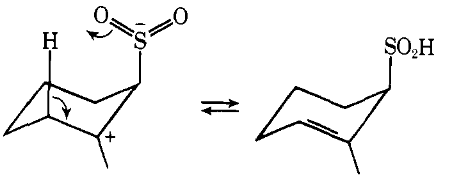
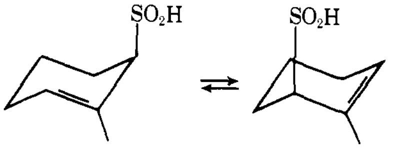
of β-pinene may be explained by a poor overlap of the allylic C–H bond with the empty p orbital in the corresponding ene transition state,[16-18] a consequence of the rigid bicyclic structure of this olefin. Furthermore, the observed large negative entropy of activation can be regarded as additional evidence for the well organized ene-type transition state.[16] While the transition state for the formation of the allylic sulfinic acid in the forward reaction would involve an abstraction of the proton from the secondary carbon atom (eq 4), in the reverse reaction the proton abstraction can take place from the primary (eq 6) or secondary carbon atom[19] (eq 8). That both reactions are indeed taking place and that the transition state for the abstraction of a secondary hydrogen (eq 8) is lower in energy than the one for the abstraction of a primary hydrogen (eq 6) are supported by the following transformations. Reaction of 2,2,6,6-tetradeuteriomethylenecyclohexane with sulfur dioxide at room temperature provided 1,2,6,6-tetradeuterio-1-methylcyclohexene in 3 h. Further reaction (24 h) resulted in statistical distribution of four deuteriums and two hydrogens among the six carbon-hydrogen bonds (eq 10). Finally, relatively fast racemization of p-menth-1-ene ([α] + 82.6°) in sulfur dioxide at room temperature (essentially completed in 4 h) provide additional evidence for the 1,3 rearrangement of the secondary allylic sulfinic acids[19] (eq 9).



(8)



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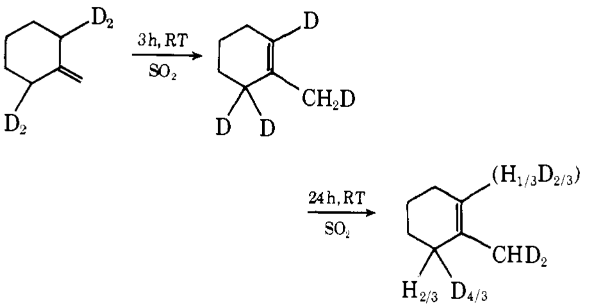

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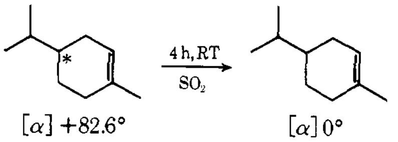

(11)

Evidently, in agreement with the preceeding experiment, the racemization did not involve the alternative higher energy pathway (i.e., eq 7–2 and 2–7).

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(19) The referee pointed out that the direct evidence for the presence of allylic sulfinic acid was not presented and that the racemization of p-menth-1-ene could also be explained if an allylic carbonium ion or free radical were formed in the course of reaction. While we do not have any evidence that the racemization (and hence isomerization) does involve either of the two possibilities, we have no evidence for the involvement of the allylic sulfinic acids either. Consequently, while the experimental facts are explained by the proposed mechanisms, the proposed mechanism should not be construed as a definite explanation of these transformations. Hopefully, further experiments, which will be published in a full paper, will elucidate this point more satisfactorily.

