Prostaglandin Endoperoxides. 12. Carboxylate Catalysis and the Effects of Proton Donors on the Decomposition of 2,3-Dioxabicyclo[2.2.1]heptane[1]

Michael G. Zagorski and Robert G. Salomon*

Contribution from the Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106. *Received October 23, 1981*

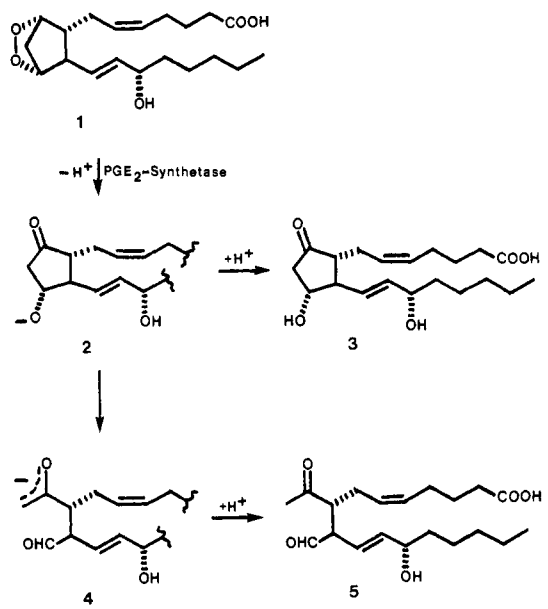
Abstract: Tri- and tetraalkylammonium acetates are potent catalysts for decomposition of the prostaglandin endoperoxide nucleus, 2,3-dioxabicyclo[2.2.1]heptane. The effectiveness of these catalysts is comparable to that of tertiary amines such as 1,4-diazabicyclo[2.2.2]octane and triethylamine. The decomposition yields both fragmentation product, levulinaldehyde, and disproportionation products, 3-hydroxycyclopentanone and cyclopent-2-en-1-one. The fragmentation reaction exhibits a deuterium isotope effect $k_H/k_D = 7.6$. Most significantly, the decomposition can be channeled to favor disproportionation by avoiding fragmentation of an intermediate keto alkoxide by conducting the acetate-catalyzed reactions in the presence of excess acetic acid.

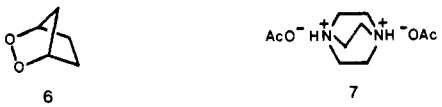
Rate-determining removal of a bridgehead proton from the prostaglandin (PG) endoperoxide PGH_2 (**1**) by a basic center at the active site of PGE_2-synthetase is suggested by a deuterium isotope effect observed during biosynthesis of PGE_2 (**3**).[2] We now report results of a model study suggesting that efficient protonation must also occur during enzymic catalysis to avoid fragmentation of an intermediate keto alkoxide **2** as, for example, in Scheme I. Thus, retro aldol cleavage of alkoxide **2** to enolate **4** is expected to produce the levulinaldehyde derivative **5** for which we suggest the trivial name levuglandin E_2 (LGE_2). In fact, we recently showed that PGH_2 (**1**) readily fragments to LGE_2 and its isomer LGD_2 related by aldol condensation to PGD_2.[3] The present study also provides the first example of catalysis of peroxide decomposition by a carboxylate. As in previous studies with amines as basic catalysts,[4] carboxylate catalyzes both disproportionation and fragmentation of 2,3-dioxabicyclo[2.2.1]heptane, the PG endoperoxide nucleus.

Results

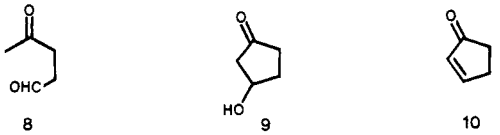
Catalysis by Acetate. Decomposition of 2,3-dioxabicyclo[2.2.1]heptane (**6**) in $CDCl_3$ or C_6D_6 solution is strongly accelerated by catalytic amounts of tetramethylammonium acetate or the trialkylammonium acetate **7** generated from 1,4-diazabicyclo[2.2.2]octane (Dabco) and acetic acid. In the absence of catalyst, only slight decomposition of **6** was observed at 45 °C in $CDCl_3$ solution. After 24 h, 85% of **6** remained unreacted which corresponds to a first-order rate constant $k_{-6} = 3.1 \times 10^{-6}$ s^{-1}. In 1.1 M HOAc in C_6D_6 decomposition was slightly faster, $k_{-6} = 3.5 \times 10^{-6}$ s^{-1}. Levulinaldehyde (**8**) was the major product in $CDCl_3$ or 1.1 M HOAc in C_6D_6 but 4,5-epoxypentanal was the major product in C_6D_6, and no disproportionation products, 3-hydroxycyclopentanone (**9**) or cyclopent-2-en-1-one (**10**), were detected in any of these reactions.

Scheme I





6 7



8 9 10

In the presence of 0.01–0.02 M Me_4NOAc at 45 °C in $CDCl_3$ solution, decomposition of **6** was at least two orders of magnitude faster, and both **8** and **9** were produced. The yields of these products as well as catalytic rate constants for appearance of **8** (k_8) and disppearance of **6** (k_{-6}) are listed in Table I for Me_4NOAc and other catalysts. The rate of appearance of **8** was determined by monitoring the ^1H NMR resonance of this aldehyde at δ 9.38 (in benzene-d_6 solution) or δ 9.77 (in $CDCl_3$ solution). The catalytic rate constant $k_8 = k_{obsd}/[base]$, where k_{obsd} is the observed pseudo-first-order rate constant for appearance of **8**. As expected, essentially the same k_8 was observed for 0.010 and 0.020 M Me_4NOAc. The catalytic rate constant for decomposition of **6** (k_{-6}) was calculated assuming parallel pseudo-first-order reactions generating **8** and **9** and assuming that cyclopent-2-en-1-one (**10**) is produced in a secondary reaction of **9**. Thus, $k_{-6} = k_8(1 + ([9]_\infty + [10]_\infty/[8]_\infty)$.[5] Indeed, control experiments showed that **8** and

(1) For previous papers in this series see footnote 4 and references cited therein.

(2) (a) Wlodawer, P.; Samuelson, B. *J. Biol. Chem.* **1973**, *248*, 5673–8. (b) For recent work see van Dorp, D. A. In "Chemistry, Biochemistry, and Pharmacological Activity of Prostanoids"; Roberts, S. M.; Scheinmann, F., Eds.; Pergamon: New York, 1979; pp 233–242, and references cited therein.

(3) (a) Miller, D. B.; Zagorski, M. G.; Salomon, R. G., unpublished observations. (b) Solvent-induced rearrangement of PGH_2 in aqueous pH 7.9 buffered solution generates levuglandins in 22% yield. Thorough characterization of these new products of prostaglandin endoperoxide chemistry will be reported in due course.

(4) Zagorski, M. G.; Salomon, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 2501–3.

