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Sulconazole reactions with peracetic acid and hydrogen peroxide

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Summary

Sulconazole (1-[2-{[4-chlorophenyl)methyl]thio}-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole) is one member of a family of antimycotic drugs. Because oxidative degradation frequently limits the shelf lives of sulfur-containing drugs, we investigated the oxidation kinetics of sulconazole and sulconazole sulfoxide in aqueous peracetic acid and hydrogen peroxide. The oxidations were studied as a function of pH (7–13) and of the concentration of peracetic acid (0.025–25 mM) and of hydrogen peroxide (100–1000 mM). Our objective was to probe the effects of peroxide structure and charge state on sulconazole loss rates and product distributions. In the presence of peroxyacetic acid or hydrogen peroxide, sulconazole converts quantitatively to the corresponding sulfoxide and sulfone. Solution pH strongly influences the overall product distribution at intermediate extents of conversion. Thus, alkaline pH favors sulfone accumulation whereas sulfoxide predominates in acidic solution. The observed relative reactivities toward sulconazole are: peroxyacetic acid (10^5), peroxyacetate anion (10^3), hydrogen peroxide (1), and hydroperoxy anion (1). Transition state intramolecular proton transfer remains the most straightforward explanation for the dependence of sulconazole oxidation rates on peroxide structure and charge state.

Introduction

Drug substance oxidation often limits drug product stability. Specifically for the case of organosulfur compounds, sulfide sequential oxidation to the sulfoxide and sulfone represents a thermodynamically favorable degradation pathway. Alkyl hydroperoxides, hydrogen peroxide, and peroxy acids accelerate organosulfur compound oxidation and even trace peroxide concentrations in pharmaceutical formulations can significantly reduce drug product shelf life.

These facile organosulfur compound oxidation reactions have enjoyed considerable attention in the literature. Thus, numerous individual contributions (Overberger and Cummins, 1953a,b; Bateman and Hargrave, 1954; Modena and Todesco, 1962; Curci et al., 1975) and several review articles (Swern, 1949; Barnard et al., 1961; Behrman and Edwards, 1967) reveal that sulfide reactions with hydroperoxy compounds proceed via S_N^2 displacement by sulfide (the nucleophile) on the hydroperoxy terminal oxygen. The initial reaction product is the corresponding sulfoxide. Subsequent peroxide attack then converts sulfoxide to the corresponding sulfone.

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Sulfides react much more rapidly with peroxy acids than with alkyl and hydrogen peroxides. Several authors (Swern, 1949; Barnard et al., 1961; Behrman and Edwards, 1967) have interpreted the reactivity differences to mean that peroxy acid (but not hydroperoxide) reaction transition states feature intramolecular five-center proton transfer from peroxide terminal oxygen to carbonyl oxygen (Scheme 1). More recently, however, others (Bruice, 1983; Bruice et al., 1983; Yamamoto et al., 1986; Druliner et al., 1988) have proposed that intramolecular proton transfer is not a driving force for sulfide oxidations and that there is no mechanistic distinction between peroxy acids and hydroperoxides. Rather, peroxy acids and hydroperoxides represent a common series of oxygen atom donors that differ in their reactivity toward sulfides only by the relative abilities of the acyloxy and alkoxy leaving groups to accept a negative charge in the transition state.

It is also known (Curci and Modena, 1963, 1965, 1966; Curci et al., 1966) that sulfoxides react more rapidly with peroxyanions than with the corresponding protonated peroxides. Furthermore, peroxyacid anions react more rapidly than hydroperoxy anions. Here, the reaction proceeds via nucleophilic attack by peroxyanion on sulfoxide as electrophile.

Thus, organosulfur compound reactivity depends strongly on peroxide structure and charge state, and the overall reaction represents a sequential sulfide-to-sulfoxide-to-sulfone conversion. Alkyl sulfide drug degradation will therefore be highly sensitive to the structure of peroxides present in the reaction mixture and to the reaction medium pH. Similarly, the product (sulfoxide vs sulfone) distribution at any sulfide fractional conversion will depend significantly on the peroxide(s) present and the medium pH. Although the pharmaceutical literature generally recognizes that peroxidic impurities can accelerate degradation of formulated organosulfur drugs, drug degradation rate and product distribution dependences on peroxide structure and charge state lack a firm, detailed quantitative basis.