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Catalysis of Superoxide Dismutation by Iron–Ethylenediaminetetraacetic Acid Complexes. Mechanism of the Reaction and Evidence for the Direct Formation of an Iron(III)–Ethylenediaminetetraacetic Acid Peroxo Complex from the Reaction of Superoxide with Iron(II)–Ethylenediaminetetraacetic Acid

Sir:

There are several protein systems which catalyze the dismutation of superoxide ions (reaction 1)

$$2O_2^- + 2H^+ \rightarrow O_2 + H_2O_2 \qquad (1)$$

and these require either Cu, Fe, or Mn ions as cofactors.[1] While the mechanism of the Cu-containing protein has been shown to involve a diffusion controlled cyclic oxidation-reduction process,[2] the Fe- and Mn-containing[3] proteins have not been studied in the same detail and their mechanisms of action remain obscure. Low molecular weight complexes also catalyze superoxide dismutation: thus, a variety of copper(II) complexes,[4] manganese-quinolinol,[5] and iron-ethylenediaminetetraacetic acid (EDTA)[6] have been shown either directly or indirectly to act as catalysts of reaction 1. Since the same metal ions are involved in the protein systems these small complexes may serve as useful models for understanding the protein catalysts. In this communication we present direct confirmation that Fe-EDTA is a catalyst of superoxide dismutation and we proffer a tentative mechanism for this catalysis which involves the formation of a Fe^{III}-EDTA-peroxo complex from the direct reaction of O_2^- with Fe^{II}-EDTA.

The peroxo complex which we observe is the same as that first described by Cheng and Lott[7] in 1956 and subsequently characterized spectrally, thermodynamically, and kinetically by others; in particular, the work of Orhanovic and Wilkins,[8] Walling et al.,[9] and Ringbom et al.[10] can be cited. The color of the peroxo complex derives from an absorption band with a maximum at 520 nm having absorptivity of 530 M^{-1} cm^{-1}.

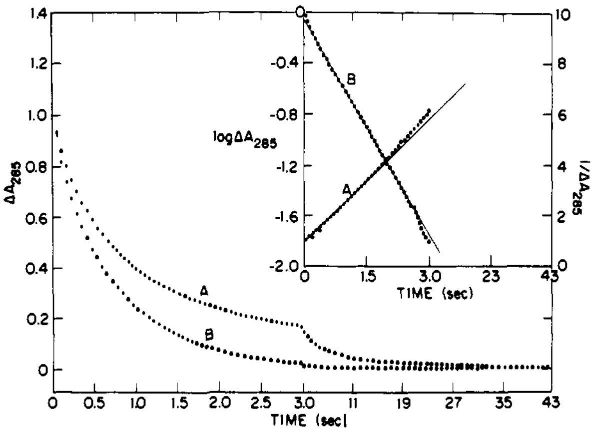

Figure 1. Stopped-flow kinetic traces for the dismutation of O^{2-} in the absence (A) and presence of 50 μM of Fe-EDTA (B). After mixing the initial concentration of O_2^- was ~1 mM. Other conditions were pH 9.7, 0.1 M carbonate buffer, 0.25 mM EDTA, 24 °C. The final reaction mixture was 3.8 (v/v) % Me_2SO (inset). Standard reciprocal and log plots for curves A and B, respectively.

According to the work of Walling et al.,[9] it is composed of a high spin ($S = \frac{5}{2}$) ferric ion, a fully ionized EDTA molecule, and the dianion of hydrogen peroxide, $[Fe^{III}\text{-EDTA-}O_2]^{3-}$, and the equilibrium between the peroxo complex, Fe^{III}-EDTA, and H_2O_2 is thought to be described by eq 2

$$Fe^{III}\text{-EDTA-}OH^{2-} + HO_2^- \rightleftarrows Fe^{III}\text{-EDTA-}O_2^{3-} + H_2O \quad (2)$$

The equilibrium constant for reaction 2 is independent of pH in the 8-12 range and has been found to have values in the range (7-10) × 10^3 M^{-1} at 23 °C[8] and ~1.4 × 10^4 M^{-1} at 13 °C.[3] Orhanovic and Wilkins[8] have established the rate law for formation of the peroxo complex to be first order in both Fe^{III}-EDTA and H_2O_2 over the pH range 9-11 and to follow the Arrhenius equation $k = 1.9 \times 10^7 \exp(-6700/RT)$. At 25 °C the rate constant was reported to be 250 M^{-1} s^{-1} when expressed in terms of free H_2O_2 concentration.