0002-7863/82/1504-3498$01.25/0

Table I. Catalytic Rate Constants

catalyst	[base]^b (M)	product yields (%) 8	9 + 10	8 + 9 + 10	$k_8 \times 10^2$ (M^{-1} s^{-1})	$k_{-6} \times 10^2$ (M^{-1} s^{-1})
Dabco	0.020	82	18	100	4.61	5.62 ± 0.11^c
Et_3N	0.010	82	18	100	4.34	5.29 ± 0.03
Me_4NOAc	0.010	51	49	100	2.96	5.69 ± 0.02
Me_4NOAc	0.020	52	48	100	3.03	5.83 ± 0.02
7	0.020	65	30	95	2.00	2.92 ± 0.04
7 + HOAc						
0.35 equiv^d	0.020	62	33	95	0.89	1.36 ± 0.01
1.00 equiv	0.020	59	37	96	0.66	1.07 ± 0.01
1.95 equiv	0.020	55	41	96	0.56	0.97 ± 0.03
7.30 equiv	0.020	46	49	95	0.27	0.56 ± 0.02

^{a} All reactions conducted at 45 °C in C_6D_6 except with Me_4NOAc as catalyst which was conducted in $CDCl_3$ since Me_4NOAc is not soluble in benzene. ^{b} For the dibasic catalysts Dabco and 7, [base] = 2[Dabco] or 2[7]. ^{c} Error limits reflect precision of [8] determinations but not inaccuracy in [base] which we estimate as less than ±5%. ^{d} Equivalents of excess acetic acid relative to acetate.

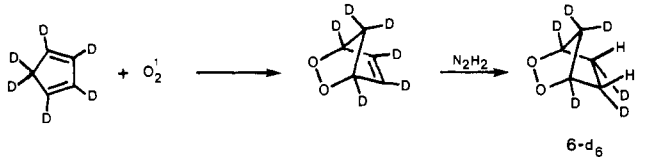
Table II. Effect of Excess Acetic Acid on Product Distribution from **6** with **7** (0.02 N) as a Basic Catalyst

excess CH_3COOH (equiv)	product yields^a (%) 8	9	10	9 + 10	8 + 9 + 10
0.03	62.5	25.9	4.2	30.1	93
0.14	64.2	27.1	4.3	31.4	96
0.87	59.2	29.0	7.9	36.9	96
1.19	59.3	31.7	7.2	38.9	98
1.92	52.4	30.4	10.6	41.1	94
4.44	50.3	30.1	16.2	46.3	97
10.3	44.4	25.6	23.5	49.1	94
20.9	40.0	22.5	31.4	53.9	94

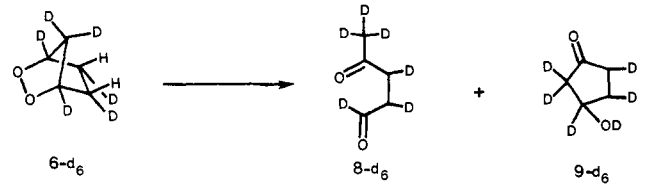
^{a} Determined by ^1H NMR with phenyltrimethylsilane (0.07 M) as internal standard and an initial concentration (0.94 M) of **6**.

10 were stable under the conditions of these experiments, but **9** is slowly and quantitatively converted to **10** by an acid-catalyzed dehydration.

Deuterium Isotope Effect. A hexadeuterated analogue of **6**, in which inter alia the bridgehead protons are replaced by deuterium, was prepared from cyclopentadiene-d_6 by photooxygenation and subsequent reduction with diimide.[6] The rate of appearance of **8**-d_6 from decomposition of **6**-d_6 in the presence



of 0.020 M Me_4NOAc was measured in $CHCl_3$ solution by monitoring the δ 9.73 ^2H NMR resonance of this aldehyde. The yields of products **8**-d_6 (49%) and **9**-d_6 (51%) were essentially the



same as found for the perprotio analogues. But $k_8 = 4.01 \times 10^{-3}$ s^{-1} was substantially smaller for **6**-d_6 than noted above for the perprotio analogue **6**, and $k_H/k_D = 7.6$.

Influence of Acid on Product Distribution. To explore the postulate that efficient protonation might favor disproportionation over fragmentation in the base-catalyzed decomposition of **6**, the influence of acetic acid on the Dabco-catalyzed reaction was examined. It was assumed that the first equivalent of acid would react with Dabco to afford the secondary ammonium acetate **7**. The results (Table II) seemed to support the hypothesis and provided the first indication that acetate might be an efficient basic catalyst for decomposition of the strained bicyclic peroxide **6**. However, since free amine might be present in equilibrium with the ammonium acetate **7**, there remained some uncertainty about the identity of the basic catalyst in this system. Therefore, the experiment was repeated with 0.014 M tetramethylammonium acetate as base. Yields of the products **8**–**10** were measured with acetic acid present in a wide range of concentrations, 0.0–33.4 equiv relative to acetate (Table III).

Table III. Effect of Acetic Acid on Product Distribution from **6** with Me_4NOAc as Catalyst

equiv of CH_3COOH	product yields^a (%) 8	9	10	9 + 10	8 + 9 + 10
0.00	51	49		49	100
1.25	34	57	2.0	59	93
1.43	38	47	7.1	54	92
2.36	39	54	5.9	60	99
4.27	29	49	19	68	97
13.1	25	49	22	71	96
27.5	21	49	30	79	100
33.4	19	62	17	79	98

^{a} Determined by ^1H NMR with phenyltrimethylsilane (0.07 M) as internal standard, Me_4NOAc (0.014 M) as catalyst, and an initial concentration (1.05 M) of **6**.

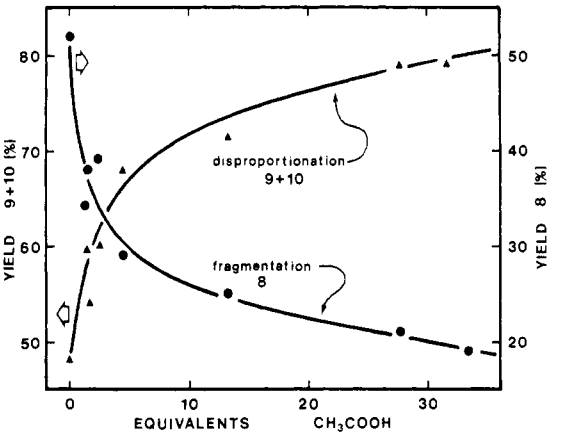
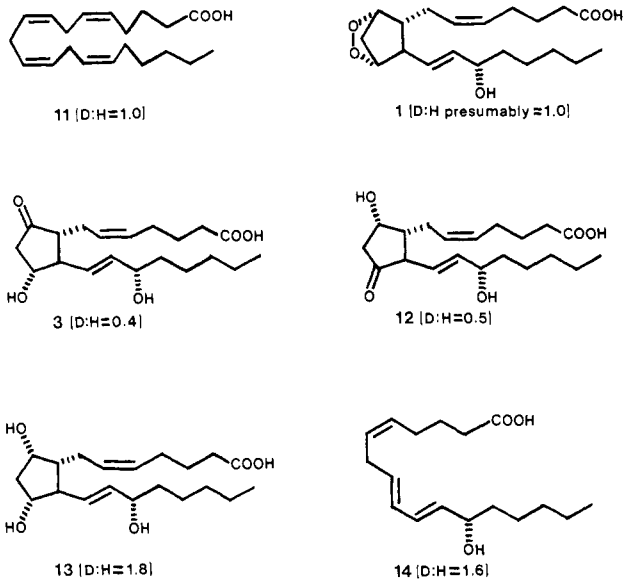


Figure 1. Correlation of disproportionation (▲) and fragmentation (●) yields with equivalents of acetic acid added to tetramethylammonium acetate (0.014 M) as catalyst.

