaks), 8.4 (m), and 8.85 (t). The relative areas under the peaks are 2:1:1:2, respectively. These are the results one could expect for **5**.[11] The protons at positions 4 and 5 of the 1-bromophenyl substituent would be virtually indistinguishable. Protons at positions 3 and 6 are in different environments and should show different resonance positions as is observed.

The most effective technique for purification of these compounds was found to be chromatography of concentrated $CHCl_3$ solutions on dry alumina (Camag, neutral, or basic) as described by Finarelli.[12] Dry alumina was packed in a column 2.5 cm in diameter to a height of about 30 cm, and a concentrated solution of porphyrin was layered onto the column and eluted with $CHCl_3$. Fractions with the same visible spectra were combined, concentrated, and rechromatographed. Fractions from the second chromatography were combined and concentrated and the porphyrins crystallized by addition of methanol. In most cases, the amount of pure product obtained was greater than 80% of the crude product.

Tetra(*o*-nitrophenyl)porphin (8). A solution of 2.27 g (0.015 mol) of *o*-nitrobenzaldehyde in 200 ml of propionic acid was brought to reflux. An equimolar amount (1.1 ml) of pyrrole was added, and refluxing was continued for 25 min. The solution was allowed to stand at room temperature overnight and then filtered. The black solid which was obtained was dissolved in $CHCl_3$ and extracted with four 50-ml portions of concentrated HCl. The HCl extracts were combined and neutralized with K_2CO_3; the neutral solution was extracted with four 50-ml portions of $CHCl_3$. The $CHCl_3$ extracts were combined, washed with water, dried briefly over $CaCl_2$, and concentrated. The porphyrin was precipitated by adding ethanol to the $CHCl_3$ solution. The solid was redissolved in pyridine, and the pyridine solution was applied to a column of dry neutral alumina. The product was eluted with $CHCl_3$–5% pyridine. Evaporation of the solvent afforded 0.286 g (5.1%) of fine purple crystals of tetra(*o*-nitrophenyl)porphin. *Anal.* Calcd for $C_{44}H_{26}N_8O_8$: C, 66.49; H, 3.30; N, 14.10. Found: C, 66.37; H, 3.41; N, 14.00.

Tetra(2,6-dichlorophenyl)porphin (7). A solution of 5.25 g (0.03 mol) of 2,6-dichlorobenzaldehyde in 200 ml of benzene and 15 ml of glacial acetic acid was brought to reflux. A solution of 2.2 ml (0.03 mol) of pyrrole in 15 ml of benzene was added to the stirred, refluxing aldehyde solution over a period of 2 hr. Refluxing was continued for an additional hour. The solution was allowed to cool to room temperature. The acid was neutralized with Na_2CO_3. The benzene layer was washed with water, dried over $CaCl_2$, and

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(5) A. D. Adler, F. R. Longo, and W. Shergalis, *J. Amer. Chem. Soc.*, **86**, 3145 (1964).

(6) A. D. Adler, L. Sklar, F. R. Longo, J. D. Finarelli, and M. G. Finarelli, *J. Heterocycl. Chem.*, **5**, 669 (1968).

(7) D. Dolphin, *ibid.*, **7**, 275 (1970).

(8) A. Treibs and N. Häberle, *Justus Liebigs Ann. Chem.*, **718**, 183 (1968).

(9) F. R. Longo, M. G. Finarelli, and J. B. Kim, *J. Heterocycl. Chem.*, **6**, 927 (1969).

(10) A. D. Adler, F. R. Longo, J. D. Finarelli, J. Goldmacher, J. Assour, and L. Korsakoff, *J. Org. Chem.*, **32**, 476 (1967).

(11) R. J. Abraham, A. H. Jackson, G. W. Kenner, and D. Warburton, *J. Chem. Soc.*, 853 (1963).

(12) J. D. Finarelli, Ph.D. Thesis, Drexel University, 1970.