The kinetic experiments described herein involve the use of a stopped-flow spectrophotometer capable of mixing 25 parts of an aqueous solution with 1 part of a water-miscible organic solvent such as dimethyl sulfoxide (Me_2SO) within 6 ms and without significant optical artifacts.[11] When potassium superoxide is dissolved in Me_2SO to a concentration of ~20-30 mM, with the aid of a crown ether to sequester the potassium ion,[12] and this solution is mixed with an aqueous buffer, it is possible to observe the disappearance of superoxide by recording optical changes at 275 nm.[11] When mixed with Fe^{II}- and Fe^{III}-EDTA, absorbance changes are observed at 520 nm which are ascribed to the formation and decay of the purple-colored peroxo complex. Mixing with neat Me_2SO causes no spectral changes. A rapid scan attachment to the stopped-flow instrument, similar to that described by Kuwana and coworkers,[13] was used to examine the spectral properties of rapidly formed species.

The evidence that Fe-EDTA is a catalyst of superoxide dismutation is presented in Figure 1. In the absence of Fe-EDTA the kinetics of superoxide decay are second order,[11] while in the presence of 50 μM Fe-EDTA a plot of log A_{275} vs. time was linear over a large percent of the reaction.[14] Under the conditions described herein Fe-EDTA is estimated to be a factor of 1000-2000 less effective as a catalyst than bovine Zn/Cu superoxide dismutase. An oxygen electrode[15] system was used to show that the presence of catalytic amounts of Fe-EDTA did not alter the quantities of O_2 and H_2O_2 formed by reaction 1 during the time of our observations.

In our initial attempts to characterize the catalysis of reaction 1, we have found, when either Fe^{II}-EDTA or Fe^{III}-EDTA is mixed with a stoichiometric quantity of superoxide, that a rapid development of absorbance at 520 nm occurs (traces A and B of Figure 2) followed by a first-order decay process having a characteristic constant of ~1 s^{-1} under the conditions described in the legend to Figure 2. Spectral scans taken in the first few milliseconds of reaction show that this absorbance is associated with the peroxo complex formed in reaction 2 (Figure 3). It is evident from the data presented in Figure 2 that the development of 520-nm absorbance is complete within the dead time of the stopped-flow system when O_2^- is mixed with Fe^{II}-EDTA. Independent experiments have shown that mixing of stoichiometric amounts of O_2^- and Fe^{II}-EDTA leads to quantitative formation of $[Fe^{III}\text{-EDTA-}O_2]^{3-}$, and excess O_2^- does not in any way alter the amount of peroxo compound formed. The decay of peroxo complex is ascribed to a relaxation of reaction 5 (see below). Trace B of Figure 2 which resulted on mixing O_2^- and Fe^{III}-EDTA showed first an increase in the peroxo compound followed by its decomposition. This behavior is ascribed to the reduction of Fe^{III}-EDTA by O_2^- followed by the rapid reac-