Decomposition of **6** in the presence of both acetate and acetic acid generated cyclopent-2-en-1-one (**10**) in amounts which increased with acid concentration (Tables II and III). The enone **10** is formed by acid-catalyzed dehydration of **9** (see Scheme II below). A continual decrease in the yield of **9** and a corresponding increase in the yield of **10** is observed if the reaction product

(5) Gilliom, R. D. "Introduction to Physical Organic Chemistry"; Addison-Wesley: Reading, Mass., 1970; p 97.
(6) (a) Coughlin, D. J.; Salomon, R. G. *J. Am. Chem. Soc.* **1977**, *99*, 655. (b) Coughlin, D. J.; Brown, R. S.; Salomon, R. G. *Ibid.* **1979**, *101*, 1533–9. (c) Adam, W.; Eggelte, H. J. *J. Org. Chem.* **1977**, *42*, 3987.

Chart I



mixture is kept at 45 °C after completion of the decomposition of **1**. Thus, the combined yield of **9** and **10** equals the yield of disproportionation. The effect of acetic acid concentration on the relative yield of disproportionation and fragmentation products with Me_4NOAc as basic catalyst is presented graphically in Figure 1.

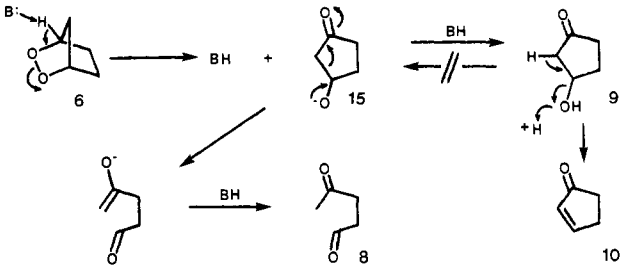
Since aldol condensation would convert the fragmentation product levulinaldehyde (**8**) into the disproportionation products **9** and **10**, it was shown in control experiments that such cyclization does *not* occur under the reaction conditions. Thus, **8** was heated at 45 °C for 72 h in a catalyst solution containing either 0.016 M Dabco and 40 equiv of acetic acid in dry C_6D_6 or 0.014 M Me_4NOAc and 30 equiv of acetic acid in $CDCl_3$. No change in the concentration of **8** and no trace of **9** or **10** could be detected by ^1H NMR.

Discussion

Disproportionation and Fragmentation of PGH_2. Isotope discrimination was observed during biosynthesis of PGE_2 (**3**), $PGF_{2\alpha}$ (**13**), and 12-hydroxyheptadeca-5,8,10-trienoic acid (**14**) from a mixture of arachidonic acid (**11**) and 5,6,8,9,11,12,14,15-octadeuterioarachidonic acid.[2] Thus, a mixture of unlabeled and deuterium-labeled arachidonic acid was incubated with sheep vesicular gland microsomes in the presence of L-epinephrine in aqueous solution at 37 °C and pH 7.2. The relative D:H ratios presented in Chart I were measured and found to remain nearly constant from 15 to 300 s of incubation. The relative D:H ratio in **3** and **12**, whose formation requires cleavage of C_{11}–H(D) or C_9–H(D), respectively, of the intermediate PGH_2 (**1**), showed a decreased D:H ratio relative to that of the precursor **11**. A corresponding increase in the relative D:H ratio was found in **13** and **14** whose formation does not involve C–H(D) cleavage. These results are readily explicable by a biosynthetic mechanism involving a common synthetase which provides the PGH_2 (**1**) precursor for **3** and **12**–**14**. The D:H ratio in this PGH_2 (**1**) is presumably the same *upon formation* as in **11** since its formation occurs without cleavage of a vinylic C–H(D) bond. The formation of **3** and **12** involves cleavage of C_9–H(D) or C_{11}–H(D), respectively. This removal of a bridgehead proton by a basic center at the active site of PGE_2-synthetase or PGD_2-synthetase apparently occurs in the rate-limiting step since $k_H/k_D = 2$–3. Since formation of **3** and **12** consumes **1**-d_0 preferentially, the common pool of PGH_2 becomes enriched in **1**-d_8. This enrichment is consequently found in **13** and **14** whose formation does not involve cleavage of a C–H(D) bond.

The formation of levuglandins LGE_2 (**5**) and LGD_2 from PGH_2 (**1**) also involves cleavage of C_9–H or C_{11}–H, respectively. Spontaneous decomposition of **1** in aqueous or dimethyl sulfoxide solution was recently shown to afford levuglandins in yields as high as 50%.[3] These fragmentation reactions were predicted by observations of analogous reactions of the model PG endoperoxide nucleus **6**.[7]

Scheme II



Acetate Catalysis of Endoperoxide Reactions. While isotopic competition experiments suggest bridgehead proton abstraction in the rate-determining step during bioconversion of PGH_2 into PGE_2 or PGD_2, these experiments do not identify the pertinent basic functional group. It is known that amines catalyze such disproportionation of secondary alkyl peroxides,[8] and these reactions exhibit substantial kinetic deuterium isotope effects.[9] Amine-catalyzed fragmentation of **6** to levulinaldehyde (**8**) also exhibits a large deuterium isotope effect ($k_H/k_D = 7.9$).[4] Thus cleavage of the bridgehead C–H bond apparently occurs in the rate-determining step generating a β-keto alkoxide which may be a common intermediate for both reactions (Scheme II). In the present study a similar deuterium isotope effect ($k_H/k_D = 7.6$) was found for acetate-catalyzed fragmentation of **6**. Thus, the carboxylate group apparently acts as a base which promotes decomposition of **6** by a mechanism similar to that found with amine catalysts. The effectiveness of the basic catalysts is directly reflected in k_{-6} (Table I). The present study demonstrates that Me_4NOAc and **7** are potent catalysts, comparable to Dabco or Et_3N, for decomposition of **6**. In *aqueous* solution, acetate is not nearly as strong a base as the amines.[10] However, it is reasonable that the basity of a carboxylate will be relatively greater under the nonaqueous conditions of the present studies.[11] It is also conceivable that a similar environment could be found at the active site of PGE_2-synthetase if the PG endoperoxide is bound in a hydrophobic pocket. It is noteworthy that the catalytic efficiency of **7**, as measured by k_{-6} (see Table I), is significantly depressed in the presence of excess acetic acid. This behavior might result from a decrease in the basicity of the acetate ion catalyst owing to hydrogen bonding with acetic acid. However, such behavior is not expected for a bifunctional enzyme if the acidic and basic functionalities at the active site are held rigidly apart. Thus, the present study raises the posibility that a carboxylate group is a viable new candidate for the basic functionality at the active site of enzymes promoting isomerization of PGH into PGE or PGD.