Accordingly, we have investigated pH and peroxide structural effects on oxidation kinetics and products of 1-[2-{[(4-chlorophenyl)methyl]thio}-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole (sulconazole; **1**). Sulconazole, a topical antifungal (Walker and Marx, 1977; Benfield and Clissold, 1988), is a convenient probe molecule because sensitive (HPLC) assay methodology is available. Furthermore, sulconazole represents a large class of sulfur-containing antimycotics (fenbendazole, oxfendazole, and butoconazole are other examples) and its oxidative transformations have meaningful practical significance with respect to drug product stability.

For aqueous 2-propanol solutions at pH 7–13 we determined sulconazole loss rates in the presence of excess peracetic acid (**2**) and hydrogen peroxide (**3**). We also examined the reaction of sulconazole sulfoxide (**4**) with **2** and **3**. The principal objective was to assess quantitatively reactivity differences between anionic and protonated peroxyacid and hydrogen peroxide toward **1**. A secondary goal was to model oxidation product distributions as a function of solution pH and sulconazole fractional conversion.

Materials and Methods

Materials

The following chemicals were obtained from the indicated sources and used without further purification: sulconazole nitrate and sulconazole sulfoxide nitrate (Syntex Research); peracetic acid and sodium perchlorate (Aldrich); sodium azide and Na_2EDTA (Fisher); hydrogen peroxide solution 30%, sodium hydroxide and sodium phosphate monobasic, monohydrate (J.T. Baker); 2-propanol (ChromAR ®, HPLC grade) and anhydrous sodium phosphate, dibasic (Mallinckrodt); methanol, B&J brand, HPLC grade (Baxter Healthcare Corp.). Water for kinetic experiments was obtained from a Nanopure Water Purification System (Barnstead, Dubuque, IA).

Apparatus

Reaction progress was measured by the disappearance of sulconazole or sulconazole sulfoxide. Sulconazole and sulconazole sulfoxide concentrations were monitored by high-pressure liquid chromatography (HPLC). A Whatman Partisil 5 ODS-3 RAC II column was used throughout. The HPLC

system included an Altex 110A pump, WISP (Waters Intelligent Sample Processor) 710B autosampler, and a Waters Lambda-Max Model 480 LC spectrophotometer. A Spectra Physics Model 4050 printer/plotter was used. The detection wavelength was 225 nm. The mobile phases for sulconazole and sulconazole sulfoxide were 80 : 20 and 60 : 40 CH_3OH : 0.01 M sodium phosphate monobasic, respectively. The flow rate was 1 ml/min. The HPLC column was maintained at ambient temperature. The column pressure was about 500 lb/inch^2 (p.s.i.). The sample injection volume was 10 μl. pH readings and adjustments were made by using a Fisher Accumet®, Model 420 Digital pH/Ion meter.

Methods

The kinetic experiments were conducted at ambient temperature (300 ± 2 K) in 80: : 20 aqueous 2-propanol. Initial reactant concentrations (mM) were as follows: **1** (0.05), **4** (0.05), peracetic acid (0.025–25), and hydrogen peroxide (100–1000). The aqueous solutions also contained: 0.1 mM Na_2EDTA, 100 mM phosphate buffer, 0.1 mM sodium azide, and sodium perchlorate added to bring the total ionic strength to 500 mM.

A 0.60 ml aliquot of reactant (**1** or **4**) in 2-propanol was transferred via a Pipetman® automatic pipettor to an autosampler vial. Peracetic acid or hydrogen peroxide solutions (2.4 ml in appropriate aqueous buffer) were similarly transferred to bring the total reactant volume to 3.0 ml. Samples were injected for analysis at timed intervals, thereby giving the time dependence for reactant loss.

Observed pseudo-first-order rate constant (k_{obs}) values were determined by linear least-squares regression of limiting reactant (i.e. **1** or **4**) vs time data according to Eqn 1:

$$\ln\{[\text{reactant}]_t/[\text{reactant}]_{t=0}\} = \text{intercept} - k_{obs} \cdot \text{time} \quad (1)$$

Similarly, biomolecular rate constant (k_2) values were determined by regressing k_{obs} vs peroxide concentration data according to Eqn 2:

$$k_{obs} = \text{intercept} + k_2 \cdot [\text{peroxide}]. \quad (2)$$

Throughout rate constants are reported as linear regression slopes with uncertainties expressed as ±95% confidence intervals.