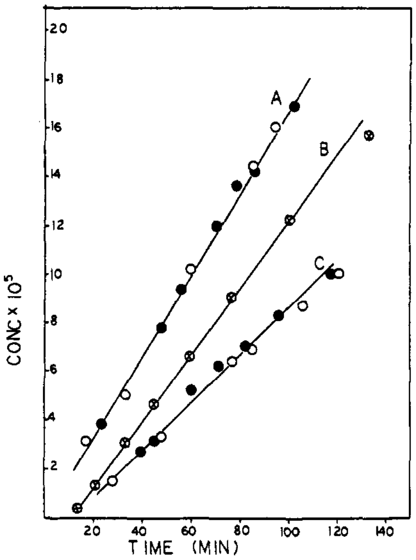


Figure 1. The variation of the concentration of TPP *vs.* time at 90°. A is a plot of the data from two experiments on the *p*-chloro compound; B is a plot of the data from a single experiment on TPP; C is a plot of the data from two experiments on the *p*-methyl compound.

concentrated. The concentrated solution was chromatographed on dry neutral alumina with benzene as eluent. The porphyrin came off the column in the first band, which appeared yellow on the column. It was followed by at least five other bands, none of which have been identified. Fractions containing porphyrin were combined and the solvent evaporated. The solid was dissolved in $CHCl_3$ and chromatographed on dry neutral alumina. Reddish-purple tetra(2,6-dichlorophenyl)porphin, 25 mg (0.7%), was obtained by addition of methanol to the concentrated eluate. *Anal.* Calcd for $C_{44}H_{22}N_4Cl_8$: C, 59.359; H, 2.490; N, 6.292; Cl, 31.856. Found: C, 59.38; H, 2.44; N, 6.33; Cl, 31.59.

Tetra(*o*-methoxyphenyl)porphin (10). A solution of 0.681 g (0.005 mol) of *o*-methoxybenzaldehyde in 50 ml of propionic acid was brought to reflux and 0.35 ml (0.005 mol) of pyrrole was added. The mixture was refluxed for 5 hr and then allowed to stand at room temperature overnight. The solid which crystallized was filtered out, dissolved in $CHCl_3$, and chromatographed twice on neutral alumina with $CHCl_3$-2% methanol as eluent. Tetra(*o*-methoxyphenyl)porphin, 0.0864 g (9.84%), was obtained as shiny purple platelets by addition of ether to the concentrated $CHCl_3$-methanol solution. *Anal.* Calcd: C, 78.45; H, 5.212; N, 7.624. Found: C, 78.41; H, 5.26; N, 7.630.

B. Solution Kinetics. Solutions of 0.025 mol of each of the substituted benzaldehydes in 250 ml of propionic acid in an open round-bottomed flask were brought to temperature equilibrium in an oil bath which was maintained at either 90 ± 0.2° or 125 ± 0.2°. An equimolar amount of freshly chromatographed pyrrole was added to each reaction. Solutions were stirred magnetically and aliquots were withdrawn at timed intervals and diluted volumetrically in benzene. Appearance of porphyrin was monitored by observing the absorbance of the Soret band (~420 nm) for each compound. Absorbances were measured on either a Bausch and Lomb Model 505 spectrophotometer or a Perkin-Elmer Model 202 spectrophotometer.

C. Oxygen Manometric Studies. The manometric oxygen consumption rate studies were carried out in an air-thermostated vacuum system. A benzaldehyde (or *o*-chlorobenzaldehyde) solution in propionic acid of the desired concentration and volume was added to a reaction vessel which was part of the vacuum system. The desired amount of pyrrole was sealed in a fragile Pyrex ampoule and placed under a magnetic hammer beneath the solution. The partial pressure of oxygen was adjusted and the system was allowed to come to temperature equilibrium. The ampoule was broken under the magnetically stirred reaction solution. A Worden quartz fiber gauge (Model PDHV; ±0.25 Torr) was used to measure the pressure at timed intervals. The air oven was controlled to ±0.5°, while the reaction vessel within the oven, because it was immersed in a thermostated oil bath, was controlled to ±0.1°. The air temperature was kept at about 1° above the oil temperature to eliminate distillation throughout the vacuum system. The partial pressure of oxygen was calculated by subtracting the vapor pressure of propionic acid from the total pressure. The reaction solution was assumed to obey Raoult's law.

These studies were carried out at two temperatures, 52.0 and 90.0°, at a series of initial partial pressures of oxygen (200–400 Torr) and at two different interfacial areas. In most cases, the initial concentrations of pyrrole and benzaldehyde were 0.02 *M* each.

D. Spectral Properties. The extinction coefficients of the new porphyrins were determined in spectral grade benzene using the Cary 14 recording spectrophotometer. Fluorescence studies were carried out on solutions in fluorescence grade benzene (Harleco) using the Aminco-Bowman spectrophotofluorometer.

Results and Discussion

1. Synthesis. Except for the 2,6-dichloro compound, all the compounds were synthesized in refluxing propionic acid. In the *o*-halo series, the yield of porphyrin decreased as the bulk of the substituent increased. The *o*-nitro compound was difficult to separate from the large amount of black solid which also formed; this compound was not very soluble in benzene or chloroform. Except for the *o*-methoxy **10**, *o*-chloro **4**, and *p*-chloro **11** compounds[4,13] all the tetraarylporphins reported are new compounds.

