It is noticeable from Table I that the hydrated form exists to the extent of as much as 81% at pD 1.30. This could very well retard the rate of decarboxylation of OPA when the partially dissociated or undissociated forms are the predominant species in solution. In this connection, it is interesting that a plot of the variation of k_1 with pD seems to resemble a plot of the percent of hydrate vs. pD more than it does the degree of dissociation of the diprotonated species (α_1) vs. pD. This interesting observation suggests that further quantitative studies of these effects should be carried out. This interpretation of the involvement of hydrate formation in rate retardation is in accord with the concept that the five-membered hydrogen-bonded chelate ring in Scheme I is the active intermediate in the decarboxylation process.

In summary, the findings in this work indicate: (1) the decarboxylation of β-keto acids that also contain α-keto acid functions must involve consideration of the hydrated form; (2) the NMR method provides an effective means of determination of the first-order rate constants of ketonization and evaluation of the equilibrium constant governing the keto-enol equilibrium. The use of NMR to sort out these microscopic rates and equilibria makes possible a more precise determination of rates of decarboxylation in these systems.

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References and Notes

(1) S. Ochoa, *J. Biol. Chem.*, **174**, 115 (1948).
(2) E. Gelles, *J. Chem. Soc.*, 4736 (1956).
(3) H. A. Krebs, *Biochem. J.*, **36**, 303 (1942).
(4) R. Steinberger and F. H. Westheimer, *J. Am. Chem. Soc.*, **71**, 4158 (1949); **73**, 429 (1951).
(5) K. J. Pedersen, *Acta Chem. Scand.*, **6**, 285 (1952).
(6) G. W. Kosicki and S. N. Lipovac, *Can. J. Chem.*, **42**, 403 (1964).
(7) R. J. Dummel, M. H. Berry, and E. Kun, *Mol. Pharmacol.*, **7**, 367 (1971).
(8) P. M. Nossal, *Aust. J. Exp. Biol. Med. Sci.*, **27**, 143, 312 (1949).
(9) E. Gelles and A. Salama, *J. Chem. Soc.*, 3689 (1958).
(10) J. F. Speck, *J. Biol. Chem.*, **178**, 315 (1949).
(11) M. Munakata, M. Matsui, M. Tabushi, and T. Shigematsu, *Bull. Chem. Soc. Jpn.*, **43**, 114 (1970).
(12) P. R. Bontchev and V. Michaylova, *J. Inorg. Nucl. Chem.*, **29**, 2945 (1967).
(13) L. O. Krampitz and C. H. Werkman, *Biochem. J.*, **35**, 595 (1941).
(14) K. H. Meyer, *Ber.*, **45**, 2843 (1912).
(15) A. Hautzsch, *Ber.*, **48**, 1407 (1915).
(16) E. Gelles and R. W. Hay, *J. Chem. Soc.*, 3673 (1957).
(17) C. I. Pogson and R. G. Wolfe, *Biochem. Biophys. Res. Commun.*, **46**, 1048 (1972).
(18) B. E. Banks, *J. Chem. Soc.*, 63, (1962).
(19) B. E. Banks, *J. Chem. Soc.*, 5043 (1961).
(20) G. W. Kosicki, *Can. J. Chem.*, **40**, 1280 (1962).
(21) W. D. Kumler, E. Kun, and J. N. Schoolery, *J. Org. Chem.*, **27**, 1165 (1962).
(22) G. A. Galegov, *Biokhimiya*, **26**, 635 (1961).
(23) P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, **64**, 188 (1960).
(24) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism", Wiley, New York, N.Y., 1965, p 166.
(25) I. Yamada in "Chemical Engineering Journal", Special Publication, Kagadu-Kogyozashi Publishing Corp., Dec 1967, p 87.
(26) E. H. Abbott and A. E. Martell, *J. Am. Chem. Soc.*, **91**, 6931 (1969).
(27) A. Schellenberger and G. Hubner, *Chem. Ber.*, **98**, 1938 (1965).

Stereospecific Aliphatic Hydroxylation by Iron–Hydrogen Peroxide. Evidence for a Stepwise Process[1]

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Abstract: Treatment of a mixture of cyclohexanol and ferrous perchlorate with hydrogen peroxide in acetonitrile led to a mixture of cyclohexanediols and cyclohexanone. In acetonitrile containing perchloric acid, *cis*-1,3-cyclohexanediol accounted for 71.9% of the diol produced. Under these conditions, hydrogen removal at C-3 occurred stereoselectively cis to the hydroxyl group. A mechanism for this aliphatic hydroxylation which involves an initial directed hydrogen abstraction ($k_H/k_D = 1.18$), free radical oxidation by Fe^{3+}, and stereoselective carbonium ion capture was proposed. Evidence for the stepwise nature of this process was derived from analysis of the Fe^{2+}/H_2O_2 oxidation of 7-hydroxynorbornane (**6**). Hydrogen abstraction from **6** was found to occur stereoselectively syn to the hydroxyl group and subsequent 2,6-hydride transfers result in a 1:1 ratio of syn,exo and anti,exo diols (**8** and **9**).

The oxidative transformations mediated by the biological oxidases have attracted much attention both for their mechanistic complexity and potential synthetic utility.[2] Of particular importance are the heme-iron mixed function oxidases such as cytochrome P-450, which are known to effect olefin epoxidation, aromatic hydroxylation, and hydroxylation of saturated carbon centers in a wide variety of organic compounds. Aliphatic hydroxylation is of interest since there exist at present no general, direct, synthetic methods for specific replacement of an unactivated carbon-bound hydrogen with an hydroxyl group. Indeed, biological fermentation is often the method of choice for such transformations.

These enzyme systems are known to activate molecular oxygen by sequential two-electron reduction to the formal oxidation state of hydrogen peroxide.[3] The subsequent processes, O–O and C–H bond scission, are extremely rapid and mechanistic details have remained obscure. If the extensive chemistry of iron–hydrogen peroxide systems is used for precedent and guidance, the closest historical "model" for aliphatic hydroxylation is Fenton's reagent,[4] a mixture of ferrous ion and hydrogen peroxide. According to the generally held mechanism first proposed by Haber and Weiss,[5] the Fenton's reagent oxidation of organic compounds proceeds by initial one-electron reduction of hydrogen peroxide to yield free hydroxyl radicals and subsequent hydrogen abstraction (Scheme I).