Results and Discussion

Kinetic order and mass balance

For **1**, pseudo-first-order kinetics obtained to long ($> 3 \cdot t_{1/2}$) conversions. Fig. 1 shows **1** loss at pH 10 in the presence of: 0.5 mM peracetic acid, 1000 mM hydrogen peroxide, and no peroxide added. Fig. 1 also plots the observed percentage sulconazole remaining on a linear scale to emphasize the fractional conversion. The solid lines represent the calculated percentage of initially added **1** remaining using experimentally determined k_{obs} values according to Eqn 1. Similarly, good adherence to Eqn 2 demonstrated the second-order dependence of **1** loss. Fig. 2 is a representative plot of k_{obs} vs peroxide concentration for **1** reaction with peracetic acid at pH 7 and at pH 12. For the sulfoxide (**4**), reaction kinetics also obeyed Eqns 1 and 2.

Sulconazole oxidation proceeded quantitatively to a mixture of **4** and the sulfone (**5**). Table 1 shows representative data for peracetic acid oxidation of **1** at pH 12.

Dependence on peroxide structure and charge state

Table 2 summarizes k_2 values for **1** and **4** oxidations at various solution pH values. Fig. 3 plots log(k_2) values vs pH for **1** reactions with

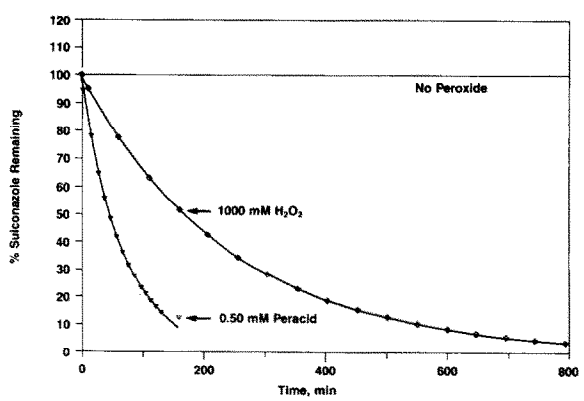


Fig. 1. Sulconazole oxidation kinetics at pH 10.

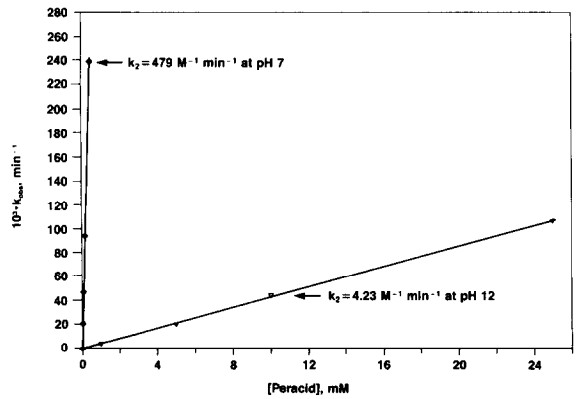


Fig. 2. Bimolecular rate constant plot for peracetic acid plus sulconazole.

peracetic acid and hydrogen peroxide. Note that the rate constant values depend very strongly on pH and peroxide type. Noteworthy reactivity differences include the following:

peroxyacetic acid is 10^5 times more reactive than hydrogen peroxide toward **1** at pH 7;
peroxyacetic acid is only 10^3 times more reactive than hydrogen peroxide toward **1** at pH 12
reaction of **1** with peroxyacetic acid is faster (by a factor of 10^2) at pH 7 than at pH 12, and
reaction of **4** with peroxyacetic acid is slower (by a factor of 10^3) at pH 7 than at pH 12.