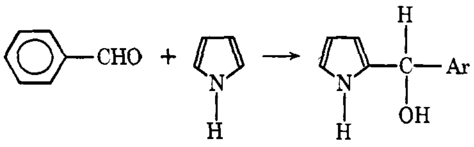
2. Mechanistic Studies. The reactions of the substituted benzaldehydes with pyrrole have the general characteristics of the reaction of unsubstituted benzaldehyde and pyrrole.[5–7] There is an initial production of an "intermediate" with an absorption maximum at 480 nm. Also, the substituted benzaldehydes give pseudo-zero-order kinetics for the major portion of the time that porphyrin is being produced (see Figure 1). The zero-order rate constants for porphyrin formation were determined by fitting the concentration–time data to a straight line by the method of least squares. The rate constants for the reactions at 90 and 125° and the activation parameters are presented in Table I. The activation parameters are similar to those which were previously obtained for the reaction between pyrrole and unsubstituted benzaldehyde.[5,6] We presume that the mechanism for the formation of porphyrins from substituted benzaldehydes must be very much like the mechanism for the benzaldehyde reaction because of all these similarities.

Table I. Kinetics of Formation of Tetraarylporphins in Propionic Acid

Compd	$k_{90°}$, mol/(l. min)	$k_{125°}$, mol/(l. min)	$\Delta E^{\ddagger}$, kcal	$\Delta H^{\ddagger}$, kcal	$\Delta S^{\ddagger}$, eu
TPP	1.40×10^{-6}	0.78×10^{-5}	14	13	−47
p-Nitro	7.85	2.70	10	9.5	−56
p-Bromo	1.78	1.10	14	13	−48
p-Chloro	1.45	0.740	13	12	−52
p-Fluoro	1.38	0.670	13	12	−53
p-Methyl	0.90	0.630	16	15	−53
o-Nitro	26.3×10^{-7}	15.3×10^{-6}	14	13	−47
o-Chloro	31.9	14.8	16	15	−43
o-Fluoro	49.5	20.0	12	11	−52
o-Methyl	6.85	1.97	9.1	8.3	−64
m-Chloro	27.5	7.03	7.3	6.6	−66

We have interpreted the results of our present study in terms of four important chemical steps. These include (a) an addition step to produce a carbinol **14**

(13) D. W. Thomas and A. E. Martell, *J. Amer. Chem. Soc.*, **78**, 1335 (1956).



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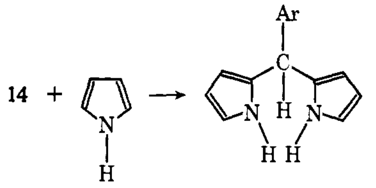
(b) a condensation, or chain-building step involving the carbinol, and another molecule of pyrrole



(we presume that the chain continues to grow by condensation reactions like the one above); (c) the closure of the open-chain tetrapyrrole to form a cyclic tetrapyrrole or porphyrinogen, and (d) oxidation. If an open-chain tetrapyrrole forms, it may be partially oxidized before ring closure, but nevertheless, the last chemical step leading to porphyrin is an oxidation.

Even in the case of ortho-substituted phenyltetraphenylporphins, models show that there is little or no steric hindrance to conversion of the bridge carbons from tetrahedral to trigonal geometry (a process which must occur during oxidation of the porphyrinogen). Therefore, electronic and steric substituent effects will be primarily exerted in the addition, condensation, and cyclization steps.

There is no difference in steric factors when we compare the reactions of benzaldehyde and the para-substituted benzaldehydes. Hence, the observed substituent effects must be the combined electronic effects on the addition–condensation reactions. An electron-withdrawing group in the para position should favor the initial steps by making the carbonyl carbon more susceptible to nucleophilic attack by the α carbon of the pyrrole. The nitro group is electron withdrawing by its inductive effect and also by its resonance effect. Thus, the *p*-nitrobenzaldehyde reaction is the fastest of the para-substituted benzaldehydes studied. In the para halogen series, the inductive and resonance effects are opposed, but the inductive effect should be weak since it must operate through four σ bonds. Hence, the electron-donating resonance effect, which tends to impede the addition reaction, predominates and the rate decreases from bromine through fluorine. The reaction of *p*-methylbenzaldehyde is the slowest of all the para derivatives; we would expect it to be slow because the methyl group is electron donating. The Hammett σ plot for the para-substituted benzaldehydes, Figure 2, is fairly linear and shows that the para substituents have their expected effect on the rates.