There has been understandable reluctance to embrace hydroxyl radical as the active oxygen species in biological oxi-

Table I. Product Distribution for Cyclohexanol Hydroxylation

Reaction conditions[a]	% cyclohexanediols						% yield		
	1,2-		1,3-		1,4-				
	Cis	Trans	Cis	Trans	Cis	Trans	Cyclohexanediols		Cyclohexanone
$Fe(ClO_4)_2$, $HClO_4$, CH_3CN	6.7	12.3	71.9	2.5	3.8	2.9	4.0[b]	(66)[c]	2.0[b]
$Fe(ClO_4)_2$, $HClO_4$, CH_3CN, 25°	4.8	8.8	70.1	5.1	3.7	7.1	4.2	(60)	2.8
$Fe(ClO_4)_3$, $HClO_4$, CH_3CN	11.9	9.1	66.5	3.5	3.0	5.6	2.9	(42)	4.1
$Fe(ClO_4)_2$, CH_3CN	1.5	2.1	30.5	19.5	20.4	25.6	2.4	(30)	7.6
$Fe(ClO_4)_3$, CH_3CN	2.1	4.1	31.7	15.3	21.6	25.4	1.9	(32)	4.1
$Cu(ClO_4)_2$, $HClO_4$, CH_3CN	0.25	4.0	30.4	26.4	17.8	21.2	2.0	(29)	5.0
$Fe(ClO_4)_2$, 1:1 CH_3CN–H_2O	5.2	14.3	37.0	15.0	17.5	11.0	6.1	(36)	10.9
$Fe(ClO_4)_2$, 9:1 H_2O–CH_3CN[d]	3.3	9.0	5.6	18.3	50.0	13.8	5.3	(35)	9.7
$Fe(BF_4)_2$, HBF_4, CH_3CN[e]	7.3	14.7	67.7	3.0	3.6	3.7	4.3	(49)	4.4

[a] See Experimental Section. [b] Absolute yield based on starting cyclohexanol. [c] Yield based on cyclohexanol consumed. [d] Data due to G. A. McClusky. [e] Data due to W. W. Swanson.

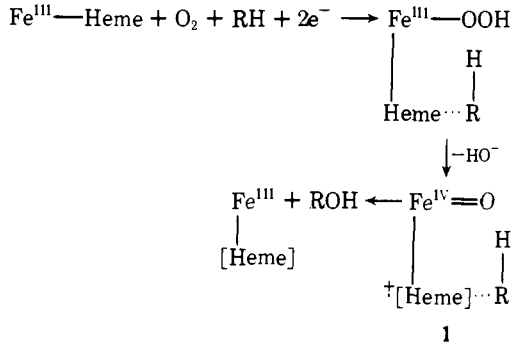
Scheme I

$$Fe^{2+} + H_2O_2 + H^+ \longrightarrow Fe^{3+} + H_2O + HO\cdot$$
$$RH + \cdot OH \longrightarrow R\cdot + H_2O$$
$$R\cdot + Fe^{3+} \longrightarrow Fe^{2+} + R^+$$
$$R^+ + H_2O \longrightarrow ROH + H^+$$

dases, since these reactions proceed with remarkable regioselectivity and stereospecificity. Further, oxidation of free radicals by iron(III), a requisite second step, is known to be selective in water and dimeric products are often obtained from primary and secondary radicals.[6]

More recently evidence has emerged from biological studies that heme-iron(III) complexes are readily oxidized to higher oxidation states and that a two-electron oxidation of chloroperoxidase, a heme-iron enzyme closely related to cytochrome P-450, leads to an iron(IV) oxo species-heme radical cation.[7] In addition, treatment of cytochrome P-450 with alkyl hydroperoxides, also two-electron oxidants, has been shown to effect a single turnover of the enzyme without additional oxygen or electrons.[8] This information strongly suggests that higher oxidation state iron species are important to the function of heme-iron hydroxylases and leads to the consideration of mechanisms such as Scheme II for the oxidative cycle. High

Scheme II



1

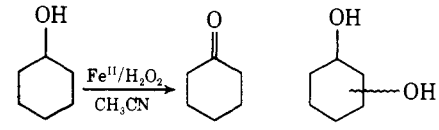
selectivity in the hydrogen abstraction step can be attributed in such a scheme to the bound nature of the active oxygen species (**1**).

The formation of a ferryl ion intermediate (Fe^{IV}=O) in nonenzymatic iron-peroxide systems was first proposed by Bray and Gorin[9] and several other suggestions of similar species have appeared.[10] Further, the possible competition of hydroxyl radical and ferryl ion paths for the Fenton's reagent mechanism have been discussed in terms of the equilibrium[11]

$$Fe^{III} + HO\cdot \rightleftarrows Fe^{IV}OH \rightleftarrows Fe^{IV}{=}O + H^+ \qquad (1)$$

We report here a study of the hydroxylation of cyclohexanol and 7-norborneol mediated by ferrous ion-hydrogen peroxide in acetonitrile. The observed regioselectivities and stereoselectivities support the formation of a ferryl ion-like intermediate in this nonaqueous system.[12]

Cyclohexanol Oxidation. Slow addition of H_2O_2 to a solution of cyclohexanol and ferrous perchlorate led to the formation of cyclohexanone and a complete family of cyclohexanediols (eq 2). Ketone-diol ratios and diol isomer distributions were



(2)

found to be sensitive to reaction conditions (Table I).

Specifically, high regioselectivity for oxidation at C-3 was observed in acetonitrile containing *either* ferric or ferrous ions and perchloric acid. This regiospecificity was altered upon addition of water to the medium, leading to predominant C-4 oxidation in 1:9 acetonitrile-water. Removal of perchloric acid and substitution of copper for iron also diminished the C-3 regioselectivity.

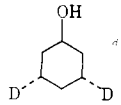
Closer examination of the data reveals that C-2 is somewhat more reactive than C-4 in acetonitrile containing perchloric acid with either ferrous ion or ferric ion. Thus, about 90% of the observed hydroxylation is found to occur at positions available to an oxidant chemically bound to the hydroxyl group, suggesting a directive effect. In contrast, the addition of water, omission of acid, and substitution of copper for iron all lead to preferential oxidation remote to the hydroxyl group. This latter mode of reactivity, apparently lacking the directive effect noted above, finds abundant precedent in hydrogen abstraction reactions by electrophilic species and can readily be attributed to a polar effect.[13]

Stereochemistry and Isotope Effect. To examine the stereochemistry of the hydrogen abstraction step, *trans*-3-*trans*-5-cyclohexanol-d_2 (**2**) was prepared by treatment of phloroglucitol ditosylate with lithium aluminum deuteride according to published procedures.[14] The deuterium content of **2** was found to be 2.0 by comparing its mass spectrum to that of cyclohexanol (Table II). Less obvious, however, was the extent to which the deuterium had been incorporated trans to the hydroxyl group.

The Eu(fod)$_3$-shifted ^{1}H NMR spectrum of **2** was found to be sufficiently well resolved to allow unambiguous assignment of all resonances.[15] Integration of this spectrum (Table III) leads to the conclusion that the lithium aluminum deuteride reduction which forms **2** proceeds with 88.5% trans deuterium incorporation.