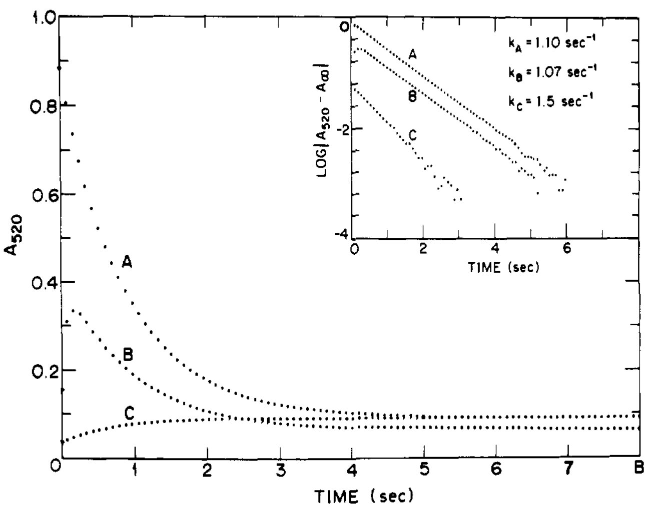

Figure 2. Stopped-flow traces describing the time course of the peroxo complex in the following reactions: A, 1.0 mM O_2^- and 0.87 Fe(II)-EDTA; B, 1.0 mM O_2^- and 0.87 mM Fe^{III}-EDTA; and C, 1.0 mM H_2O_2 and 0.87 mM Fe^{III}-EDTA. Other conditions were pH 10.0, 25 mM carbonate buffer, 1.0 mM EDTA (total), 22 °C, and the final reaction mixture was 3.8 (v/v) % Me_2SO.

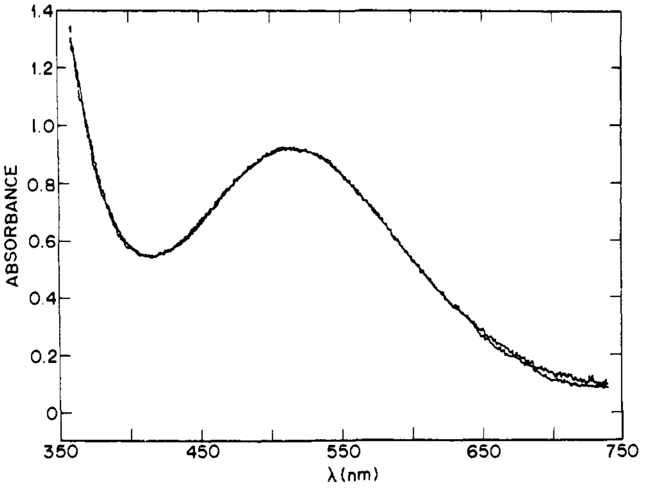

Figure 3. Spectrum of the peroxo complex formed from the reaction of 1 mM O_2^- with 0.87 mM Fe^{II}-EDTA and from the reaction of 300 mM H_2O_2 with 0.87 mM Fe^{III}-EDTA. Both spectra were recorded in 4-ms time periods using the rapid scan attachment to the stopped-flow instrument described in the text. The conditions were pH 10.0, 25 mM carbonate buffer, 1.0 mM EDTA (total), 22 °C, and the final reaction mixture in the first experiment was 3.8 (v/v) % Me_2SO.

tion of O_2^- with the resulting Fe^{II}-EDTA to form the peroxo complex which in turn decomposes to Fe^{III}-EDTA and H_2O_2. Finally, trace C of Figure 2 shows the rate and extent to which equimolar amounts of Fe^{III}-EDTA and H_2O_2 combine to form the peroxo complex. It should be noted that traces A and C converge as nearly equal amounts of total peroxide are present, while in experiment B the final absorbance value is less, consistent with the reduction of Fe^{III}-EDTA to Fe^{II}-EDTA by O_2^- to form O_2 resulting in a lower final concentration of H_2O_2. The results of Figure 2 are thus rationalized in terms of reactions 3-5.

$$\mathrm{Fe^{II}\text{-}EDTA} + O_2^- \rightarrow [\mathrm{Fe^{III}\text{-}EDTA\text{-}O_2}]^{3-} \quad (3)$$

$$\mathrm{Fe^{III}\text{-}EDTA} + O_2^- \rightarrow \mathrm{Fe^{II}\text{-}EDTA} + O_2 \quad (4)$$

$$[\mathrm{Fe^{III}\text{-}EDTA\text{-}O_2}]^{3-} \overset{H^+}{\rightleftarrows} \mathrm{Fe^{III}\text{-}EDTA} + H_2O_2 \quad (5)$$

From a knowledge of the dead time of the stopped-flow instrument we estimate $k_3 \gtrsim 10^7\ M^{-1}\ s^{-1}$. The values of the other rate constants were estimated from experiments similar to those described in Figure 2 in which the rate of formation and breakdown of the peroxo complex was observed; estimates are $k_4 \sim 6 \times 10^3\ M^{-1}\ s^{-1}$, $k_5 \sim 1\ s^{-1}$, and $k_{-5} \sim 500\ M^{-1}\ s^{-1}$. Equations 3-5 describe a minimal scheme for the catalytic dismutation of superoxide by Fe-EDTA which is qualitatively and quantitatively consistent with all of our observations and which involves the well-known and relatively stable iron-peroxo complex as an obligatory intermediate. The details of this general scheme and its putative relationship to the mechanism of the iron-superoxide dismutase[16] are currently under investigation.