Interpretation of the results of our studies on the ortho series is much more difficult. Factors are present which, by different modes of action, both impede and enhance the addition and condensation reactions. Models indicate that there should be a definite steric hindrance to the attack at the carbonyl carbon during the addition, condensation, and ring-closure steps. Models also show that a bulky substituent in the *o*-phenyl positions of the open-chain tetrapyrrylcarbinol should force it into a conformation more favorable to ring closure. Treibs has postulated this conformational effect for both bridge and β-pyrrole substituents.[8] Also, one may no longer dismiss the inductive effect because it operates through only two σ bonds and for the extremely electronegative fluorine it may dominate the rate-retarding resonance effect of the halogen substituents. If this were true we would find $k_{o\text{-F}} > k_{o\text{-Cl}} > k_{o\text{-Br}}$. Table II shows that $k_{o\text{-F}} > k_{o\text{-Cl}}$ but, unfortunately, we could not determine the pseudo-zero-order rate constant for the *o*-bromobenzaldehyde reaction. This particular benzaldehyde decomposes, forming a black material on standing. The freshly purified material (from recrystallization of the bisulfite addition product) reacted faster after standing for a few days; the pseudo-zero-order rate "constants" varied by as much as 50% for the *o*-bromobenzaldehyde reactions and we cannot include this derivative in our general discussion of the reaction. The *o*-nitrobenzaldehyde does not fit our idea of predominance of the inductive effect over the resonance effect for the ortho-substituted benzaldehydes; by this scheme we would expect its reaction to be the fastest. In this case we may be seeing the effect of intramolecular hydrogen bonding, which has been reported for ortho-substituted benzaldehydes.[14] Such interactions should increase the electron density at the carbonyl carbon and thus make it less susceptible to nucleophilic attack. It is also possible that the *o*-nitro group could impede the cyclization of the open-chain tetrapyrrole if the *o*-nitrophenyl group is hydrogen bonded to the somewhat acidic hydrogen of the pyrryl residue, as shown in Figure 3. If this were true, cyclization would be impeded, and the *o*-nitrobenzaldehyde reaction would be slow, as is observed. The methyl group of *o*-methylbenzaldehyde is electron donating, and thus this compound reacts most slowly of the ortho series.

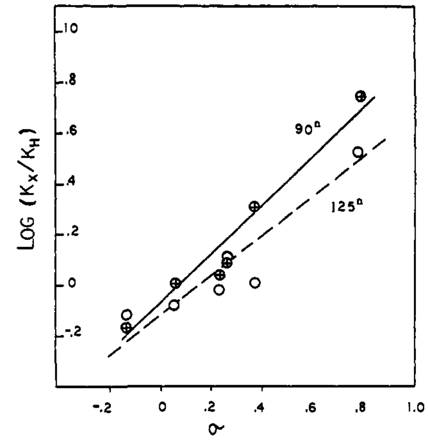


Figure 2. A plot of the log of the ratio of rate constants *vs.* the Hammett σ constants at 90 and 125°.

The sole meta-substituted benzaldehyde which we studied seems to fit our general scheme. There should be no resonance effect in *m*-chlorobenzaldehyde and little steric hindrance to addition and condensation reactions. The small inductive effect exerted by chlorine in the meta position explains why the compound reacts slightly faster than benzaldehyde.

The data from our oxygen consumption rate studies at 52 and 90° show that the initial rates of oxygen con-

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(14) P. J. Krueger and H. W. Thompson, *J. Chem. Soc.*, 22 (1958).

Table II. Extinction Coefficients and Oscillator Strengths of Tetraarylporphins in Benzene Solution[a]