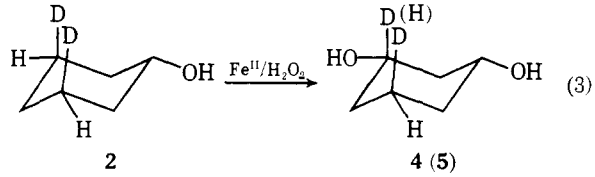
Oxidation of **2** with Fe^{2+}/H_2O_2 in acetonitrile again gave *cis*-1,3-cyclohexanediol (**3**) as the major hydroxylation

Table II. Mass Spectra of Cyclohexanols and Cyclohexanone (70 eV)

Compd	m/e						
	112	111	110	109	108	107	106
	7.4	100	4.7	17.2	15.3		
					52.6	10.5	14.5
	103	102	101	100	99	98	97
			8.0	100	31	8.5	3.0
 (2)	7.2	100	30.0	13.0	2.0		
				97.6	41.8	30.2	
						100	

[a] Cyclohexanol isolated from Fe^{2+}/H_2O_2 oxidation of cyclohexane–cyclohexane-d_{12} (1.05:1). Intensity assigned to cyclohexanol-d_{11} = 31.1, that assigned to cyclohexanol = 38.5 k_H/k_D = 1.18. [b] Cyclohexanone isolated from oxidation of cyclohexane–cyclohexane-d_{12}. Intensity assigned to cyclohexanone-d_{10} = 20, that assigned to cyclohexanone = 38. [c] Cyclohexanol reference. [d] *trans*-3-*trans*-5-Cyclohexanol-d_2 (2).

product. Analysis of the mass spectrum of **3** showed that the product was a 3:1 mixture of d_2 and d_1 diols, **4** and **5**, respectively (Table IV). Clearly there is a preference for cis-hydrogen abstraction at C-3. This preference could be due either to a large intrinsic stereoselectivity or to a substantial isotope effect.



2 4 (5) (3)

The kinetic isotope effect for cyclohexane hydroxylation was determined by examination of the deuterium content of the products of a competitive oxidation of cyclohexane and cyclohexane-d_{12} (Table II). The value of k_H/k_D was observed to be 1.18 ± 0.01.[16] Since oxidation of C-3 in cyclohexanol represents a process very similar to cyclohexane hydroxylation, it is assumed that the isotope effect will be similar, although the value 1.18 appears to be quite low.

The relative reactivity of the cis and trans hydrogens at C-3 are related to the isotope effect and the known stereochemical integrity of **2** according to the equation

$$\frac{3\text{-}d_2}{3\text{-}d_1} = 3.0 = \frac{0.885k_{cis} + 0.115k_{trans}}{(k_D/k_H)(0.115k_{cis} + 0.885k_{trans})} \quad (4)$$

Solution of eq 4 leads to k_{cis}/k_{trans} = 3.6, indicative of 78% cis-hydrogen abstraction at C-3.

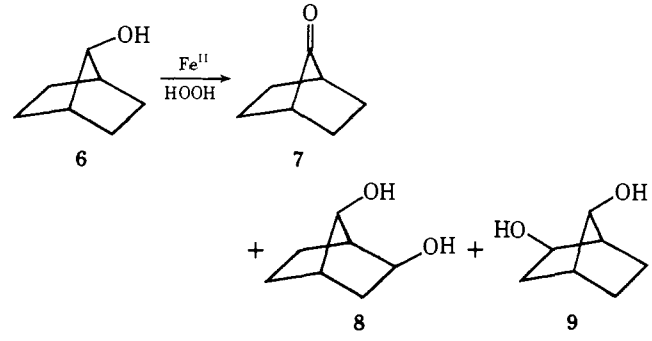
Oxidation of 7-Hydroxynorbornane. Further insight into the nature of this Fe^{2+}/H_2O_2-mediated hydroxylation was obtained by the oxidation of 7-hydroxynorbornane (**6**). Addition of an acetonitrile solution of 30% hydrogen peroxide to **6** and ferrous perchlorate in acetonitrile led to the formation of 7-norbornanone (**7**), *exo,syn*-2,7-dihydroxynorbornane (**8**) and *exo,anti*-2,7-dihydroxynorbornane (**9**) (Scheme III) in a ratio of 1:5:5.

Table III. Assignments for Absorptions in Eu(fod)$_3$-Shifted ^{1}H NMR Spectrum of *trans*-3-*trans*-5-Cyclohexanol-d_2 (2)

Chemical shift, δ	ΔEu	Multiplicity	Integration[a]	Assignment
3.3	−4.8	Doublets of triplets	1.01	trans-H_4
3.8	−5.8	Doublet	1.24	cis-H_4, trans-H_3
4.5	−6.9	Singlet	1.79	cis-H_3
7.68	−13.8	Doublet	2.05	trans-H_2
8.16	−16.1	Triplet	1.97	cis-H_2
13.22	−22.5	Broad multiplet	0.93	H_1

[a] Normalized to nine protons.

Scheme III



6 7 8 9

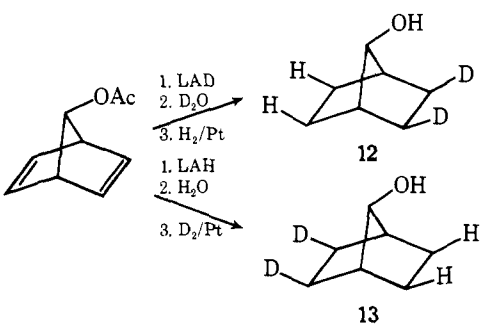
Superficially, the formation of equal amounts of **8** and **9** would appear to indicate indiscriminate oxidation of the syn

Table IV. Mass Spectra of *cis*-1,3-Cyclohexanediols (3) (20 eV)

Compound	m/e					
	119	118	117	116	115	114
3-d_0			7.2	100	4.3	5.3
3-d_2	8.0	100	36.9	10.7		

and anti bridges and the absence of any other diol isomers, particularly the 2,3 isomer, would appear to mitigate against carbonium ion intermediates. Typical 1,2-alkyl shifts of an intermediate norbornyl carbonium ion would be expected to produce rearranged products. Closer examination reveals that 2,6-hydride transfers in intermediate 7-hydroxy-2-norbornyl carbonium ions could submerge any regioselectivity for syn-hydrogen abstraction. An obvious clue that 2,6-hydrogen migrations had occurred emerged when norbornylene was oxidized with performic acid in acetonitrile. A 1:1 mixture of exo,syn and exo,anti diols again was obtained, suggesting that these products represent an equilibrium mixture.

The occurrence of rapid 2,6-hydride shifts in the Fe^{2+}/H_2O_2 oxidation of **6** was confirmed by analysis of the products of two 7-hydroxynornanes (**12** and **13**) with complementary deuterium labels.[17]



13

Mass spectral data (Table V) indicated deuterium incorporations in **12** and **13** to be in excess of 97%. Subsequent hydroxylation of **12** and **13** again gave the syn and anti diols **8** and **9**. The mass spectra of these products are compared in Table V. As expected, parent ions were extremely weak but parent–H_2O ions gave a prominent spectral pattern and these peaks were used to determine the deuterium content of the product.[18]

Inspection of the mass spectra of the diols **8** and **9** derived from **12** indicated similar deuterium contents for *both* stereoisomers, with most of the product having lost *one* deuterium atom upon hydroxylation. Diols **8** and **9** derived from **13** also have similar deuterium content, but significantly, most of the deuterium has been *retained* in the course of the oxidation. Thus, significant quantities of **9**-d_2 are formed from **13** while **9**-d_1 is derived from **12**.

The only reasonable explanation for this result is hydride migration subsequent to hydrogen abstraction (Scheme IV). Further, the similarity in deuterium content of the stereoisomers **8** and **9** indicate that the 2,6-hydride shifts are rapid with respect to diol formation, as would be expected if a bona fide 2-norbornyl carbonium ion is an intermediate in the reaction.

