Tetrahedron Letters No. 24, pp 1953 - 1956, 1975. Pergamon Press. Printed in Great Britain.

STEREOSPECIFIC ALIPHATIC HYDROXYLATION UPON PHOTOREDUCTION OF IRON(III)

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(Received in U.S.A. 18 March 1975; received in UK for publication 28 April 1975)

Until recently aliphatic hydroxylation by mixed function oxidases has lacked a classical chemical analog.[1] Our initial studies into the nature of Fenton's reagent in nonaqueous solutions[2] were designed to gather extrakinetic data which might improve the conceptual base for the nature of reactive intermediates involved in these enzymatic oxidations and lead to the development of remote functionalization reagents based on metal redox systems.

The demonstration that directed hydroxylation through an iron-bound oxidant can result from the ferrous ion-hydrogen peroxide oxidation of cyclohexanol,[2] in direct stereochemical analogy to the biological oxidases, has led us to search for independent routes to this manifold of reactive intermediates. In principle, the dramatic differences in the nature of Fenton's reagent as a function of solvent can be rationalized by considering kinetic or thermodynamic changes in the interconversion (I) resulting from the medium.[3] Accordingly, whereas free hydroxyl radical may be the stoichiometrically important oxidant in water, ferryl ion (**1**) is obtained in acetonitrile. This hypothesis suggests that any route to **1** should result in characteristic regioselectivity and stereoselectivity.

$$Fe^{+++} + HO\cdot \rightleftharpoons \underset{\mathbf{1}}{FeO^{++}} + H^{+} \qquad \text{(I)}$$

The photoreduction of iron(III) salts has long been proposed to generate hydroxyl radicals by the dissociation of Fe^{III}-OH.[4] We report here that the photoreduction of iron(III) hydrate in the presence of cyclohexanol leads to a distribution of diols which parallels that observed in the ferrous ion-hydrogen peroxide oxidation. We interpret this result as evidence for an alternate route to reactive iron(IV) intermediates[5] and offer new evidence that the regiospecificity observed is due to alcohol-oxidant complexation.

In a typical reaction, a solution of 20 mmole of ferric perchlorate hexahydrate and 50 mmole cyclohexanol in 250 ml acetonitrile was purged with nitrogen and photolyzed with a 450-watt Hanovia lamp through Pyrex. The solution, which was initially red-orange became colorless after 4 hr ($\phi/\phi^\circ \sim 0.1$). Products were analyzed after acetylation as previously described (10 ft, 20% DEGS, 135°).[2] Inspection of the data (Table I) reveals that the same preference for *cis*-1,3-cyclohexane diol formation is found in the iron(III) photoreduction as was observed in the ferrous ion-hydrogen reaction.

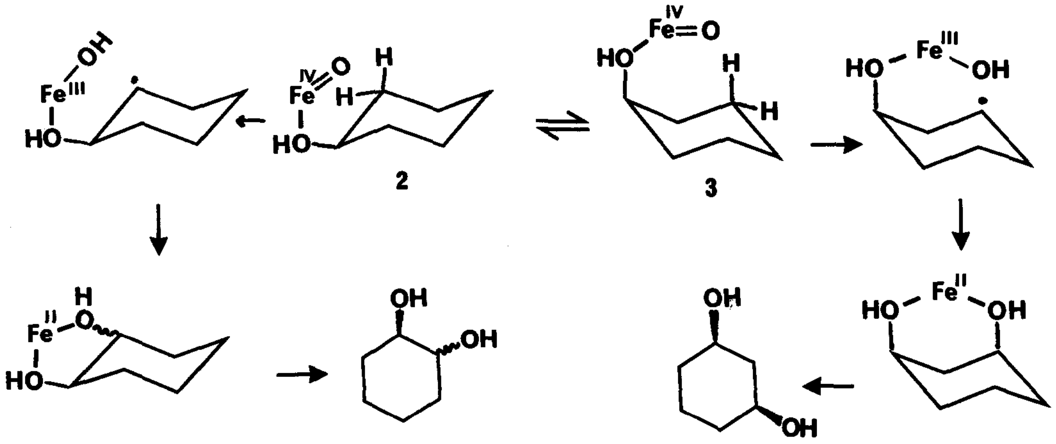
Table I. Product Distribution for Cyclohexanol Hydroxylation

	%[d]			
Isomer	a	b	c	d
cis-1,2	13	16	19	6.7
trans-1,2	16	12	20	12.3
cis-1,3	55	61	41	71.9
trans-1,3	6.9	6.0	9.0	2.5
cis-1,4	5.0	3.0	5.0	3.8
trans-1,4	3.9	2.5	4.6	2.9

[a] Photolysis at 25°; [b] Photolysis at −25°; [c] Photolysis at −40°; [d] Ferrous ion-hydrogen peroxide at −18°, *cf.* Ref. 2; [d] Photolyses were run to 10% conversion. The major product, cyclohexanone, accounted for 80% of the organic product.

As was noted in our initial report,[2] conditions which lead to large amounts of *cis*-1,3-cyclohexane diol also afford enhanced amounts of 1,2-diols. To the extent that the ferryl ion initiated hydroxylation of cyclohexanol proceeds through a cyclic transition state as proposed, and since hydrogen abstraction is likely to be faster than chair-chair interconversion or ligand exchange on iron,[6] product distributions should be sensitive to changes in conformational equilibria (Scheme I).

Scheme I



Specifically, the equatorial conformer **2** can reasonably lead only to 1,2-diols while the axial conformer allows access to the *cis*-hydrogen on carbon-3.

In the accompanying paper[7] we describe a determination of the A-value for cyclohexanol complexed to europium as a model of the cyclohexanol-iron complex **2** ⇌ **3** and conclude that at room temperature about 30% of the axial conformer **3** is present. This result is satisfying given the strong preference for C-3 oxidation. Lower temperatures should disfavor **3** with respect to **2** and lead to the production of *more* 1,2-diols.

This expectation is at least qualitatively borne out by the examination of diol distributions resulting from photolyses at low temperature. Although there is observed little change in regiospecificity between +25° and -25°, there is a distinct increase in the relative amounts of 1,2-diols at the expense of *cis*-1,3-cyclohexane diol when the photoreduction is run at -40°.[8] Thus, in accord with predictions derived from Scheme I, the oxidant in the photoreduction and that produced by the oxidation of ferrous ion by hydrogen peroxide respond similarly to substituent-derived directive effects supporting its formulation as a ferryl ion (**1**).[9]

Acknowledgements. Financial support of this work by the Petroleum Research Fund, administered by the American Chemical Society, and The University of Michigan is gratefully acknowledged.

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