Compound	I-Q_x(0–0)	II·Q_x(0–1)	III-Q_y(0–0)	IV-Q_y(0–1)	4800 Å	Soret
o-Fluoro	6414	5860	5416	5097	4770	4160
	1.2×10^{3}	5.80×10^{3}	4.50×10^{3}	2.06×10^{4}	3.04×10^{3}	3.85×10^{5}
	1.97×10^{-3}	1.59×10^{-2}	1.45×10^{-2}	4.48×10^{-2}	1×10^{-2}	1.27
o-Chloro	6450	5890	5430	5130	4780	4180
	1.1×10^{3}	6.1×10^{3}	3.8×10^{3}	1.64×10^{4}	3.1×10^{3}	3.71×10^{5}
	1.26×10^{-3}	1.48×10^{-2}	1.14×10^{-2}	6.11×10^{-2}	0.9×10^{-2}	
o-Bromo	6431	5878	5419	5127	4792	4185
	0.940×10^{3}	6.32×10^{3}	4.11×10^{3}	2.16×10^{4}	3.09×10^{3}	4.17×10^{5}
	1.29×10^{-3}	1.59×10^{-2}	1.40×10^{-2}	8.04×10^{-2}	1.28×10^{-2}	1.37
2,6-Dichloro[b]	6440	5885	5390	5120	4750	4185
	0.383×10^{3}	5.56×10^{3}	2.35×10^{3}	1.83×10^{4}	2.76×10^{3}	2.99×10^{5}
	7.80×10^{-4}	1.40×10^{-2}	9.20×10^{-3}	7.39×10^{-2}		1.06
Pentachloro[c]	6630	5910	Absent	5150		4220
	3.65×10^{3}	7.02×10^{3}		2.35×10^{4}		3.70×10^{5}
Pentafluoro[c]	6590	5860	Absent	5080		4170
	3.46×10^{3}	5.81×10^{3}		1.91×10^{4}		
o-Nitro	6517	5930	5495	5160	4800	4224
	1.32×10^{3}	4.08×10^{3}	4.37×10^{3}	1.42×10^{4}	3.16×10^{3}	2.29×10^{5}
	2.63×10^{-3}	1.13×10^{-2}	1.46×10^{-2}	5.84×10^{-2}		0.932
m-Chloro	6445	5885	5465	5125	4805	4195
	2.91×10^{3}	5.86×10^{3}	6.89×10^{3}	2.07×10^{4}	3.47×10^{3}	4.52×10^{5}
	5.60×10^{-3}	1.71×10^{-2}	2.10×10^{-2}	7.93×10^{-2}		1.42
o-Methyl	6467	5876	5436	5111	4782	4170
	4.83×10^{3}	5.62×10^{3}	6.05×10^{3}	2.11×10^{4}	3.26×10^{3}	4.80×10^{5}
	5.48×10^{-3}	1.37×10^{-2}	1.47×10^{-2}	7.46×10^{-2}		1.42
p-Fluoro[d]	6472	5890	5490	5120		4200
	2.47×10^{3}	3.49×10^{3}	4.92×10^{3}	1.21×10^{4}		3.37×10^{5}
	4.75×10^{-3}	9.85×10^{-3}	1.53×10^{-2}	4.59×10^{-2}		1.16
p-Chloro	6460	5895	5495	5140	4815	
	3.93×10^{3}	5.63×10^{3}	8.51×10^{3}	2.04×10^{4}	3.59×10^{3}	5.12×10^{5}
	6.20	1.51×10^{-2}	2.51×10^{-2}	7.55×10^{-2}		1.16
p-Bromo	6465	5910	5483	5134		4200
	3.78×10^{3}	5.83×10^{3}	8.90×10^{3}	2.06×10^{4}		5.12×10^{5}
	6.54×10^{-3}	1.59×10^{-2}	2.74×10^{-2}	8.21×10^{-2}		1.46
meso-Tetraphenylporphin[e]	6470	5910	5490	5140	4850	4190
	3.4×10^{3}	5.4×10^{3}	7.7×10^{3}	1.87×10^{4}	3.4×10^{4}	4.7×10^{5}
			Sum for all visible bands = 0.12			1.551[f]

[a] The three numbers listed for each compound for each absorption band are λ_{max}, the wavelength of the maximum absorption, ϵ_{max}, the extinction coefficient at the maximum, and *f*, the oscillator strength, respectively. [b] There is a very pronounced shoulder on the long-wavelength side of band II. [c] See ref 8. [d] This compound is not very soluble in benzene and our ϵ and *f* values may be low. [e] Our measurements are in good agreement with previous reports.[f,g,4] [f] G. D. Dorough and K. T. Shen, *J. Amer. Chem. Soc.*, **72**, 3929 (1950). [g] G. D. Dorough, J. R. Miller, and F. M. Huennekens, *ibid.*, **73**, 4319 (1951).

sumption are approximately linearly dependent on the oxygen pressure at both temperatures. Figure 4 shows a plot of log P_{O_2} *vs.* time using data for an experiment at 90° with an initial oxygen pressure of 226.0 Torr; data from the other experiments give similar results. When we plot log [initial rate] *vs.* log [initial partial pressure of O_2] we obtain a linear plot, which, for the 52° data, has a slope of 0.8 ± 0.2. Considering the uncertainty in the slope we feel that we have established that in the pressure range of our manometric experiments, the reaction is first order with respect to P_{O_2}.