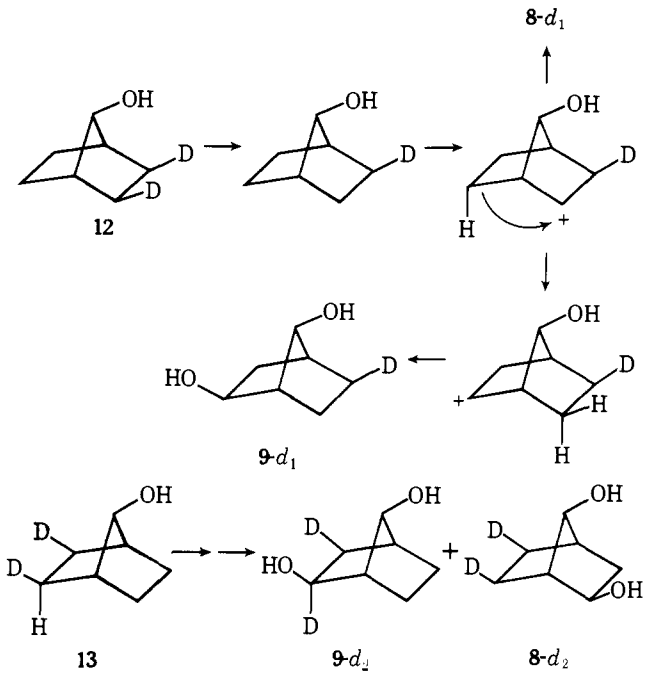
A more quantitative and illuminating interpretation of these data can be made by employing the known mass spectral behavior of **8** and **9**.[18] Specifically, the M − H_2O ion in the mass spectrum of **8** has been found to result from loss of the elements of water from hydroxyl groups, and the M − H_2O ions in Table V for **8** accurately reflect deuterium content of the parent diol. Less selective loss of H_2O has been observed for **9**. Thus, the loss of carbon-bound hydrogen in the mass spectral fragmentation of **9** derived from **12** and **13** would account for the small

Table V. Mass Spectra of Norbornyl Derivatives (Relative Intensities at 16 eV)

m/e	6	12	13	8	9	8 from 12	9 from 12	8 from 13	9 from 13	8 from 14
115		8.37	8.26							
114		100	100							
113	8.21	13.7	17.2			5.2	5.7	11.0	8.5	8.8
112	100		7.3			46.1	52.6	100	100	100
111	14.8			7.8	9.1	100	100	32.6	47.7	19.0
110				100	100	23.8	10.2	9.2	11.5	3.7
109				11.8	11.7	3.3	1.2	2.0	1.5	0.8
%D_2[a]		≥99	97			33	≥36	88	≥74	95[b]
%D_1[a]			3			67	≤64	12	≤26	5[b]
%D_0	100			100	100					

[a] Determined by assuming that observed spectra are a composite of d_1 and d_2 compounds. [b] Determined from the mass spectrum of the corresponding diacetate (**14**); *m/e* (relative intensity) 215 (16), 214 (100), 213 (6.6); undeuterated **14** had a negligible (1%) peak at *m/e* 211 (m − 1).

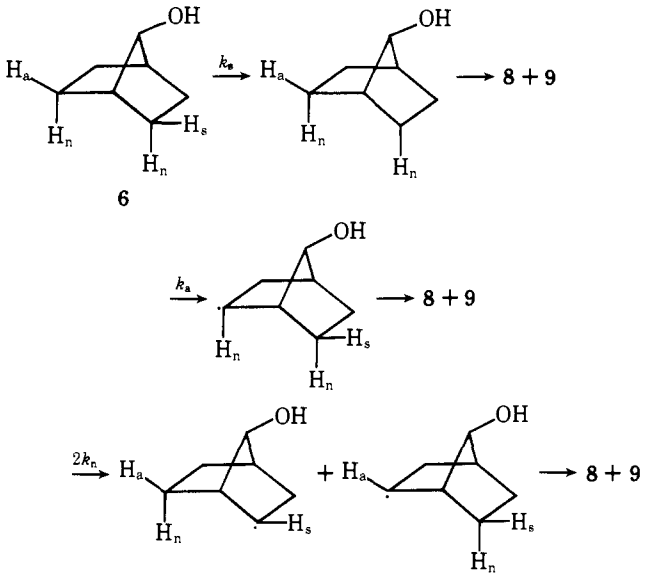
Scheme IV



but significant difference in the *apparent* deuterium content of syn and anti isomers.

This information allows the construction of a complete reactivity profile for the Fe^{2+}/H_2O_2 hydroxylation of **6.** If it is assumed that the only reasonable path to **8** and **9** is initial hydrogen abstraction at C-2 or C-6 in **6,** three mechanistically discreet hydrogen-abstraction processes must be considered, abstraction of the syn,exo hydrogen (k_s), the anti,exo hydrogen (k_a), and the endo hydrogens (k_n) (Scheme V). Thus, from the

Scheme V



deuterium content of **8** from **12,** one obtains eq 5 and 6 and, similarly from the isotopic content of **8** from **13,** eq 7 and 8 can be derived.

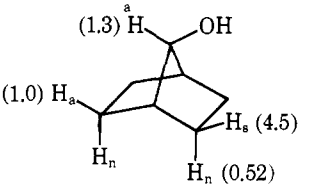
$$\frac{k_s(k_D/k_H)}{2k_n + k_a} = \frac{0.672}{0.275} = 2.05 \quad (5)$$

$$k_s = 2.05(2k_n + k_a)(k_H/k_D) \quad (6)$$

$$\frac{k_a(k_D/k_H)}{k_s + 2k_n} = \frac{0.119}{0.881} = 0.135 \quad (7)$$

$$2k_n = \frac{k_a(k_D/k_H)}{0.135} - k_s \quad (8)$$

From substitution of eq 8 into eq 5 with an isotope effect assumed to be in the range of that obtained for cyclohexane, $k_H/k_D = 1.2$, the relative reactivity of the exo,syn and exo,anti hydrogens (k_s/k_a) is found to be 5.1. Similarly, k_n/k_a is found to be 0.54. It should be noted that the ratio k_s/k_a calculated in this way is relatively insensitive to the isotope effect. For example, an isotope effect of 2.0, certainly outside the limits of experimental error, gives $k_s/k_a = 3.8$, still an appreciable directive effect. We conclude, therefore, that the Fe^{2+}/H_2O_2

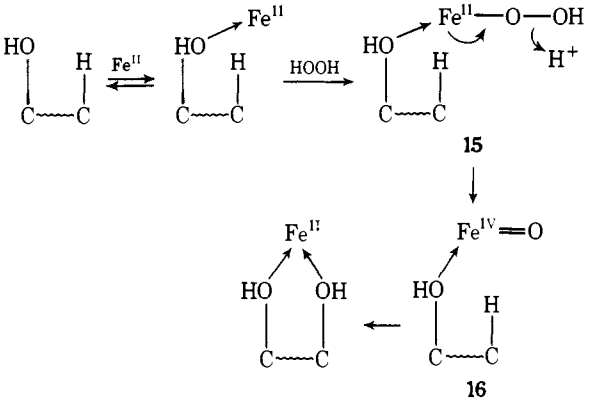


[a] Relative reactivity (per hydrogen) toward Fe^{2+}/H_2O_2 in CH_3CN.

induced hydroxylation of **6** proceeds predominantly by initial stereoselective syn,exo-hydrogen abstraction reflecting the directive effect ($k_s/k_a = 5.1$) of the proximate hydroxyl group. Further, the regioselectivity observed here is in reasonable quantitative agreement with that observed for cyclohexanol. Subsequent oxidation of the carbon radical by ferric ion gives the rapidly equilibrating 7-hydroxy-2-norbornyl carbonium ions **10** and **11.** In contrast to cyclohexanol, these carbonium ions are then captured to give the 1:1 mixture of product diols **8** and **9,** perhaps reflecting the greater stability of the 2-norbornyl cation.