Reaction 3 bears considerable analogy to the oxidation of animopolycarboxylate complexes of several bivalent transition ions by halogens as studied by Woodruff and Margerum.[17] These authors observed that the oxidation of Fe^{II}-EDTA by Br_2 and I_2 proceeded at a rate on the order of $10^7\ M^{-1}\ s^{-1}$, and they suggested that this was determined by the rate at which the oxidant could enter the inner coordination sphere of the complex. This is formally a one-electron oxidative addition reaction as surveyed by Halpern.[18] Reaction 4 appears to be a direct one-electron reduction of Fe^{III}-EDTA; it is not known whether the O_2^- must enter the first coordination sphere or if an outer-sphere reaction occurs.

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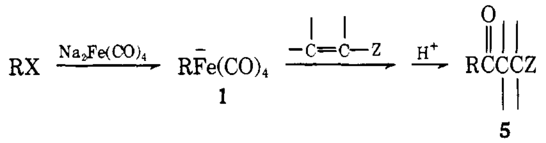
Hydroacylation of Michael Acceptors through Sequential Insertion Reactions of Organotetracarbonylferrates

Sir:

While reagents abound for the introduction of acyl anion equivalents via displacement and carbonyl addition reactions,[1] relatively few methods exist for the introduction of such units in a conjugate manner to Michael-type acceptors.[2] We now wish to report a new method for the direct hydroacylation of such acceptors.

We[3] and others[4] have previously shown that organotetracarbonylferrates, **1**, prepared in high yield through the alkylation of $Na_2Fe(CO)_4$ with ordinary halides and tosylates, undergo facile carbonyl insertion reactions in the presence of suitable ligands to give acylferrate complexes which in turn serve as acyl anion equivalents. We have also shown that in the presence of ethylene, **1** undergoes sequential migratory insertion reactions whereby the olefin is incorporated in the product.[5] We now find that **1** undergoes multiple insertion reactions with a variety of Michael-type acceptors (C=C—Z) giving β-ketoesters, ketones, and nitriles from common alkylating agents as shown in eq 1. Illustrations[6] of this transformation using simple alkyl halides are shown in Table I.



$$\mathrm{RX} \xrightarrow{\mathrm{Na_2Fe(CO)_4}} \underset{\mathbf{1}}{\mathrm{R\overset{-}{Fe}(CO)_4}} \xrightarrow{-\overset{|}{C}=\overset{|}{C}-Z} \xrightarrow{H^+} \underset{\mathbf{5}}{\mathrm{R\overset{O}{\overset{\|}{C}}\underset{|}{\overset{|}{C}}\underset{|}{\overset{|}{C}}Z}} \quad (1)$$

In the case of unsaturated esters and nitriles, the transformation may be performed in a single operation by the alkylation of $Na_2Fe(CO)_4$ in the presence of the desired acceptor followed by quenching with acetic acid.[6] The addition of unsaturated ketones, which are often incompatable with $Na_2Fe(CO)_4$ owing to polymerization or reduction, is deferred until formation of **1** is complete.

While anionic acyl nickel complexes derived from the addition of alkyllithium reagents to nickel tetracarbonyl have been reported to serve in a similar fashion as acyl donors with Michael acceptors,[2a] it is noteworthy that the potential synthetic utility of the presently reported method is enhanced by the use of the limiting and often more valuable component as the electrophile. Alkylations with $Na_2Fe(CO)_4$ have also been shown to have a wide tolerance for other functional groups.[4a]