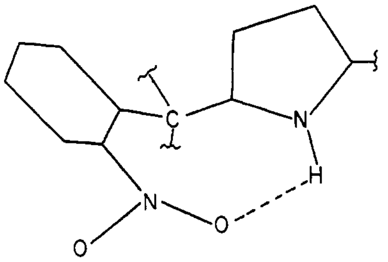

Figure 3. Structure of a possible intermediate in which a nitro group impedes the cyclization by H bonding with the N-hydrogen atom at the pyrryl residue.

We also determined that propionic acid solutions of benzaldehyde alone, or of pyrrole alone, do not consume measurable amounts of O_2 under the conditions of our experiments. The variation of interfacial area from 37.4 to 58.5 cm² has no effect on the rate. Increases in the pyrrole concentration caused slight, nonreproducible, but definite increases in the initial rate

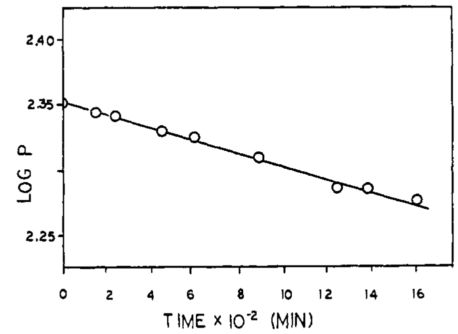

Figure 4. A plot of the log P_{O_2} *vs.* time for the reaction at 90° with $(P_{O_2})_i$ = 226.0 Torr.

of the reaction. A single experiment in a Parr bomb at 20° and 30 ± 2 atm of O_2 gave a yield of 28%. Assuming that, like the reaction under ordinary atmospheric conditions, the reaction at the high pressure is pseudo zero order, we calculate a rate constant of 21.6 $\times 10^{-9}$ mol/(l. sec) and, therefore, the reaction is at least 15.4 times greater initially than that at $^1/_5$ atm (ordinary conditions). This result, aside from its mechanistic implications, has obvious practical significance with respect to the synthesis of porphyrins by the condensation of aldehydes with pyrroles.

The initial rate at 90° is only 30% higher than that at 52°. We feel that this small temperature effect must be due to the difference in the Henry's law constants for O_2 in propionic acid at the two temperatures. In view of this problem, we cannot really calculate the activation parameters for the oxygen consumption studies.

When the reaction is run open to the atmosphere, any particular porphyrin product forms at a constant rate. Presumably, the concentration of dissolved oxygen remains approximately constant. Our observation that the rate of oxygen consumption is independent of the interfacial area suggests that transport of O_2 across the gas–liquid interface is rapid relative to the reaction of dissolved oxygen. Hence, the concentration of dissolved oxygen would be expected to remain fairly constant in reactions open to the atmosphere. The observations that the oxygen consumption rate is linearly dependent on the pressure of oxygen, that the porphyrin appearance rate is independent of benzaldehyde and pyrrole concentration,[5] and that there are substituent effects must mean that an oxygen-oxidation step is the rate-determining step or precedes it. In view of the fact that the last step in the reaction sequence must be an oxidation, it appears that this must be the rate-determining step. The fact that the initial rate of oxygen consumption in the *o*-chlorobenzaldehyde reaction is two times greater than the value for benzaldehyde is consistent with our conclusion; this particular aldehyde produces the corresponding porphyrin twice as fast as benzaldehyde does at 90° (Table I). Our observation that a 150-fold increase in O_2 pressure (from 0.2 to 30 atm) causes a 15-fold increase in the rate suggests that at very high pressure the oxygen-oxidation step is not the rate-controlling step.

We would presume that the rate of porphyrin formation would not be pseudo-zero-order under the conditions of our oxygen consumption rate studies since the oxygen pressure is not constant; but with our technique we could not obtain experimental verification of this point. We found no good way of monitoring the concentration of TPP and measuring P_{O_2}, simultaneously.

3. **Spectral Properties.** Table II presents the results of our absorption studies. It is clear from a study of Table II that when there is an electron-withdrawing substituent in the ortho position the extinction coefficients of the following normal bands are diminished with respect to the unsubstituted *ms*-TPP: I, III, 4800 Å, and Soret. The effect on bands II and IV is negligible. When substitution occurs in other positions, the substituent effect is very small. Thus, we have found the phenomenological cause of the anomaly which we have previously reported.[9]