Mechanism. The regioselectivity observed for hydrogen abstraction from cyclohexanol and 7-hydroxynorbornane clearly indicates a directive role of the hydroxyl group. The most reasonable explanation of this behavior is metal-alcohol complexation, which is expected to be appreciable in acetonitrile. Indeed, obvious spectral changes observed upon addition of cyclohexanol to acetonitrile solutions of ferrous or ferric perchlorate indicate appreciable metal-alcohol interaction in this medium.[19] The nature of this directive effect can be considered economically in terms of two mechanistic extremes: (a) a *propinquity* effect in which a free hydroxyl radical is generated close to the hydroxyl function as a result of metal-alcohol complexation, and (b) formation of a reactive ferryl ion species (Fe^{IV}=O) by two-electron oxidation of ferrous ion and subsequent methylene hydroxylation by an intracomplex reaction (Scheme VI).

Scheme VI

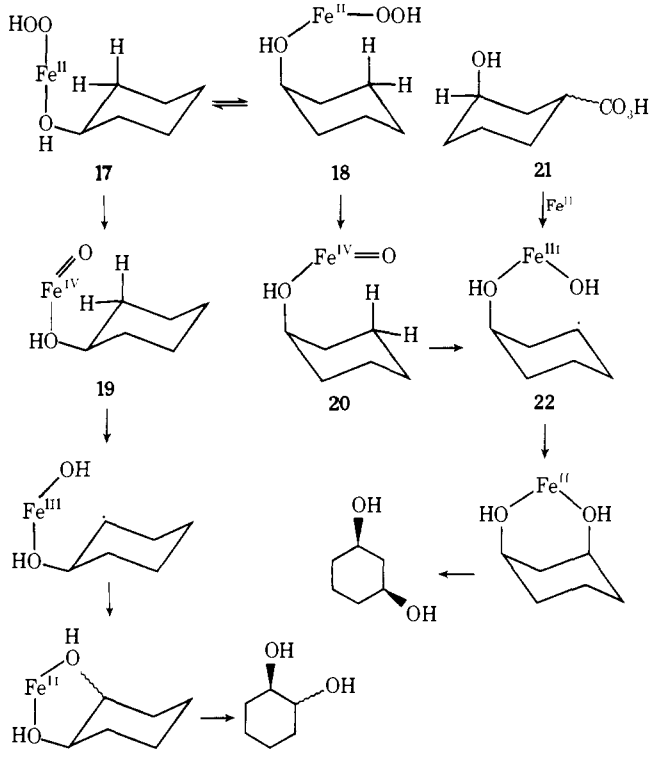


Several arguments favor Scheme VI. There is ample evidence for the oxidation of Fe(II) and Fe(III) salts by hydrogen

peroxide to give Fe(VI) in alkaline aqueous solution,[20] and since hydrogen peroxide is a two-electron oxidant, intermediate Fe(IV) and Fe(V) states are implicated in these reactions.[21] Stable salts of Fe(IV) have been isolated recently by electrochemical oxidation well below the oxidation potential of water, and ozonization of ferrous ion has been proposed to afford transient Fe(IV) species in water.[22] The decomposition of a ferrous ion–alcohol–hydrogen peroxide complex (**15**) by formal loss of water to give **16** would be analogous to ferrous ion ozonization. The observed regioselectivities for cyclohexanol and 7-hydroxynorbornane parallel the anticipated chemical availability of nearby hydrogen toward hydrogen abstraction by the iron–oxo intermediate **16** through a cyclic transition state reminiscent of the Barton reaction.[23]

For the hydroxylation of cyclohexanol two stereoisomeric complexes representing the equatorial and axial conformers of the alcohol would be expected (Scheme VII). Only the cis

Scheme VII



hydrogen at C-3 would be accessible to the bound ferryl ion and accordingly predominant cis-hydrogen abstraction is observed there. We have recently shown that metal complexation does not appreciably alter the equatorial–axial equilibrium for cyclohexanol and approximately 30% of this less stable complex (**18**) would be expected in solution.[15]

The higher relative reactivity of C-3 vis-a-vis C-2 is more difficult to explain, but may be due either to a polar effect or to a more favorable transition-state geometry in the axial complex **20**. CPK space filling models of **19** and **20** indicate approach of the iron-bound oxygen to the side of the C–H bond at C-2, but end-on approach occurs at C-3. Thus, in further analogy with the Barton reaction, the cyclic hydrogen abstraction observed here appears to favor a collinear O···H···C geometry.[24-26]

Another important conclusion derived from the deuterated cyclohexanol oxidation was that the stereoselectivity for hydrogen abstraction at C-3 (78% cis) is *less* than the observed stereoselectivity for C-3 diol formation (96%). Accordingly, some radicals generated by trans-C-3 hydrogen abstraction, presumably from a nondirected component of this reaction, lead to cis diol formation. This result suggests that if hydrogen abstraction is the intial step in this process, 3-hydroxycyclohexyl radicals generated by an independent route would lead to stereoselective radical oxidation by ferric ion, until recently an unprecedented process. Indeed, we have found that the *reductive decarboxylation* of *cis*- and *trans*-3-hydroxycyclohexanepercarboxylic acid (**21**) gave rise to the same mixture of cis and trans diols (85:15, respectively) with a pronounced preference for cis diol formation.[27]

Accordingly, 3-hydroxycyclohexyl radicals (**22**), generated by decarboxylation, do undergo a stereoselective oxidation in accord with their intermediacy in Scheme VII. Subsequent electron transfer to give carbonium ions is supported both by the loss of stereospecificity in more aqueous media and by the clear indication of 2,6-hydride transfers observed during the hydroxylation of 7-hydroxynorbornane.[28]

These findings have important implications with regard to the mechanism of biological hydroxylation. Mechanisms have been proposed which involve an "oxene" insertion process for these enzymic reactions largely to explain the net retention which is observed. As we have shown here, however, oxidation with net retention can also be the result of two successive stereoselective processes, hydrogen abstraction and radical oxidation, both of which now find precedent in simple, nonenzymic iron chemistry.