Model for Bifunctional Catalysis of Endoperoxide Disproportionation. Most significantly, the influence of added acetic acid on the ratio of disproportionation to fragmentation supports the hypothesis that base-catalyzed transformation of a prostanoid

(7) (a) Salomon, R. G.; Salomon, M. F. *J. Am. Chem. Soc.* **1977**, *99*, 3501–3. (b) Salomon, R. G.; Salomon, M. F.; Coughlin, D. J. *Ibid.* **1978**, *100*, 660–2.

(8) (a) Mageli, O. L.; Sheppard, C. S. In "Organic Peroxides"; Swern, D., Ed.; Wiley; New York, Vol. I, 1970; p 56. (b) Gollnick, K.; Schenck, G. O. In "1,4-Cycloaddition Reactions"; Hamer, J., Ed.; Academic Press: New York, 1967; p 255.

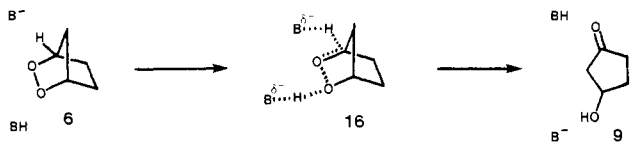
(9) (a) Clark, S. L. Thesis, Purdue University, 1955; Kornblum, N., personal communication. (b) Bell, R. P.; McDougal, A. O. *J. Chem. Soc.* **1958**, 1697–8. (c) Kornblum, N.; De La Mare, H. E. *J. Am. Chem. Soc.* **1951**, *73*, 880–1.

(10) Jencks, W. P.; Carriuolo, J. *J. Am. Chem. Soc.* **1960**, *82*, 1778–85.

(11) (a) Liotta, C. L., personal communication. (b) The nucleophilicity of acetate is enhanced under such conditions toward both carbon and protons: Liotta, C. L.; Harris, H. P.; McDermott, M.; Gonzalez, T.; Smith, T. *Tetrahedron Lett.* **1974**, 2417–20. (c) A related and even more dramatic enhancement of basicity is found for weakly solvated fluoride ions: Liotta, C. L.; Harris, H. P. *J. Am. Chem. Soc.* **1974**, *96*, 2251–2.

endoperoxide can be channeled to hydroxycyclopentanone product by efficient protonation. Thus, fragmentation and disproportionation of **6** are equally important, 51 and 49%, respectively, with Me_4NOAc as catalyst. However, the relative yield of disproportionation increases sharply to 68% in the presence of about 4 equiv of HOAc and continues to rise to 79% with 0.46 M HOAc, 33 equiv relative to Me_4NOAc (Figure 1).

The influence of added acetic acid might be exerted after deprotonation of **6** by diverting a common keto alkoxide intermediate **15** to hydroxy ketone **9** (Scheme II). Alternatively, the added acid might influence the product ratio by providing an additional route to hydroxycyclopentanone involving simultaneous bridgehead proton abstraction by acetate and protonation of the remote peroxidic oxygen by acetic acid as in **16**. Since a keto



alkoxide is not generated in such a push–pull process, fragmentation could be circumvented. It is tempting to speculate that such bifunctionality might be found at the active site of enzymes which catalyze production of PGE or PGD from PGH. Although the requisite acidic and basic sites must be intimately juxtaposed, they could be held sufficiently apart that the endoperoxide substrate would not have to break a salt bridge in order to arrive at the catalyst–substrate complex. Furthermore, these sites could be rigidly positioned to optimize steric effects[12] and the spatial arrangement of reacting centers, i.e., "approximation".[13]

Experimental Section

General. All proton nuclear magnetic resonance (NMR) spectra were recorded on Varian A-60-A, Varian EM-360-A, or Varian XL-100 spectrometers. Deuterium NMR spectra were recorded on a Varian XL-100 spectrometer at 15.36 MHz in the FT mode with an external ^{19}F lock. NMR spectra were automatically accumulated and stored by a computer-controlled Varian XL-100 spectrometer. The computer program permits storage of FID's on cassette tapes using a Sykes Compu-Corder.[14] Mass spectra were recorded on a Dupont Model 21-094 GC-MS instrument with an interfaced computer. Analysis of kinetic data was done using Univac-1108 or PDP-11/45 minicomputer systems.

Materials. Benzene and benzene-d_6 were purified by distillation from potassium. Chloroform and chloroform-d_1 were boiled under reflux over P_2O_5 for 4 h followed by distillation. Acetic acid was stirred over Na_2EDTA for 2 days, and then distilled. Hexamethylphosphoric triamide (Aldrich) was used without further purification. 1,4-Diazabicyclo[2.2.2]octane (Dabco) was sublimed at 40 °C (0.05 mm) onto a cold finger under an atmosphere of dry N_2. Tetramethylammonium acetate from Matheson Coleman and Bell was recrystallized in dry methylene chloride and dried at 100 °C (760 mm) for 3 days. Triethylamine was stirred over KOH for 1 day, then distilled from BaO. 2,3-Dioxabicyclo[2.2.1]heptane (**6**) was prepared[6b,c] and purified[15] according to methods established in our laboratories.

Preparation of Hexadeuteriocyclopentadiene. The procedure of Gallinella and Mirone[16a] was modified. Dry, freshly distilled, cyclopentadiene (14.4 mL, 11.6 g, 0.176 mol) was transferred to a dry 250-mL three-necked flask containing 130 mL of hexamethylphosphoramide (HMPA), equipped with magnetic stirring bar, N_2 inlet, and serum cap. A 0.30 M NaOD–D_2O solution was prepared by addition of a clean-shaven 8 × 10 × 10 mm (800 mg, 35 mmol) piece of sodium to 115 mL of D_2O (99+ atom % D) under an atmosphere of dry nitrogen. The 0.30 M NaOD–D_2O solution (30.4 mL) was transferred by a dry syringe to the cyclopentadiene–HMPA solution, and the mixture was stirred at room temperature for 2 h. The solution was cooled to 0 °C and quenched with 1 equiv of acetic-d_1 acid (99+ atom % D) (0.6 mL, 9.0 mmol), and the deuterated cyclopentadiene product was vacuum transferred (0 °C, 20 mm) through a 60° bent adapter packed with $CaCl_2$ and glass wool into another dry 250-mL three-necked flask kept at −78 °C. Assuming an 82% recovery[16b] of cyclopentadiene from the vacuum transfer (average percent recovery obtained from several trial runs), HMPA and NaOD–D_2O were added to the 250-mL flask containing the cyclopentadiene in amounts to maintain constant cyclopentadiene:NaOD–D_2O:HMPA ratios throughout the remaining four exchanges. After five exchanges, 5.6 g (77.8 mmol) of cyclopentadiene-d_6 was obtained in 44% yield. Mass spectrum (70 eV): *m/e* (rel intensity) 72 (1000), 70 (290), 44 (215), 42 (321), 40 (112), 28 (174).