Table 2 and Fig. 3 are best interpreted with respect to solution pH effects on peroxide charge state. The acid dissociation constant (pK_a) values for peroxyacetic acid and hydrogen peroxide in water are, respectively, 8.2 and 11.6 (Everett and Minkoff, 1953). Thus, at pH 7, both peroxyacetic acid and hydrogen peroxide are predominantly

TABLE 1

Sulconazole (1) loss and sulfoxide (4) plus sulfone (5) production for sulconazole reactions with 5 mM peracetic acid at pH 12 in 80:20 aqueous 2-propanol

Time (min)	[1] (μM)	[4] (μM)	[5] (μM)	[1]+[4]+[5] (μM)
0	51.6	0	0	51.6
3	48.1	3.0	0	50.1
44	19.0	22.7	10.2	51.8
85	8.8	23.0	22.6	54.4
125	4.1	18.9	32.0	55.1
166	1.6	14.4	37.9	53.9
207	0.30	10.8	41.0	52.1
247	0.10	8.4	44.4	52.9
288	0	6.7	46.8	53.5

TABLE 2

Bimolecular rate constant (k_2) values [a] for sulconazole (1) and sulconazole sulfoxide (4) reaction with peracetic acid (2) and hydrogen peroxide (3)

Reactant	peroxide	pH	k_2(±95% CI) [b] (M^{-1} min^{-1})
1	**2**	7	479 ±11
		8	310
		9	254
		10	29.5
		11	6.37
		12	4.23 ± 0.17
1	**3**	7	0.0038 ± 0.0004
		10	0.0040 ± 0.0003
		12	0.0039 ± 0.0005
		13	0.0040 ± 0.0027
4	**2**	7	0.0695 ± 0.018
4	**2**	12	239 ±17
4	**3**	7	[c]
4	**3**	10	0.00033
4	**3**	12	0.00019

[a] Determined according to Eqns 1 and 2.
[b] Rate constants without uncertainties indicated were determined at a single concentration of peroxide and were calculated from the ratio of k_{obs} to [peroxide] according to Eqn 2. Values with indicated uncertainties were determined from k_{obs} values at various peroxide concentrations.
[c] No reaction.

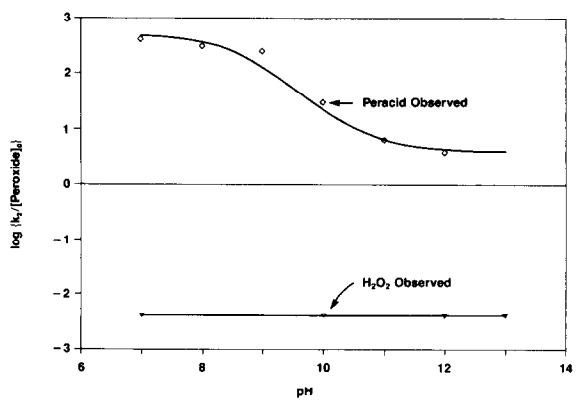
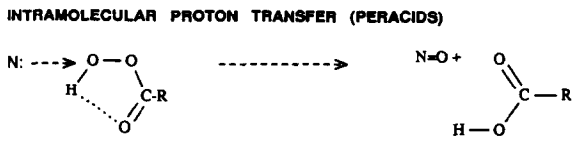


Fig. 3. pH dependence of sulconazole oxidation by H_2O_2 and peracetic acid.



Scheme 1.

nonionic. Above pH 8.2 for peroxyacetic acid and above pH 11.6 for hydrogen peroxide, the peroxyanions predominate.

The sigmoidal dependence of k_2 on pH for **1** oxidation by peroxyacetic acid indicates significantly higher reactivity for peroxyacetic acid than for peroxyacetate anion. For hydrogen peroxide, however, the protonated and anionic species are essentially equally reactive toward **1**. The most straightforward explanation for the especially high reactivity of peroxyacetic acid toward **1** is transition state intramolecular proton transfer (Scheme 1). Intramolecular proton transfer is not available for hydrogen peroxide, hydroperoxy anion or peroxyacetate anion and does not offer a driving force for **1** oxidation.

For **4** oxidation, peroxyacetate and hydroperoxy anions react more rapidly than the corresponding protonated peroxides. This indicates nucleophilic attack by peroxide on sulfoxide as discussed by Curci and Modena (1963, 1965, 1966) and Curci et al. (1966).

Concerning product distributions, **4** represents an intermediate on the sulfide-to-sulfoxide-to-sulfone reaction pathway. Note that **4** reacts more rapidly with peroxyanions than with the protonated peroxide. For starting sulfide (**1**), however, peroxyacetic acid reacts more rapidly than the peroxyanion and the protonated and anionic forms of hydrogen peroxide are equally reactive. These relative reactivities indicate that **4** accumulation will depend strongly on medium pH. That is, acidic solutions will favor **4** accumulation over the sulfone (**5**), whereas the opposite will be true for alkaline solutions. The following section quantitatively addresses **1** oxidation product distributions as a function of medium pH.

