Geometric requirements in the ferriin oxidation of benzylic 1,2-diols

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Received (in Corvallis, OR, USA) 12th July 1999, Accepted 8th October 1999

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The rates of ferriin [*i.e.* tris(1,10-phenanthroline)iron(III)] oxidation of *cis*- and *trans*-1,2-diphenylcyclohexane-1,2-diol have been found to be dramatically different; *cis*-1,2-diphenylcyclohexane-1,2-diol reacts a minimum of 10^4 times faster than the corresponding *trans*-isomer; implications for the oxidation of benzylic diols by ferriin are discussed.

The oxidative cleavage of 1,2-diols by a variety of reagents has been extensively studied.¹ The mechanisms are conventionally classified into several types.¹ In the first class of oxidative cleavage of *vic*-diols [eqn. (1)], a bidentate complex between

$$HO \qquad OH \qquad + M^{(n+2)+} \qquad \xrightarrow{-2 H^{+}} \qquad O \qquad H \qquad O \qquad H \qquad O \qquad H \qquad (1)$$

$$HO \qquad OH \qquad HO \qquad OH \qquad HO \qquad OH \qquad H^{(n+2)+} \xrightarrow{-H^+} HO \qquad OM^{(n+2)+} \xrightarrow{OH} \stackrel{I}{\to} \stackrel{OH}{IH_2} + M^{(n+1)+} + \stackrel{O}{\parallel} (2)$$

HO OH
$$M^{(n+2)*} \xrightarrow{-e^-} HO$$
 OH OH $H^{-}O^+$ (3)
+ e^- CH₂·+CH₂ \rightarrow OH $H^{-}O^+$ $H^{-}O^+$ (3)

the oxidant and the glycol breaks down by an apparent sixelectron process (two electrons to the oxidant).¹ The second general class of oxidative cleavage mechanisms of *vic*-diols [eqn. (2)] invokes a monodentate complex, which yields an intermediate radical *via* a one-electron process, followed by C–C fission and then further oxidation of the resulting radical.¹ A third general class of oxidative cleavage reactions for appropriately substituted *vic*-diols [eqn. (3)] is a single electron transfer to form a radical cation, that can subsequently undergo bond cleavage to form fragments similar to those formed in [eqn. (2)].^{2,3}

In our laboratories, we hoped to use *vic*-diols that undergo cleavage by the general mechanism shown in [eqn. (3)] in order to determine fundamental reaction rate constants. Our initial studies demonstrated that ferriin readily oxidized tetraaryl-ethane-1,2-diols to the corresponding ketones [eqn. (4)].⁴ By

applying a mechanism in which a slow rate-determining outersphere electron transfer was followed by rapid bond cleavage {general mechanism of [eqn. (3)]}, we reported endergonic electron transfer rate constants that were faster than expected, based upon estimates of the solution phase oxidation potential.⁵ As we have varied functionality in standard structure-reactivity probes in an attempt to understand this anomalously fast electron transfer rate, we have observed non-isosbestic point behavior during a kinetics experiment on appropriately substituted compounds. This has served as an indication that the reaction mechanism is more complex than originally thought.⁶

As part of our reinvestigation of this reaction mechanism, we have studied the geometric relationship of the hydroxy groups in this oxidation reaction. Our preliminary investigation of the reactivity differences exhibited by dl- and meso-1,2-diphenylethane-1,2-diol indicated to us that steric requirements existed in this reaction and that the geometry of the reacting groups might be important. The free rotation of the central C-C bond in the *dl*- and *meso*-isomers of 1,2-diphenylethane-1,2-diol does not allow for a definitive analysis of the various intramolecular interactions, which may be responsible for the observed reactivity. In order to lock the geometry of all components in place, we chose to study cis- and trans-1,2-diphenylcyclohexane-1,2-diol. These compounds were synthesized based on Tomboulian's method.⁷ In brief, *cis*-3 was obtained from 1,4-dibenzoylbutane in a McMurry coupling reaction with TiCl₃/LiAlH₄ followed by OsO₄ oxidation to give the cis-1,2-diphenylcyclohexane-1,2-diol 27% in yield [mp 86.5-87.5 °C (lit.,7 86-87 °C)]. trans-1,2-Diphenylcyclohexane-1,2-diol was obtained from reaction of cyclohexane-1,2-dione with excess (3 equiv.) of PhLi at reflux in dry THF for 20 h, followed by appropriate work-up to yield the resultant white needle-like crystals, mp 122-123 °C (lit.7 121-122 °C).

Quantitative analysis of the reaction of ferriin (10 mM) with cis- and trans-3 (5 mM) in MeCN at room temperature was accomplished by reverse-phase HPLC on a C-18 column eluted with $MeCN-H_2O$, using methyl benzoate as an internal standard. A base (2,6-di-tert-butylpyridine) was added to avoid the possible carbocation-induced rearrangement product (i.e. the pinacol rearrangement). cis-3 reacted quantitatively (mass balance = 98.9% at 34% conversion) to form the anticipated bond cleavage product (i.e. 1,4-dibenzoylbutane). The error limits for this determination are $\pm 5\%$, which means that a small amount of the trans-1,2-diphenylcyclohexane-1,2-diol could have been formed in this reaction. The data were carefully analyzed for the appearance of the trans-1,2-diphenyl-1,2cyclohexanediol. Since no trans-diol was observed and the appearance of 1,4-dibenzoylbutane was near quantitative, we conclude that the major reaction pathway (by a factor of >20:1) is oxidative cleavage of the 1,2-diol C–C bond.