Experimental Section

General. Analytical GLC work was done on a Varian Aerograph gas chromatograph Model 1200, equipped with a flame-ionization detector. Preparative VPC was done on a Varian Aerograph 90-P gas chromatograph. Infrared spectra were recorded on a Perkin-Elmer 457 model and NMR spectra were taken on a Varian Associates T-60 or T-60A spectrometer or a Joel PS-100 NMR spectrometer. Mass spectra were run on an Associated Electrical Industries MS-902 spectrometer. Melting points are uncorrected as recorded with a Mel-Temp melting-point apparatus.

Cyclohexanol was treated with $NaBH_4$ and distilled, and acetonitrile, unless reagent grade, was distilled over P_2O_5. Commercial H_2O_2 was used without further treatment. Ferrous, ferric, and cupric perchlorates were used as received from the G. Frederick Smith Chemical Co. (reagent grade). All other common materials were reagent grade. Where necessary, hydrogen peroxide was titrated with permanganate and ferrous perchlorate was titrated with potassium dichromate using sodium diphenylaminesulfonate as the indicator.

Oxidation of Cyclohexanol by Metal–Hydrogen Peroxide. A mixture of 0.69 g (6.9×10^{-3} mol) of cyclohexanol, an equivalent amount of metal perchlorate or fluoroborate as indicated in Table I, and 0.6 ml of 70% perchloric or 2 ml of 50% fluoroboric acid in 50 ml of acetonitrile was placed in a jacketed reaction vessel and purged with nitrogen for 20–30 min. The mixture was cooled to −18° with a refrigerated circulator bath. Hydrogen peroxide (3.68 equiv, 3.0 g of 30%) was dissolved in 10 ml of acetonitrile and purged with nitrogen for 20–30 min. The hydrogen peroxide solution was added to the metal–alcohol solution by slow constant addition over 30 min with continuous stirring and nitrogen purging. The product distribution was independent of the rate of peroxide addition. After stirring for about 0.5 h after complete addition of the peroxide, 1 ml of 15% Na_2SO_3 was added to insure complete decomposition of hydrogen peroxide. Metal salts were precipitated by the addition of 2 ml of 50% sodium hydroxide. Two phases were present at this time. Potassium carbonate was added until the lower aqueous phase was saturated, resulting in a thick sludge. The clear acetonitrile layer was filtered through Whatman No. 3 filter paper and the sludge was washed several times with CH_3CN. The combined acetonitrile portions were dried over K_2CO_3–Na_2SO_4. GLC analysis for cyclohexanol and cyclohexanone were not reliable prior to this point. For analysis of the diol products, the above dilute solution was concentrated under vacuum, dissolved in 50 ml of 5:1 acetic anhydride–pyridine and refluxed for 1 h. The reaction mixture was poured onto ice and extracted with three 50-ml portions of ether. The combined ether extracts were washed with 10% HCl, 5% sodium bicarbonate, and saturated NaCl. Quantitative analysis for cyclohexyl diacetates was performed on this solution.

The amounts of alcohol and ketone were determined by glc analysis

on a 10 ft, 20% DEGS column at 100 °C, adding 1-phenylethanol as the internal standard to the acetonitrile solution after removal of metal salts with NaOH. For the cyclohexyl diacetates the conditions were 80–160 °C at 6 °C/min on the same column; retention times: cis-1,2 (24 min), trans-1,2 (25.6 min), trans-1,3 (29.5), trans-1,4 (32), cis-1,3 and cis-1,4 (34.3). The yields of diols could be determined prior to acetylation on an OV-225 at 100 °C.

Cyclohexanols and cyclohexenyl acetates were shown to be absent by GLC comparison of reaction mixtures to authentic materials.

Ditosylate of *cis*-Phloroglucitol. Anhydrous phloroglucitol (10 g, 0.0757 mol) was dissolved in 150 ml of anhydrous pyridine at 0°. Freshly purified tosyl chloride (28.85 g, 0.148 mol) in 80 ml of dry pyridine was added slowly to the above with stirring. After chilling in the refrigerator overnight, the precipitated pyridine hydrochloride was removed by filtration and the filtrate was poured onto 1 l. of ice and water. The gummy mass which formed was extracted with three 500-ml portions of ether. The combined ether extracts were washed with cold 10% HCl and water and dried over Na_2SO_4. Evaporation of the ether gave 24 g of crude product, which was recrystallized from $CHCl_3$–pentane and dried in vacuo: NMR ($CDCl_3$) δ 7.52 (d of d, 8 H), 4.37 (br s, δ 4.7–4.0, 2 H), 3.42 (br s, δ 3.9–3.0, 1 H), 2.67 (s, 6 H), 2.6–1.8 (m, 4 H), 1.5 (t, 3 H, J = 12 Hz).

***trans*-3-*trans*-5-Cyclohexanol-d_2 (2).** The ditosylate of *cis*-phloroglucitol (3.0 g, 7.35 mmol) was added to 0.626 g of $LiAlD_4$ (14.7 mmol) in 50 ml of dry ether and stirred at room temperature for 21.5 h. The mixture was quenched by the addition of saturated Na_2SO_4. The ether layer was separated and dried over Na_2SO_4. The product was purified by preparative GLC (10 ft, 20% DEGS at 85 °C; yield: 0.1165 g, 16%).

Determination of the Stereospecificity of Hydrogen Abstraction at C-3. The above dideuteriocyclohexanol (**2**, 0.0980 g), 0.06 ml of 70% $HClO_4$, and 0.381 g of ferrous perchlorate hexahydrate were dissolved in 5 ml of acetonitrile. While under N_2, 0.08 ml of 30% H_2O_2 in 2 ml of CH_3CN was added to the above at −14 °C over 13 min. Workup and acetylation were performed as described earlier and the *cis*-1,3-cyclohexane diacetate was isolated and purified by preparative VPC (5 ft, 20% DEGS, 150 °C). The sample weighed 5.0 mg. This product was reduced with $LiAlH_4$ in ether and the product again was isolated and purified by VPC (3% OV-225, 120 °C) and submitted for mass spectral analysis (see Table IV).

Oxidation of Cyclohexane. Determination of the Deuterium Isotope Effect. In 60 ml of acetonitrile was placed 2.015 g of $Fe(ClO_4)_2{\cdot}6H_2O$, 0.5321 g (6.33 mmol) of cyclohexane, 0.5775 g (6.02 mmol) of cyclohexane-d_{12} (99.0%), and 0.5 ml of 70% $HClO_4$. The entire mixture was cooled to −11 °C and purged with nitrogen. A solution of 0.8 ml of 30% H_2O_2 in 5 ml of CH_3CN was then added over a period of 35 min, and the reaction was quenched immediately by the addition of Na_2SO_3. The yield of cyclohexanol was 0.045 g and the yield of cyclohexanone was 0.0064 g, as determined by GLC. The deuterium content of the products was determined by mass spectrometry (Table II).

Oxidation of 7-Hydroxynorbornane. The procedure was similar to that used with cyclohexanol. A solution of 0.48 g of 7-hydroxynorbornane, 1.9 g of ferrous perchlorate hexahydrate, and 0.1 ml of 70% perchloric acid in 20 ml of acetonitrile was purged with nitrogen and cooled to −16 °C. A solution of 0.5 ml of 30% H_2O_2 in 2.5 ml of CH_3CN was then added over 35 min. Stirring was continued for 1 h. Yields of dihydroxynorbornanes were determined by GLC (10 ft, 20% DEGS, 110–160 °C at 6 °C/min). The yields of **7**, **8**, and **9** were 10, 45, and 42%, respectively; conversion was 6.7%.