The theoretical explanation for the anomaly is more difficult. According to the four-orbital model for the porphyrins the basic intensity relationships are determined by the degree of degeneracy of the top filled orbitals $b_1(a_{2u})$ and $b_2(a_{1u})$.[15] When these orbitals are exactly degenerate the Q(0–0) band should have zero intensity. As the degeneracy is lifted the band is intensified. The relative energy of these two orbitals has been determined for different porphyrins; in the free base *meso*-tetraphenylporphin the $b_1(a_{2u})$ orbital is higher in energy. From intensity effects in the *meso*-tetraarylporphyrins it is obvious that electron-withdrawing groups in ortho positions make the orbitals more degenerate, but it is difficult to say which orbital is affected. The electron-withdrawing groups are more electron rich than hydrogen and an inductive effect would raise whichever orbital the group was closer to. Since we see an approach to degeneracy we assume that the electron-withdrawing groups interact more strongly with $b_2(a_{1u})$. Thus, the energy of this orbital may be raised and b_1 and b_2 are more nearly equal in energy. Infrared spectra which show a decrease in the pyrryl C–H stretching frequency[9] support this picture. We guess, therefore, that the aryl groups of our new tetraarylporphyrins are closer to coplanarity than the phenyl groups of TPP. (We are collaborating with Dr. A. Tulinsky of Michigan State University who is studying the crystal and molecular structure of *meso*-tetra(2,6-dichlorophenyl)prophin.)

The fact that the intensity of the 4800-Å band is affected by substituents is very significant. This band has always been considered to be a higher vibronic (0–2) of the Q_y system. But, since substituents show a greater effect on 0–0 transitions, it has been suggested to us that the 4800-Å band may represent a 0–0 transition. This supports the theoretical work of Gouterman who has predicted a Soret-associated 0–0 transition in this region of the spectrum.[16]

Fluorescence is observed in these compounds when they are excited from 4000 to 6500 Å, with the most intense emission occurring when the excitation is near the absorption maxima. The emission data were obtained by using results from the analysis of the linear region of the plot of the log of the concentration *vs.* log of the relative intensity of emission. The fluorescence data were corrected for the nonuniform response of the phototube by using the 4-dimethyl-4′-nitrostilbene emission data of Lippert, *et al.*,[17] as a standard. The Soret excited fluorescence data show two expected results. The fluorescence intensity is diminished as the mass of the phenyl substituent and its nearness to the porphyrin nucleus increase. The normal heavy-atom, spin–orbit coupling effect is observed. For example, at 6500 Å, the emission intensities of the chloro derivatives **4**, **6**, and **11** are 3.7, 39.6, and 64.6%, respectively, of the emission intensity of TPP. The fluorescence of the *o*-bromophenyl derivative in benzene is so highly quenched that the emission cannot be detected

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(15) (a) M. Gouterman, *J. Mol. Spectrosc.*, **6**, 138 (1961); (b) M. Gouterman, G. H. Wagniere, and L. C. Snyder, *ibid.*, 11, 108 (1963); (c) C. Weiss, H. Kobayashi, and M. Gouterman, *ibid.*, **16**, 415 (1965).

(16) M. Gouterman, *ibid.*, in press. We are grateful to Dr. Gouterman for enlightening discussions concerning the significance of our spectral data.

(17) E. Lippert, W. Nägele, I. Seibold-Blankenstein, U. Staiger, and W. Voss, *Z. Anal. Chem.*, 170, 1 (1959).

by the naked eye. The mirror image rule is obeyed by these compounds. The ratio of emission at 7100 Å to that at 6500 Å goes as the ratio of absorption at 5900 Å to that at 6500 Å. Also, the energy spacings between the emission peaks (1400–1500 cm^{-1}) are approximately equal to the energy spacings between the absorption maxima.

We are continuing the investigation of these new materials. We are hopeful that some of these new derivatives, tetra(*o*-bromophenyl)porphin in particular, will exhibit easily detectable phosphorescence as the free bases since the fluorescence is appreciably quenched. As far as we can determine, there has been only one positive report on the observation of phosphorescence of metal-free porphyrinic materials.[18] We have begun a more quantitative study of the emission properties and a broad matrix isolation study of the infrared and electronic spectra of these porphyrins.

(18) K. E. Riekhoff and E. M. Voigt, "Molecular Luminescence," E. C. Lim, Ed., W. A. Benjamin, New York, N. Y., 1969, p 295ff.

Nucleoside *S*-Alkyl Phosphorothioates. VII.[1] A Fragment from the Nonsense Strand of a Modified *S*-Peptide "Gene"

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Abstract: The chemical synthesis of a dodecadeoxyribonucleotide of sequence AAGACAGCATAT is described. Using the *S*-ethyl group for protection of the 5′ terminus of an anchoring dinucleotide, fragment condensation consisted of three sequential dimer additions, followed by a tetramer addition. This sequence constitutes a portion of the nonsense strand of a double-stranded polymer coding for a modified *S*-peptide of pancreatic ribonuclease A.