Preparation of *exo,exo*-5,6-Diprotio-2,3-dioxabicyclo[2.2.1]heptane-d_6 (6-d_6). The procedure for preparation of **6**-d_6 was identical with that for preparation of **6**, except that cyclopentadiene-d_6 was used instead of cyclopentadiene:[6] ^1H NMR ($CDCl_3$–Me_4Si) δ 1.65 (s); ^1H decoupled ^2H NMR (benzene as solvent, $CDCl_3$ as internal standard) δ 4.67 (s, 2 ^2H), 2.34 (s, 1 ^2H), 2.09 (s, 2 ^2H), 1.83 (s, 1 ^2H).

Kinetics of Peroxide Decomposition. (a) Rate Determinations. In general, rates for appearance of the products levulinaldehyde (**8**) and levulinaldehyde-d_6 (**8**-d_6) from decomposition of peroxides **6** and **6**-d_6 were monitored by ^1H and ^2H NMR, respectively. Integration of the aldehydic protons of **8** and **8**-d_6 (δ 9.38 (s, 1 H) (C_6D_6–Me_4Si), 9.77 (s, 1 H) ($CDCl_3$–Me_4Si) and δ 9.86, (s, 1 ^2H) (C_6H_6–$CDCl_3$ as internal standard), 9.73, (s, 1 ^2H) ($CHCl_3$–$CDCl_3$) for **8** and **8**-d_6, respectively) and an inert internal standard was recorded at measured time intervals during reaction. From the ratio of the integral area of the aldehydic NMR signal to that for the internal standard, the concentration of **8** and **8**-d_6 was determined at each time interval. The concentration of **8** or **8**-d_6 at time = ∞, [8_∞ or $8\text{-}d_{6\infty}$], was extrapolated from graphical representations of [**8**] or [**8**-d_6] vs. time. Since base-catalyzed decomposition of **6** is pseudo first order,[4] the following relation for an exponential first-order decay[5]

$$(8_\infty - 8) = (8_\infty - 8_0)e^{-tk}$$

or

$$\ln (8_\infty - 8) = \ln (8_\infty - 8_0) = -tk$$

or

$$\ln\left(\frac{8_\infty - 8}{8_\infty - 8_0}\right) = -tk$$

[where 8_∞ is the final concentration for the product levulinaldehyde, 8 is the concentration of levulinaldehyde at time t, 8_0 is the initial concentration of levulinaldehyde at $t = 0$] was used to evaluate the rate constant k for appearance of levulinaldehyde (**8**). Alternatively, since it was often difficult to obtain an exact value for 8_∞, k was evaluated with a computer program which changed 8_∞ in small increments until a value for k was reached giving a minimum in the root-mean-square deviation between observed and calculated values of [**8**].[17]

(b) Method for Obtaining Kinetic Data. For all studies, the probes of the A-60-A or XL-100 NMR spectrometers were preheated to 45.0 °C by careful adjustment of each instrument's variable-temperature controller and careful inspection of the probe's temperature with a thermometer (Brooklyn P-M, 6N328, 76 mm × 1 mm, ±0.2 °C) specially designed to fit inside the NMR probe. After careful tuning of the NMR spectrometer, 0.4 mL of each catalyst solution (vide infra) was added to a clean 5-mm NMR tube containing 40 mg (0.40 mmol) of **6** or **6**-d_6. The catalyst–endoperoxide solution was immediately mixed throughly by shaking and placed into the NMR probe at 45.0 °C, thereafter, simultaneously, a timer and data accumulation are initiated. The computer program used on the XL-100 accumulated FT spectra at predetermined time intervals, and stored each FID and its parameters on a cassette tape.[14] At the instant each rf pulse was applied to the sample, a resulting FID appeared on the instrument's oscilloscope, and, if more than one transient per spectrum was taken, the timer reading for the "middle" transient was taken as the time for the particular spectrum. When the A-60-A NMR spectrometer was used, data are acquired by recording the time and immediately integrating the resonances for the aldehydic proton of **8** and the internal standard. Integrals were taken as often as required which depended upon how fast decomposition of **6** was occurring.

(c) Preparation of Catalyst Solutions. (i) Dabco and Et_3N. A solution (10.0 mL) was prepared volumetrically containing 0.112 M *p*-dichlorobenzene (165 mg, 1.12 mmol) in dry C_6D_6. A solution (2.0 mL) was prepared volumetrically from dry triethylamine (2.8 μL, 2.0 mg, 0.019

(12) For a pertinent example, see: Stevens, J. C.; Busch, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 3285–7.

(13) For a pertinent example, see: Jacob, J. M.; Nelson, J. A.; Spencer, T. A. *J. Org. Chem.* **1980**, *45*, 1645–50.

(14) Cassette tapes used were made by Sykes Datatronics, Inc., Rochester, N.Y.

(15) Coughlin, D. J., Thesis, Case Western Reserve University, 1979, p 139.

(16) (a) Gallinella, E.; Mirone, P. *J. Labelled Compd.* **1971**, *III(2)*, 183. (b) Yield of cyclopentadiene-d_6 in ref 16a was 75%.

(17) (a) Wiberg, K. B. "Physical Organic Chemistry"; Wiley, New York, 1964; p 558. (b) Feltch, S., Thesis, Case Western Reserve University, 1979.

mmol) and 0.112 M *p*-dichlorobenzene in C_6D_6. The concentration of triethylamine relative to the internal standard *p*-dichlorobenzene was determined by ^1H NMR spectroscopy using the average of repeated integrations of the peaks at δ 6.83 (s, 4 H) and 2.51 (q, 6 H) for internal standard and catalyst, respectively. Similarly, a solution (2.0 mL) was prepared volumetrically from freshly, sublimed Dabco (2.2 mg, 0.020 mmol) and 0.112 M *p*-dichlorobenzene in C_6D_6, and the concentration of Dabco relative to *p*-dichlorobenzene was determined by ^1H NMR using ratios of intergrated areas of the signals at δ 6.83 (s, 4 H) and 2.53 (s, 12 H) for the standard and catalyst, respectively.