In contrast, the *trans*-1,2-diphenylcyclohexane-1,2-diol did not react within a time period of two days. In fact, we were unable to see a reaction under any conditions employed by us. Therefore, we were unable to confirm that the expected oxidation product arose from this reaction. Under controlled conditions where both *cis*-3 and *trans*-3 were reacted in the same solution, we were able to show that a minimum reactivity difference of 10^4 exists between these isomers. Thus, there is a significant reactivity difference between *cis*-3 and *trans*-3 for ferriin oxidation.

This extreme reactivity difference between the two isomers required an analysis of the possible conformations of *cis*- and *trans*-**3**. These conformations are shown in Fig. 1. For *cis*-**3**, both available ring-flipped conformations have one phenyl group in the axial conformation and one phenyl group in the equatorial conformation. Thus, the energetics of these two



Fig. 1 Conformations of cis- and trans-1,2-diphenylcyclohexane-1,2-diol.

alternative conformations are equivalent. In contrast, trans-3 does not have equivalent conformational energies. Since the phenyl group is larger than the hydroxy group,8 one would anticipate that the conformation in which the phenyl groups are equatorial would be quite a bit more stable than the conformation in which the hydroxy groups are in the axial position. This conformational preference tends to 'lock' the cyclohexanediol into the conformation with both phenyl groups in the equatorial position in the same way that the *tert*-butyl group is said to 'lock' the conformation of substituted cyclohexanes. In this conformation, the hydroxy groups are in an anti-relationship to each other. This expectation is consistent with molecular mechanics calculations in which the energetic difference between the conformation in which the phenyl groups are axial and the conformation in which the phenyl groups are equatorial is 5.4 kcal mol⁻¹. From this relative arrangement of groups, we conclude that either syn-OH groups or an antiperiplanar phenyl-OH arrangement can lead to the observed bond cleavage reactions.

The results of this study have important implications for the ferriin oxidation of vic-diols. A simple outer-sphere electron transfer reaction, in which an electron is transferred from the electron donor to the ferriin molecule, cannot explain the observed reactivity differences. One would anticipate that the oxidation potentials of cis-3 and trans-3 would be identical, since cis- and trans-1,2-diphenylcyclohexane have identical photoelectron spectra (identical ionization potentials).9 Our estimate of a minimum rate differential for these two compounds of 10^4 would be inconsistent with the energetic equivalence of these two reactions.

Alternatively, one could argue that electron transfer occurs in both species, but that *trans*- $3^{\bullet+}$ is a stable species and does not lead ultimately to the dione, while *cis*-**3**^{•+} is relatively unstable and reacts rapidly to form the dione. This argument is ruled out by two experimental results. First, there is no trace of trans-1,2-diphenylcyclohexane-1,2-diol in the reactions starting from the *cis*-1,2-diphenylcyclohexane-1,2-diol isomer. This argues against equilibration of cis-3^{•+} and trans-3^{•+}. Further, preliminary experimental results in which $cis-3^{\bullet+}$ and $trans-3^{\bullet+}$ were generated by single electron transfer to excited state dicyanoanthracene showed similar non-reactivity for both the cis- and trans-isomers.

The reactivity differences between cis- and trans-3 seem to preclude reaction through a general mechanism such as that shown by the general cleavage mechanism of eqn. (2). A mechanistic interpretation that there is a sufficient energetic difference for complexation of an equatorial OH group as compared to an axial OH group is, in principle, possible. Combined with evidence that the monomethyl ethers of both meso- and dl-1,2-diphenylethane-1,2-diol are unreactive in comparison¹⁰ allows us to definitively rule out the general mechanism of eqn. (2), since two OH groups are required for the reaction.

To the best of our knowledge, such geometric requirements for the two hydroxy groups are unprecedented in the cleavage of vic-diols by one-electron oxidizing reagents [general oxidative cleavage mechanism shown in eqn. (2)]. We are continuing our efforts to fully understand the mechanism of this reaction in order to better understand the oxidation reaction mechanisms of one electron oxidants in reactions such as the Belousov-Zhabotinski (B-Z) reaction.11,12

The geometric requirements for the ferriin oxidation of aromatic 1,2-diols involve the orientation of the two OH groups in a syn-position or an anti-periplanar phenyl-OH arrangement. The differing reactivity of **3a** and **3b** with ferriin indicates a very unexpected and unusual non-outer sphere oxidation mechanism for this type of compound.

We gratefully acknowledge the financial support of the West Virginia University Department of Chemistry.

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Communication 9/05728E