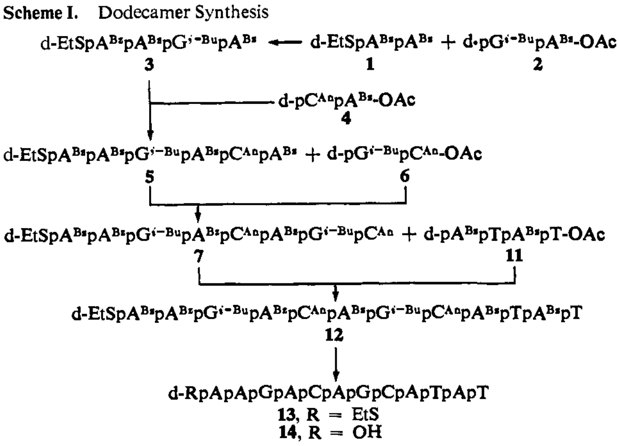
Previous papers from this laboratory[1,2] have described synthetic work on deoxyribonucleotide oligomers constituting fragments of a projected double-stranded array of DNA coding for a derivative of the *S*-peptide from ribonuclease A. The present work is a continuation in part, describing the synthesis of a dodecanucleotide run in the nonsense chain. It will be seen that the oligomer in question (upper line) overlaps, by antiparallel base pairing in the sense of Watson and Crick, a previously described[2] tridecadeoxyribonucleotide

5′--A-A-G-A-C-A-G-C-A-T-A-T--3′
3′--C-G-T-A-T-A-C-C-T-A-A-T-T--5′

(bottom line) which is to form a part of the complementary chain (the sense strand) of the "gene."

Scheme I summarizes the synthetic scheme. Synthesis proceeded in the usual 5′ to 3′ direction, the 5′ terminus being protected by the *S*-ethyl phosphorothioate function throughout. The starting dimer **1**[1] was condensed with **2**[1] to give tetramer **3**, a species which, upon removal of protecting groups, is isomeric to the AAAG previously described.[3] Purification of the blocked tetramer required two successive fractionations with DEAE-cellulose, the final yield being 17.3%.

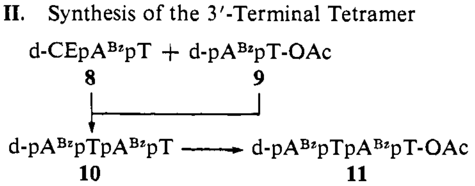
Scheme I. Dodecamer Synthesis



A second condensation with the dimer d-pC$^{\mathrm{An}}$pA$^{\mathrm{Bz}}$-OAc[4] (**4**) gave the hexamer **5** in similar yields as before (17.4%). Further condensation with considerable excess (23-fold) of d-pG$^{i\text{-}\mathrm{Bu}}$pC$^{\mathrm{An}}$[5] (**6**) gave a rather higher yield (48%) of the octamer **5** although the latter was not entirely pure. The material could, however, be used in the next step.

Synthesis of the 3′-terminal tetramer, shown in Scheme II, was carried out in the conventional manner.

Scheme II. Synthesis of the 3′-Terminal Tetramer



Dimers d-CEpA$^{\mathrm{Bz}}$pT (**8**) and d-pA$^{\mathrm{Bz}}$pT-OAc[6] (**9**) gave the desired tetramer **10**, which was acetylated to **11** for protection of the 3′ terminus.

The final condensation employed a 50-fold excess of the incoming (*i.e.*, phosphate donor for the newly

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(1) Paper VI in this series: E. Heimer, M. Ahmad, A. Ramel, and A. L. Nussbaum, *J. Amer. Chem. Soc.*, 94, 1707 (1972).

(2) A. F. Cook, E. P. Heimer, M. J. Holman, D. T. Maichuk, and A. L. Nussbaum, *ibid.*, 94, 1334 (1972).

(3) T. M. Jacob, S. A. Narang, and H. G. Khorana, *ibid.*, 89, 2177 (1967).

(4) A. Kumar and H. G. Khorana, *ibid.*, 91, 2743 (1969). For nomenclature, see earlier references.[1,2]

(5) H. Schaller and H. G. Khorana, *ibid.*, 85, 3841 (1963).

(6) S. A. Narang, S. K. Dheer, and J. J. Michniewicz, *ibid.*, 90, 2702 (1968).