(ii) Me_4NOAc. A solution (2.0 mL) was prepared volumetrically containing phenyltrimethylsilane (27.6 μL, 24.1 mg, 0.160 mmol, 0.080 M) and dry $CDCl_3$ saturated with dry tetramethylammonium acetate. The concentration of Me_4NOAc relative to the internal standard phenyltrimethylsilane was determined by ^1H NMR using ratios of integrated areas of the signals at δ 6.95–7.32 (m, 5 H) or 0.01 (s, 9 H) and δ 3.12 (s, 16 H) for the standard and catalyst, respectively. For the "Deuterium Isotope Effect" study (see Results section) a 0.20 M Me_4NOAc solution in dry $CDCl_3$ (2.0 mL) was equally divided into two parts. One part was concentrated to dryness by blowing a small, steady stream of N_2 onto the solution, then refilling to its original volume (1 mL) with dry $CDCl_3$ (25.0 μL, 37.5 mg, 0.312 mmol, 0.312 M) and dry $CHCl_3$. The latter solution in $CHCl_3$ was used for following appearance of **8**-d_6 from **6**-d_6 by ^2H NMR using $CDCl_3$ as an internal standard, and the solution in $CDCl_3$ was used for following appearance of **8** from **6** by ^1H NMR using phenyltrimethylsilane as an internal standard.

(iii) Dabco Plus Acetic Acid. A solution (10.0 mL) was prepared volumetrically containing freshly sublimed Dabco (11.2 mg, 0.100 mmol, 0.010 M) and dry $CHCl_3$ (0.32 mL, 477 mg, 3.99 mmol, 0.399 M) in dry C_6D_6. The concentration of Dabco relative to the internal standard $CHCl_3$ was determined by ^1H NMR spectroscopy using ratios of integrated areas of the peaks at δ 6.60 (s, 1 H) and 2.53(s, 12 H) for internal standard and Dabco, respectively.

A solution (2.0 mL) was prepared volumetrically containing purified acetic acid (0.230 mL, 241 mg, 4.02 mmol, 2.01 M) in dry C_6D_6.[18] To five aliquots (1.0 mL) of 0.010 M Dabco was added 2.01 M acetic acid (10.0, 15.0, 20.0, or 40.0 μL) or neat, purified acetic acid (8.0 μL). The concentration of acetic acid relative to the internal standard $CHCl_3$ was determined by ^1H NMR spectroscopy using ratios of integrated areas of the peaks at δ 6.60 (s, 1 H) and 1.65–1.50 (s, 3 H)[19] for internal standard and acetic acid, respectively. The amount of excess acetic acid relative to Dabco was calculated and is reported in Table I.

Determination of Product Distributions from Decomposition of 6 with Dabco or Me_4NOAc Plus Acetic Acid. (a) Dabco Plus Acetic Acid. A solution (2.0 mL) was prepared volumetrically containing pure 2,3-dioxabicyclo[2.2.1]heptane (**6**) (400 mg, 4.00 mmol) and phenyltrimethylsilane (48.2 μL, 42.1 mg, 0.280 mmol) in dry C_6D_6. The concentration of **6** relative to the internal standard phenyltrimethylsilane was determined by ^1H NMR spectroscopy using ratios of integrated areas of the peaks at δ 4.14 (s, 2 H) and 0.01 (s, 9 H) for **6** and internal standard, respectively. A solution (10.0 mL) of fresly sublimed Dabco (22.4 mg, 0.199 mmol, 0.019 M) in dry C_6D_6 was prepared volumetrically and separated into 10 aliquots (1.0 mL).

A solution (2.0 mL) was prepared volumetrically containing purified acetic acid (0.230 mL, 241 mg, 4.02 mmol, 4.02 M) in dry C_6D_6.[18] To eight aliquots (1.0 mL) of 0.019 M Dabco was added 4.02 M acetic acid (10.0, 13.0, 17.0, 20.0, or 30 μL) or neat, purified acetic acid (11.5, 23.0, or 46.0 μL). The concentration of acetic acid relative to Dabco was determined by ^1H NMR spectroscopy using ratios of integrated areas of the peaks at δ 2.53 (s, 12 H) and 1.65–1.50 (s, 3 H)[19] for Dabco and acetic acid, respectively. The amount of excess acetic acid relative to ammonium acetate **7** was calculated and is reported in Table II. Eight aliquots (0.2 mL) of 2.0 M **6** and 0.14 M phenyltrimethylsilane in C_6D_6 was placed into eight 5-mm NMR tubes, and each was combined with an aliquot (0.2 mL) containing 0.019 M **7** and various amounts of acetic acid in C_6D_6. The solutions were immediately mixed thoroughly by shaking and placed into an ice bath (0 °C) After all solutions were mixed, all solutions were removed from the ice bath and simultaneously heated in a thermostated oil bath at 45.0 °C for 65 h.

The concentrations of the three products, levulinaldehyde (**8**), 3-hydroxycyclopentanone (**9**), and cyclopent-2-en-1-one (**10**), from decomposition of **6** were determined relative to the internal standard phenyltrimethylsilane by ^1H NMR spectroscopy using ratios of integrated areas of the peaks at δ 9.38 (s, 1 H), 4.15 (m, 1 H), 5.84 (d of d, 1 H), and 0.01 (s, 9 H) for the three products (**8**, **9**, and **10**) and phenyltrimethylsilane (0.070 M), respectively. The concentrations of **8**, **9**, and **10** were divided by the initial concentration of **6** (which was determined with respect to phenyltrimethylsilane by ^1H NMR spectroscopy) and multiplied by 100 to give the percent yields for each of the products (see Table II).

(b) Me_4NOAc Plus Acetic Acid. A solution (10.0 mL) was prepared volumetrically from *p*-dichlorobenzene (8.0 mg, 0.054 mmol, 0.054 M) and $CDCl_3$ which was saturated with purified tetramethylammonium acetate (Me_4NOAc). The concentration of Me_4NOAc relative to *p*-dichlorobenzene was determined by ^1H NMR spectroscopy using ratios of integrated areas of the peaks at δ 3.12 (s, 12 H) and 6.87 (s, 4 H) for Me_4NOAc and *p*-dichlorobenzene, respectively.

A solution (1.0 mL) was prepared volumetrically containing purified acetic acid (0.230 mL, 241 mg, 4.02 mmol, 4.02 M) in dry $CDCl_3$.[18] To seven aliquots (1.0 mL) of the above solution of Me_4NOAc in $CDCl_3$ was added 4.02 M acetic acid (5.9, 6.9, 10.5, or 17.4 μL) or neat, purified acetic acid (16.0, 28.0, or 40.0 μL). The concentration of acetic acid relative to Me_4NOAc was determined by ^1H NMR spectroscopy using ratios of integrated areas of the signals at δ 3.12 (s, 12 H) and 1.72–1.50 (s, 3 H)[19] which corresponded to resonances for the *N*-methyl substituents or the acetate methyl group of Me_4NOAc and acetic acid, respectively. Using the resonance at δ 3.12, the portion of integral area of the δ 1.72–1.50 resonance corresponding to the catalyst, Me_4NOAc, was calculated, and the remaining area was used to calculate the amount of acetic acid present relative to Me_4NOAc. The calculated equivalents of acetic acid relative to Me_4NOAc are reported in Table III.