***exo,exo*-2,3-Dideuterio-*syn*-7-hydroxynorbornane.** A modification of the procedure described by Franzus and Snyder[22] resulted in a somewhat better yield. 7-Acetoxynorbornadiene (1.46 g) was dissolved in 20 ml of dry ether (freshly distilled from $LiAlH_4$) and added to a solution of 0.738 g of $LiAlD_4$ in 30 ml of dry ether over a period of 20 min. The mixture was stirred overnight at room temperature under nitrogen. Unreacted $LiAlD_4$ was decomposed by the addition of 3 ml of D_2O saturated with anhydrous Na_2SO_4, followed by 2 ml of D_2O. A small sample of the product, *exo,exo*-5,6-dideuterio-*anti*-7-hydroxynorbornene, was isolated by preparative VPC from the concentrated ether solution. Its NMR spectrum was identical with that reported:[22] NMR ($CDCl_3$) δ 5.92 (t, 2), 3.55 (br s, 1), 2.5 (q, 2), 2.09 (s, 1), 1.0 (d, 2). The product was then combined with 15 ml of ethanol and 0.055 g of Pd/C, and hydrogenated at atmospheric pressure and room temperature. The 7-hydroxynorbornane obtained was sublimed twice to give 0.474 g (43% yield).

***exo,exo*-5,6-Dideuterio-*exo*-2-*syn*-7-dihydroxynorbornane (14).** *exo*-5-*anti*-7-Diacetoxynorbornene[29] (0.41 g) was dissolved in 10 ml of absolute ethanol and 0.065 g of 5% palladium on carbon was added. The mixture took up 42 cm^3 of D_2 after 20 min at room temperature and atmospheric pressure (0.96 equiv). A small sample of crude *exo,exo*-dideuterio-*exo*-2-*syn*-7-diacetoxynorbornane was purified by GLC (5 ft DEGS at 150 °C) and analyzed for deuterium content by mass spectrometry (Table V). Three-quarters of the crude diacetate was dissolved in 2 ml of ether and added dropwise to a mixture of 0.25 g of $LiAlH_4$ in 20 ml of ether at 0°. After 15 min, unreacted $LiAlH_4$ was decomposed with aqueous Na_2SO_4. After recrystallization from ether, 0.13 g (69%) of *exo*-2-*syn*-7-dihydroxynorbornane (**14**) was obtained. The presence of two exo-deuterium atoms was evident by the appearance of a two-proton *singlet* at δ 1.0 in the NMR spectrum for the endo hydrogens at C-5 and C-6.

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References and Notes

(1) Abstracted in part from the Ph. D. thesis of M. Van Der Puy, The University of Michigan, 1975.
(2) (a) J. A. Peterson, Y. Ishimura, J. Baron, and R. W. Estabrook, *Oxidases Relat. Redox Syst., Proc. Int. Symp., 2d*, 568 (1973); (b) T. A. Van der Hoeven and M. J. Coon, *FEBS Lett.*, **38**, 337 (1974); (c) M. J. Coon, T. A. Van der Hoeven, R. M. Kaschnitz, and H. W. Strobel, *Ann. N.Y. Acad. Sci.*, **212**, 449 (1973); (d) I. C. Gunsalus, J. R. Meeks, and J. D. Lipscomb, *ibid.*, **212**, 107 (1973); (e) W. A. Pryor, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **32**, 1862 (1973); (f) G. S. Fonken and R. A. Johnson, "Chemical Oxidations with Microorganisms", Marcel Dekker, New York, N.Y., 1972.
(3) For a detailed analysis of two cytochrome P-450 reductase systems see ref 2b and 2d.
(4) For a recent review of Fenton's Reagent chemistry see C. Walling, *Acc. Chem. Res.*, **8**, 125 (1975).
(5) F. Haber and J. Weiss, *Proc. R. Soc. London, Ser. A*, **147**, 332 (1934).
(6) (a) C. Walling and S. Kato, *J. Am. Chem. Soc.*, **93**, 4275 (1971); (b) C. Walling and G. El-Taliawi, *ibid.*, **95**, 844 (1973).
(7) (a) R. H. Felton, G. S. Owen, D. Dolphin, and J. Fajer, *J. Am. Chem. Soc.*, **93**, 6332 (1971); (b) L. P. Hager, D. L. Doubek, R. M. Silverstein, J. H. Hargis, and J. C. Martin, *ibid.*, **94**, 4364 (1972).
(8) E. G. Hrycay and P. J. O'Brien, *Biochem. J.*, **125**, 12 (1971).
(9) (a) W. C. Bray and M. H. Gorin, *J. Am. Chem. Soc.*, **54**, 2124 (1932); (b) I. M. Kolthoff and A. I. Medalia, *ibid.*, **71**, 3777, 3784 (1949).
(10) (a) D. L. Ingles, *Aust. J. Chem.*, **26**, 1621 (1973); (b) G. S. Hammond and C. S. Wu, *Adv. Chem. Ser.*, **No. 77**, 186 (1968); (c) G. A. Hamilton, J. R. Giacin, T. H. Hellman, M. E. Snook, and J. W. Weller, *Ann. N.Y. Acad. Sci.*, **212**, 449 (1973).
(11) A. E. Cahill and H. Taube, *J. Am. Chem. Soc.*, **74**, 2312 (1952).
(12) J. T. Groves and M. Van Der Puy, *J. Am. Chem. Soc.*, **96**, 5274 (1974).
(13) (a) C. Walling and B. Miller, *J. Am. Chem. Soc.*, **79**, 4181 (1957); (b) G. A. Russell, *J. Org. Chem.*, **23**, 1407 (1958).
(14) M. M. Green and R. J. Cook, *J. Am. Chem. Soc.*, **91**, 2129 (1969).
(15) For a reproduction of this spectrum see J. T. Groves and M. Van Der Puy, *Tetrahedron Lett.*, 1949 (1975).
(16) Competitive oxidation of cyclohexanol and 2,2,6,6-cyclohexanol-d_4 gave a similar value for C-2 hydroxylation.
(17) (a) B. Franzus and E. I. Snyder, *J. Am. Chem. Soc.*, **87**, 3427 (1965); (b) R. G. Weiss and E. I. Snyder, *J. Org. Chem.*, **35**, 1627 (1970).
(18) For an analysis of the mass spectra of all norbornane diols, see H. F. Grützmacher and K. H. Fechner, *Tetrahedron*, **27**, 5011 (1971).
(19) (a) W. W. Swanson, unpublished results; (b) J. T. Groves and W. W. Swanson, *Tetrahedron Lett.*, 1953 (1975); (c) J. T. Groves, *ibid.*, 3113 (1975).
(20) G. L. Kochanny, Jr. and A. Timnich, *J. Am. Chem. Soc.*, **83**, 2777 (1961).
(21) Also by implication, the *reduction* of Fe(VI) salts should lead to reactive Fe(IV) or Fe(V) intermediates capable of allphatic hydroxylation. Reactions of this type have now been observed in our laboratories and will be reported separately; D. M. Stone, unpublished results.
(22) (a) L. F. Warren and M. A. Bennett, *J. Am. Chem. Soc.*, **96**, 3340 (1974); (b) T. J. Conocchioli, E. J. Hamilton, Jr., and N. Sutin, *J. Am. Chem. Soc.*, **87**, 926 (1965). These authors concluded that Fe(IV) was not trapped when H_2O_2 was reacted with Fe(II) in water. This observation may be related to the change in regiospecificity for cyclohexanol hydroxylation observed here when water was added to the medium (Table I).
(23) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechot, *J. Am. Chem. Soc.*, **82**, 2640 (1960); **83**, 4076 (1961).
(24) E. J. Corey and W. R. Hertler, *J. Am. Chem. Soc.*, **80**, 2903 (1958); **81**, 5209 (1959); **82**, 1657 (1960).
(25) In order for the less abundant complex **18** to give rise to more diol product than **17**, it has been assumed that reduction of **19** and **20** by ferrous ion or solvent is competitive with hydrogen abstraction.
(26) As one of us has demonstrated elsewhere, the observed regioselectivity for the cyclohexanol hydroxylation accompanying the photoreduction of ferric perchlorate shifts in favor of C-2 at low temperature in accord with expectations based on equilibrium (**9**) (Scheme VII). The data in Table I also reveal a perceptible temperature-dependent shift.