Modeling reactivity and product distributions

For simultaneous reactions of added sulconazole (**1**) with protonated and anionic peroxide, we must consider the following minimum reaction set:

$$R_2S + ROOH \xrightarrow{k_{ROOH}} R_2SO + ROH$$

$$\xrightarrow[+ROOH]{k'_{ROOH}} R_2SO_2 + ROH \tag{3}$$

$$R_2S + ROO^- \xrightarrow{k_{ROO^-}} R_2SO + RO^-$$

$$\xrightarrow[+ROO^-]{k'_{ROO^-}} R_2SO_2 + RO^- \tag{4}$$

From this scheme, we can obtain Eqn 5:

$$-d[R_2S]/dt = [R_2S]\{k_{ROOH}[ROOH] + k_{ROO^-}[ROO^-]\} \tag{5}$$

Define the fraction, F, of added ROOH present as peroxy anion as:

$$F = K/\{K + [H^+]\} \tag{6}$$

where K is the ROOH acid dissociation constant. Then

$$-d[R_2S]/dt = [R_2S][ROOH]_0 \times \{k_{ROOH}(1-F) + k_{ROO^-}F\} \tag{7}$$

when $[ROOH]_0 \gg [R_2S]$, pseudo-first-order kinetics obtain, and:

$$-\ln([R_2S]_t/[R_2S]_0) = k_{obs} \cdot t \tag{8}$$

where:

$$k_{obs} = [ROOH]_0\{k_{ROOH}(1-F) + k_{ROO^-}F\} \tag{9}$$

Thus, a plot of k_{obs} vs $[ROOH]_0$ has slope = $k_{ROOH}(1-F) + k_{ROO^-}F$.

Now consider two limiting cases based on pH extremes: (case 1) low pH where $[H^+] \gg K$, and $F \sim 0$; or (case 2) high pH where $[H^+] \ll K$, and $F \sim 1$.

In case 1, the slope value above gives k_{ROOH}, and in case 2, the slope values above gives k_{ROO^-}.

Finally, an analogous treatment applies to reactions of R_2SO with peroxides.

The above reaction set is a classic example of series first-order reactions ($A \rightarrow B \rightarrow C$), and an algebraic solution is available for the reaction kinetics (Frost and Pearson, 1961).

First, make the following definitions:

$$A = [R_2S]_t/[R_2S]_0 \tag{10}$$

$$B = [R_2SO]_t/[R_2S]_0 \tag{11}$$

$$C = [R_2SO_2]_t/[R_2S]_0 \tag{12}$$

$$1 = A + B + C \tag{13}$$

$$k = k_{ROOH}(1 - F) + k_{ROO^-}F \tag{14}$$

$$k' = k'_{ROOH}(1 - F) + k'_{ROO^-}F \tag{15}$$

$$R = k'/k \text{ (for either ROOH or } ROO^-) \tag{16}$$

From the preceding expressions, Eqns 17–19 follow:

$$A = \exp(-k \cdot t) \tag{17}$$

$$B = (1/(R-1)) \cdot \{\exp(-k \cdot t) - \exp(-k' \cdot t)\} \tag{18}$$

We can calculate A, B, and C vs time at any pH using the above equations and independently determined values of k and k'.

Another way of expressing the product profiles is to solve, for example, for B as a function of A.

First, solve Eqn 17 for t as a function of A:

$$t = -(1/k) \cdot \ln(A) \tag{20}$$

Next, substitute for t in Eqn 18 to give:

$$B = (1/(R-1)) \cdot \{A - \exp(R \cdot \ln(A))\} \tag{21}$$

Eqn 21 permits calculation of B as a function of the percent of R_2S remaining at any pH.

Fig. 4 is a representative product distribution for **1** oxidation by peroxyacetic acid at a pH (8.6) where the anionic and protonated peroxide concentrations are approximately equal. Fig. 4 uses Eqns 17–19 to calculate the fractional **1**, **4**, and **5** amounts as a function of time. The equations use rate constant values (taken as k_2 values in units of M^{-1} min^{-1} from Table 2) as follows: $k_{ROOH} = 479$, $k_{ROO^-} = 4.23$, $k'_{ROOH} = 0.0695$, and $k'_{ROO^-} = 239$. Fig. 4 clearly shows the transient accumulation of **4** and the subsequent **5** formation with increasing extents of conversion.

