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METALLOPORPHYRIN-MEDIATED RADICAL CYCLOADDITIONS OF p-CYANO-N,N-DIMETHYLANILINE

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Abstract: Tetrahydroquinolines are formed via metalloporphyrin-catalyzed radical cycloadditions of olefins (2,3-dimethyl-2-butene and norbornene) and p-cyano-N,N-dimethylaniline; their synthesis, characterization and a mechanistic rationale of their formation are presented.

The cytochrome P-450 and peroxidase enzymes contain iron(III) protoporphyrin(IX) at their active site. In our kinetic studies a variety of metalloporphyrins have been employed as models for the heme prosthetic group.[2] In the work reported here we utilized p-cyano-N,N-dimethylaniline N-oxide (NO) as our oxygen source and the SbF_6^- salt of the C_2-capped meso-tetraphenylporphyrin iron(III) of Baldwin ($(TPPC_2cap)Fe^{III}SbF_6$) as catalyst (see Figure 1). The turnover process that was investigated is given in Scheme I.

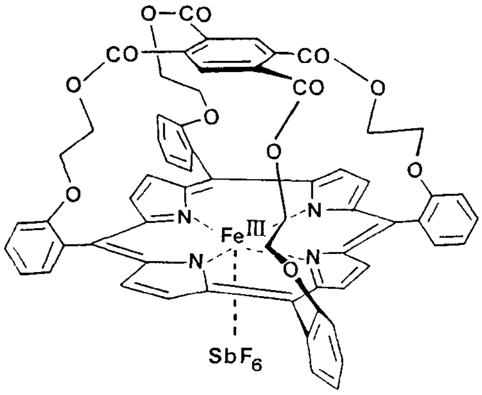
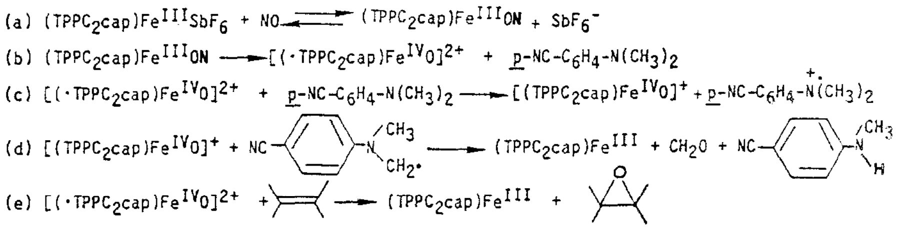


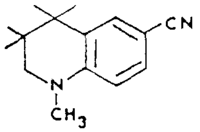
Figure 1. Iron(III)C_2-capped porphyrin of Baldwin

The higher valent iron-oxo species ($[(\cdot TPPC_2cap)Fe^{IV}O]^{2+}$) that is produced upon oxygen atom transfer from the N-oxide is also capable of epoxidizing olefins as well as oxidizing p-cyano-N,N-dimethylaniline (eq. c, d, Scheme I).[3]

Scheme I



In the course of product identification two unexpected tetrahydroquinolines were obtained (1 and 2). We report herein their synthesis and characterization and offer a possible mechanism for their formation.



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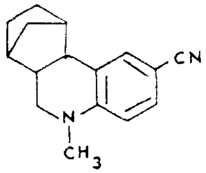
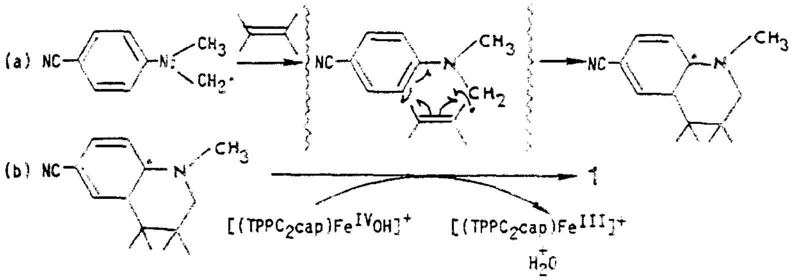