(27) For a complete account, see J. T. Groves and M. Van Der Puy, *J. Am. Chem. Soc.*, **97**, 7118 (1975).
(28) It is important to note that no evidence for 1,2-hydride shifts (loss of deuterium) were observed when cyclohexanol deuterated at C-2 or C-4 was hydroxylated with $Fe(II)H_2O_2$ in contrast to the stereospecific hydride shift that has been reported to accompany cyclohexyl tosylate solvolysis. (a) J. B. Lambert, G. J. Putz, and C. E. Mixan, *J. Am. Chem. Soc.*, **94**, 5132 (1972); (b) J. E. Nordlander and T. J. McCrary, Jr., *ibid.*, **94**, 5133 (1972).
(29) K. Alder, F. H. Flock, and H. Wirtz, *Chem. Ber.*, **91**, 609 (1958).

Hydroboration. 43. Effect of Structure on the Reactivity of Representative Olefins toward Hydroboration by 9-Borabicyclo[3.3.1]nonane

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Abstract: The relative reactivities of 37 selected olefins toward hydroboration by 9-borabicyclo[3.3.1]nonane (9-BBN) in tetrahydrofuran solution were determined by two competitive techniques. The data for these reactions are presented to make clear the effect of each structural feature on the relative rate. Wherever comparable data are available, a comparison is made between 9-BBN and a second dialkylborane, disiamylborane, and the similarities and differences in the selectivities of the two reagents are pointed out. Both reagents have large steric requirements, reacting preferentially with the least hindered double bond. On the other hand, 9-BBN is far more sensitive to electronic influences, attributed to the greater electrophilic character of the bridging >BH moiety in the strained 9-BBN structure.

The utility of the 9-BBN group as a blocking group in syntheses via organoboranes[2] and its highly selective hydroborating ability[3] have been reported. 9-BBN exhibits remarkable regio- and stereoselectivity giving the highest degree of selectivity yet achieved.[3] For example, 1-hexene reacts to give 99.9% of the 1 isomer (regioselectivity) and norbornene reacts to yield 99.5% of the exo isomer (stereoselectivity). 9-BBN shows a remarkable preference for forming a carbon–boron bond to the least hindered terminal of a double bond, 4-methyl-2-pentene reacting to give 99.8% of the 2 isomer.[3] In view of these unique characteristics, it appeared appropriate to explore the effect of olefin structure on the rate of hydroboration with 9-BBN. Accordingly, we undertook a relative rate study of olefin hydroboration utilizing 9-BBN in THF solution at room temperature.

Results

Competitive Hydroboration of Olefins with 9-BBN in THF. The previous study[3] established the time required to achieve essentially complete hydroboration for olefins of different structural types. To obtain more precise reactivity data, selected pairs of olefins were treated with 9-BBN and the relative reactivities determined competitively. Two different experimental procedures were utilized. Both involved the mixing of two olefins in equimolar amounts (0.5 M in THF) in a reaction flask and the subsequent addition of only 1 equiv of 9-BBN (0.5 M in THF). An inert hydrocarbon (internal standard) was also added. In procedure A the mixture was analyzed by GLC for residual olefin after the hydroboration was complete. A stripper column[4] (¼ × 6 in. – 20% THEED column) was used to retain the intermediate organoborane and not allow it to pass into the second column (⅛ in. × 6 ft – 10% adiponitrile). The ratio of unreacted olefin to internal standard could now be easily determined. In procedure B the intermediate organoborane was oxidized with alkaline hydrogen peroxide to give 1,5-cyclooctanediol and the two alcohols corresponding to the organoboranes produced from the starting olefins. The alcohol to internal standard ratio was determined by GLC (⅛ in. × 12 ft – 10% SE-30) for each product. In both procedures the concentration of unreacted olefin can be determined following completion of the hydroboration. With these values in hand along with the initial concentration of each olefin, the relative rate is obtained by use of the Ingold and Shaw[5] expression: relative rate $= k_x/k_y = (\ln x_0 - \ln x)/(\ln y_0 - \ln y)$, where x_0 and y_0 are the initial concentrations and x and y are the residual concentrations of the two olefins being compared. Many olefin pairs were run using both procedures A and B and the results proved consistent.[6] Unless otherwise stated, the reactions lead cleanly to a quantitative conversion of product and all relative rates reported are at 25.00 ± 0.03 °C (procedure A) or ambient room temperature (procedure B).

The relative reactivities data for 9-BBN are summarized in Table I.

Discussion

9-BBN proved to be a highly selective reagent, with major similarities and difference from the selectivity exhibited by disiamylborane.[7,8] (On the other hand, diborane itself is a relatively insensitive reagent, exhibiting only minor effects of structure upon rate.[8]) Accordingly, it is of interest to compare the selective properties of 9-BBN with those of disiamylborane where such data are available, for examination of the similarities and differences.

Terminal Olefins, $RCH{=}CH_2$. The data for straight-chain 1-alkenes indicate that the rate of hydroboration is nearly independent of chain length. Thus, 1-hexene, 1-octene, 1-decene, and 1-dodecene all show similar reactivity with either 9-BBN or disiamylborane, as indicated by the relative rates.

	$CH_3(CH_2)_3CH{=}CH_2$	$CH_3(CH_2)_5CH{=}CH_2$
9-BBN	1.00	1.10
Sia_2BH	1.00	1.08

Branching in the R group decreases the rate of hydroboration significantly. Thus in going from 1-hexene to 3-methyl-1-butene, the rate with 9-BBN decreases by a factor of two and 3,3-dimethyl-1-butene reacts four times slower than the straight-chain olefin. A more dramatic decrease in rate is realized with disiamylborane.