A solution (2.0 mL) was prepared volumetrically containing pure 2,3-dioxabicyclo[2.2.1]heptane (**6**) (400 mg, 4.00 mmol) and phenyltrimethylsilane (48.2 μL, 42.1 mg, 0.280 mmol) in dry $CDCl_3$. The concentration of **6** relative to the internal standard phenyltrimethylsilane was determined by ^1H NMR spectroscopy using ratios of integrated areas of the peaks at δ 4.53 (s, 2 H) and 0.01 (s, 9 H) for **6** and internal standard, respectively. Seven aliquots (0.2 mL) containing 2.0 M **6** and 0.14 M phenyltrimethylsilane in $CDCl_3$ were placed into 5-mm NMR tubes, and each was combined with an aliquot (0.2 mL) containing Me_4NOAc and various amounts of acetic acid in $CDCl_3$. Each solution was immediately mixed thoroughly by shaking and placed into an ice bath (0 °C). All of the solutions were then removed together from the ice bath and simultaneously heated in a thermostated oil bath at 45.0 °C for 65 h.

The concentrations of the three products, levulinaldehyde (**8**), 3-hydroxycyclopentanone (**9**), and cyclopent-2-en-1-one (**10**), from decomposition of **6** were determined relative to the internal standard phenyltrimethylsilane by ^1H NMR spectroscopy using ratios of integrated areas of the peaks at δ 9.77 (s, 1 H), 4.31 (m, 1 H), 5.95 (d of d, 1 H), and 0.01 (s, 9 H) for the three products (**8**, **9**, and **10**) and phenyltrimethylsilane (0.070 M), respectively. The concentrations of **8**, **9**, and **10** were divided by the initial concentration of **6** (which was determined previously by ^1H NMR with respect to phenyltrimethylsilane) and multiplied by 100 to give the percent yields for each of the products. The data are presented in Table III and shown graphically in Figure 1.

Control Experiments. (a) Stability of Levulinaldehyde (8) toward Dabco or Me_4NOAc Plus Acetic Acid. A solution (1.0 mL) was prepared volumetrically containing freshly sublimed Dabco (2.0 mg, 0.018 mmol, 0.018 M, 0.036 N), *p*-dichlorobenzene (20.0 mg, 0.136 mmol, 0.136 M), and purified acetic acid (82.0 μL, 86.0 mg, 1.44 mmol, 1.44 M, 40.0 equiv relative to Dabco) in dry C_6D_6. Another solution (1.0 mL) was prepared volumetrically containing *p*-dichlorobenzene (30.0 mg, 0.204 mmol, 0.204 M), purified acetic acid (27.0 μL, 28.0 mg, 0.470 mmol, 0.470 M, 34 equiv relative to Me_4NOAc), and 0.014 M Me_4NOAc in dry $CDCl_3$. Levulinaldehyde (**8**) was prepared,[20a] purified,[20b] and weighed into two 5-mm NMR tubes (40 mg, 0.40 mmol) and combined with the above solutions (0.40 mL) of 0.036 N Dabco and acetic acid or 0.014 M Me_4NOAc and acetic acid. The solutions were mixed thoroughly and the concentration of **8** relative to the internal standard *p*-dichlorobenzene was determined by ^1H NMR spectroscopy using ratios of the integrated areas of the peaks at δ 9.38 (C_6D_6), 9.77 ($CDCl_3$) (s, 1 H), and δ 6.38 (C_6D_6), 6.87 ($CDCl_3$) (s, 4 H) which corresponded to **8** and *p*-dichlorobenzene, respectively. The two NMR tubes were heated simultaneously at 45.0 °C in a thermostated oil bath for 72 h. ^1H NMR spectra were recorded periodically from which [**8**] was determined relative to the inert internal standard, *p*-dichlorobenzene.

(b) Stability of 2,3-Dioxabicyclo[2.2.1]heptane (6) in C_6D_6, $CDCl_3$, and 1.1 M CH_3COOH in C_6D_6 at 45.0 °C. Three solutions (1.0 mL) were

(18) All measurements of acetic acid were done using a special, nonmetal syringe to avoid possible contamination by trace metal ions. Syringes used were purchased from Oxford Laboratories, Inc., and were called "Adjustable Samplers".

(19) The chemical shift of the methyl signal of acetic acid varied about 0.15 ppm depending upon its concentration.

(20) (a) Mondon, V. A. *Angew. Chem.* **1952**, *64*, 224. (b) Purified by gas–liquid phase chromatography at 120 °C through a 3 ft × 0.25 in. column packed with 10% Dow Corning 710 silicone oil on 60/80 Chromosorb W.

prepared containing *p*-dichlorobenzene (22.0 mg, 0.150 mmol, 0.150 M) in dry $CDCl_3$, dry C_6D_6, or 0.15 M *p*-dichlorobenzene and acetic acid (63 μL, 66 mg, 1.1 mol, 1.1 M) in dry C_6D_6. The peroxide **6** was weighed into three 5-mm NMR tubes (40 mg, 0.40 mmol) and combined with 0.15 M *p*-dichlorobenzene in $CDCl_3$, 0.15 M *p*-dichlorobenzene in C_6D_6, or 0.15 M *p*-dichlorobenzene and 1.1 M acetic acid in C_6D_6 (0.40 mL). The solutions were mixed thoroughly, and the concentration of **6** relative to the internal standard, *p*-dichlorobenzene, was determined by ^1H NMR spectroscopy using the ratio of integrated areas of the peaks at δ 6.83 (C_6D_6) or 6.87 ($CDCl_3$) (s, 4 H) and δ 4.14 (C_6D_6) or 4.53 ($CDCl_3$) (s, 2 H) which corresponded to the internal standard and **6**, respectively.

The three NMR tubes were heated at 45.0 °C in a thermostated oil bath for 66 h. ^1H NMR spectra were recorded periodically and [**6**] relative to the internal standard was calculated for each time. Graphs were constructed from these data showing the decrease in [**6**] vs. time, and a value of $t_{1/2}$ (half-life) of [**6**] was determined from the graphs. Since thermolysis of **6** in nonpolar solvents is first order in [**6**],[21] the rate constant for disappearance (k) of **6** was calculated from the relation of $k = 0.693/t_{1/2}$.

Acknowledgment. We thank Professors S. R. Wilson, L. J. Marnett, and R. F. Borch for helpful discussions, and the National Institutes of Health for financial support of this research through Grant GM-21249 from the Division of General Medical Sciences.

Registry No. 6, 279-35-6; **6**-d_6, 81477-78-3; **8**, 626-96-0; **9**, 26831-63-0; **10**, 930-30-3; hexadeuteriocyclopentadiene, 2102-16-1.

(21) Coughlin, D. J.; Salomon, R. G. *J. Am. Chem. Soc.* **1979**, *101*, 2761.