2

A CH_2Cl_2 solution of p-cyano-N,N-dimethylaniline N-oxide was added to a round bottom flask containing the catalyst, $(TPPC_2cap)Fe^{III}SbF_6$, and a large excess of 2,3-dimethyl-2-butene in CH_2Cl_2.[4] The final concentrations of the reactants were 3.0×10^{-3} M, 1.0×10^{-4} M and 0.10 M, respectively. The reaction was stirred at room temperature for 12 h and work-up of the reaction mixture by HPLC (hexane/ethyl acetate) followed by column chromatography (4:1 hexane/ethyl acetate) yielded p-cyano-N,N-dimethylaniline (57%), 2,3-dimethyl-2-butene oxide (50%) and the tetrahydroquinoline 1 (36%).[5,6] Tetrahydroquinoline 2 was prepared in 15% yield in an analogous manner utilizing norbornene in lieu of 2,3-dimethyl-2-butene.[7] The initial concentration of norbornene was 1.00 M instead of 0.10 M as was the case for the reaction involving the formation of 1.

The concentrations of the alkenes employed were extremely important. Compound 1 was obtained in 36% yield when the initial concentration of the olefin was 0.01 M or 0.10 M. At a concentration of 1.00 M alkene, none of the tetrahydroquinoline 1 was formed. The only oxidation products were p-cyano-N,N-dimethylaniline (100%) and 2,3-dimethyl-2-butene oxide (100%). In order for compound 2 to be formed norbornene had to be present at a concentration of 1.00 M.[8] These results support a competition between the p-cyano-N,N-dimethylaniline radical and the olefin for the higher valent iron-oxo species ($[\cdot(TPPC_2cap)Fe^{IV}O]^{2+}$). A proposed mechanism for the formation of the quinolines is given in Scheme II.

Scheme II



Literature precedence exists for radical cycloadditions involving N,N-di-substituted anilines. Swan and co-workers[8] have reported the reactions of benzyl peroxides and N,N-disubstituted anilines in the presence of N-phenylmaleimide to yield tetrahydroquinoline derivatives.

In summary, this communication supports the idea that metalloporphyrin-catalyzed oxidations of N,N-dimethylanilines proceed via single electron transfer and reports on the formation of reaction products not previously observed.

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References and Notes:

1. Present address: Department of Pharmaceutical Research & Technologies, Smith Kline & French Laboratories, Philadelphia, PA 19101.

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4. Due to the weak ligation of SbF_6^- and its ease of exchange, the solvent was highly purified as described in detail in ref. 2g, and the reaction was carried out in an anhydrous oxygen-free, nitrogen-filled glove box. Work-up was performed on the bench top, and the presence of oxygen did not have an affect on the product yields or distribution.

5. All yields reported here are based on the initial concentration of N-oxide employed (limiting reagent in these processes).

6. 6-Cyano-3,3,4,4-tetramethyl-N-methyl-1,2,3,4-tetrahydroquinoline (1) was identified by ^1H NMR, high resolution mass spectrometry and UV/visible spectroscopy: ^1H NMR ($CDCl_3$): δ 0.89 (s, 6H), 1.17 (s, 6H), 2.98 (s, 3H), 3.09 (s, 2H), 6.47 (d, 1H, J = 3 Hz), 7.31 (d, 1H, J = 3 Hz), 7.40 (s, 1H); high resolution mass spectrum, m/z 228.1616 (M^+, calcd. for $C_{15}H_{20}N_2$, 228.1628); visible spectrum: λ_{max} 304 nm ($\varepsilon = 1.2 \times 10^4\ M^{-1}\ cm^{-1}$).

7. 6-Cyano-3,4-norbornyl-N-methyl-1,2,3,4-tetrahydroquinoline (2) was identified by ^1H NMR, high resolution mass spectrometry and UV/visible spectroscopy: ^1H NMR ($CDCl_3$): δ 0.89-1.75 (complex m, 6H), 2.13 (m, 1H), 2.19 (m, 1H), 2.36 (m, 1H), 2.68 (d, 1H, J = 9 Hz), 2.79 (dd, 1H, j = 6, 12 Hz), 2.84 (s, 3H), 3.10 (dd, 1H, J = 6, 12 Hz), 6.61 (m, 1H), 7.35 (m, 1H), 7.41 (broad s, 1H); high resolution mass spectrum m/z 238.1462 (M^+, calcd. for $C_{16}H_{18}N_2$, 238.1471); visible spectrum: λ_{max} 306 nm ($\varepsilon = 1.0 \times 10^4\ M^{-1}\ cm^{-1}$).

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