Communications to the Editor

Arylation and Vinylation of Iron Porphyrins. Double Electrochemical Induction of a Nucleophilic Substitution

Doris Lexa and Jean-Michel Savéant*

Laboratoire d'Electrochimie, Université Paris 7
75251 Paris Cedex 05, France
Received December 28, 1981

There have been so far relatively few reports of the synthesis of σ-alkyl-, σ-aryl-, and σ-vinyliron porphyrins. A first route to these complexes is carbanion transfer from a Grignard reagent to the iron(III) porphyrin. Ethyl-[1a] phenyl- (or *p*-tolyl)-),[1] and 1,1′-diphenylethenyliron(III)[2] porphyrins have been prepared according to this reaction. Another possible way of generating the σ-alkyl complexes is by reacting an alkyl radical with an iron(II) porphyrin. Evidence has been provided for the formation along this route of σ-methyl- and mono-, di-, and trichloromethyliron porphyrins in pulse radiolysis studies.[3] More recently, several σ-alkyl iron porphyrins have been prepared in solution both under their Fe(III) and Fe(II) oxidation states by reacting aliphatic halides with electrogenerated iron(I) porphyrins.[4] The iron(I) complex there appears to function as the nucleophile in an S_N2-type nucleophilic substitution.

The extension of such a reaction to arylations and vinylations involving nonactivated aryl or vinyl halides seems a priori precluded by the inertness of these reagents toward nucleophilic substitution. It has, however, been shown that aromatic nucleophilic substitutions can be triggered electrochemically through reduction of the aryl halide.[5] The aryl radical thus generated is able to react with soft nucleophiles yielding the anion radical of the substitution product (SR_N1 substitution[6a]). Vinylic substitutions have also been carried out in the same context by using photostimulation.[6b] It is therefore conceivable that σ-aryl- and σ-vinyliron porphyrins could be formed by reacting the corresponding halides with electrogenerated iron(I) porphyrins under electrochemical stimulation of the substitution reaction. The electrochemical inducement would thus serve a double purpose: generate the nucleophile, i.e., the iron(I) porphyrin from the starting iron(III) complex and provide the electrons required for the stimulation of the aromatic (or vinylic) substitution. The preliminary results reported hereafter do show that σ-aryl- and σ-vinyliron porphyrins are formed upon electrolysis of a mixture of aryl or vinyl halides with an iron porphyrin provided the electrode potential is such that the aryl (or vinyl) radicals be generated in the presence of the iron(I) complex. To our knowledge, this is the first report of electrochemical induction of a nucleophilic substitution reaction in the field of organometallic chemistry.

A first example is shown on the Figure 1. The iron porphyrins display three chemically reversible waves corresponding to the successive formation of the species indicated on the figure. 4-Bromobenzonitrile shows one irreversible wave featuring the reductive cleavage into benzonitrile followed by the reversible one-electron wave of benzonitrile. The former is located slightly in front of the $Fe(I)/Fe(I)^{-}\cdot$ wave. When the potential scan is started in between the first and second 4-bromobenzonitrile wave and is swept anodically and then cathodically (Figure 1c), a new set of waves appears at the expense of that featuring the original porphyrin. This indicates the formation of a new complex. The location and characteristics of its waves (one reversible wave at $E^\circ = -0.84$ V vs. SCE and one irreversible wave at $E_p = 0.2$ V for $v = 0.2$ V s^{-1}) are very close to those of the σ-alkyl complexes previously described.[4] Further evidence that a σ-aryliron complex is actually formed is provided by thin-cell spectroelectrochemistry. Electrolysis at −1.8 V, i.e., at the first 4-bromobenzonitrile wave, leads to the observation of a spectrum (λ_{max} = 348 nm (ϵ 4.50 × 10^4 M^{-1} cm^{-1}), 422 (1.76 × 10^5), 506 (1.76 × 10^4), 536 (1.61 × 10^4), 777 (0.56 × 10^4)) similar to those of the $Fe^{III}R^-$ complexes previously described.[4] Reoxidation at −0.7 V leads to a spectrum (λ_{max} = 422 (ϵ 1.49 × 10^5 M^{-1} cm^{-1}), 536 (1.27 × 10^4) similar to that of a $Fe^{III}R^-$ complex.[4] It is noted that no arylation occurs when the starting potential is set up just beyond the Fe(II)/Fe(I) wave (Figure 1d). This points to the necessity of generating aryl

(1) (a) Clarke, D. A.; Dolphin, D.; Johnson, A. W.; Pinnock, H. A. *J. Chem. Soc. C* **1968**, 881. (b) Clarke, D. A.; Grigg, R.; Johnson, A. W. *J. Chem. Soc., Chem. Commun.* **1966**, 208. (c) Reed, C. A.; Mashiko, T.; Bentley, S. P.; Kastner, M. E.; Scheidt, W. R.; Spartalin, K.; Lang, G. *J. Am. Chem. Soc.* **1979**, *101*, 2948. (d) Ogoshi, H.; Sugimoto, H.; Yoshida, Z., IXth International Conference on Organometallic Chemistry, 1979, Dijon, France.

(2) (a) Lexa, D.; Savéant, J. M.; Battioni, J. P.; Lange, M.; Mansuy, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 578. (b) Battioni, J. P.; Lexa, D.; Mansuy, D.; Savéant, J. M., submitted for publication.

(3) (a) Brault, D.; Bizet, C.; Morliere, P.; Rougée, M.; Land, C. J.; Santus, R.; Swallow, A. J. *J. Am. Chem. Soc.* **1980**, *102*, 1015. (b) Brault, D.; Neta, P. *Ibid.* **1981**, *103*, 2705.

(4) Lexa, D.; Mispelter, J.; Savéant, J. M. *J. Am. Chem. Soc.* **1981**, *103*, 6806.

(5) (a) Savéant, J. M. *Acc. Chem. Res.* **1980**, *13*, 323. (b) Amatore, C.; Pinson, J.; Savéant, J. M.; Thiébault, A. *J. Am. Chem. Soc.* **1981**, *103*, 6930. (c) Amatore, C.; Pinson, J.; Savéant, J. M.; Thiébault, A. *Ibid.* **1982**, *104*, 817.

(6) (a) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413. (b) Bunnett, J. F.; Creary, X.; Sundbery, J. E. *J. Org. Chem.* **1976**, *41*, 1707.

(7) C_{12}(TPP) designates a cross-trans-linked basket-handle porphyrin with two 12-carbon aliphatic chains bound through an ether linkage to the ortho positions of two opposite phenyl rings, one chain above the porphyrins ring, the other below.[8] This structure possesses the advantage of preventing μ-oxo dimer formation.

(8) (a) Momenteau, M.; Loock, B.; Mispelter, J.; Bisagni, E. *Nouv. J. Chim.* **1979**, *3*, 77. (b) Momenteau, M.; Loock, B. *J. Mol. Catal.* **1980**, *7*, 315.

0002-7863/82/1504-3503$01.25/0