It is also interesting to explore the product distribution dependence on pH for **1** oxidation by peroxyacetic acid. Fig. 5 plots the fractional accumulation of **4** (i.e. the ratio **[4]**/{**[4]** + **[5]**} calculated as in Eqn 21 as a function of percentage **1** loss for 0.1 mM peroxyacetic acid at pH 8, 9, and 10. Fig. 5 shows that at pH 8, **4** represents the major product to greater than 90% loss of **1**. At pH 10, however, where peroxyacetate ion reactivity is important, **4** represents the minor component of the product mixture at **1** conversions exceeding approx. 20%. Thus, the actual oxidation product mixture is very sensitive to medium pH.

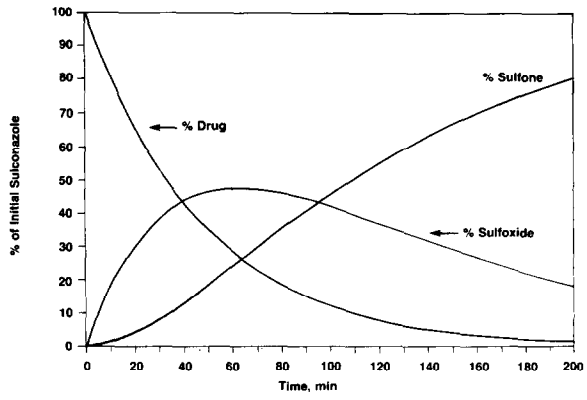


Fig. 4. Sulconazole oxidation product profiles; 0.1 mM peracid at pH 8.6.

Conclusions

Sulconazole oxidation kinetics and product distributions depend strongly on peroxide structure and charge state. Sulconazole reacts extremely rapidly with peroxyacetic acid, but the reaction with hydrogen peroxide is slower by a factor of approx. 10^5. Similarly, **1** reacts 10^2 times more rapidly with peroxyacetic acid than with the peroxyacetate anion. Oxidation of **1** yields the corresponding sulfoxide (**4**) and sulfone (**5**) in stepwise fashion. In acid solutions, **4** represents the major product to very high extents of conversion. At alkaline pH, however, **5** predominates early in the reaction profile.

Mechanistically, transition state intramolecular proton transfer is the simplest explanation for the hydrogen peroxide vs peroxyacetic acid reactivity toward **1**. A five-center cyclic transition state is available to the protonated peroxyacid but not to hydrogen peroxide or to peroxy anions.

In a practical context, at pH 7, peroxyacetic acid reactions with **1** are sufficiently fast to limit significantly the shelf life of formulated drug product. Assuming sulconazole as limiting reagent, **1** suffers 10% loss at ambient temperature in approx. 10 min for peroxyacetic concentrations as low as 1.65 mg/l (parts per million, ppm). Hydrogen peroxide reacts with **1** much more slowly than peroxyacetic acid, and to achieve 10% loss in **1** at the 1.65 ppm level requires approx. 1 year.

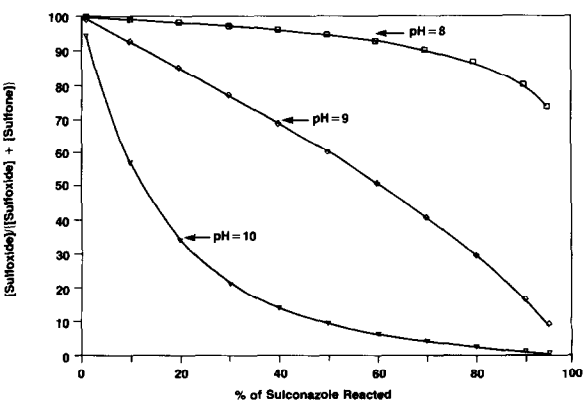


Fig. 5. Sulconazole product profiles; % sulfoxide vs % conversion.

Finally, the quantitative aspects of oxidation reactions presented here apply specifically to the sulconazole. The overall perspective on reactivity and product dependence on peroxide type and charge is general, however. Certainly, the oxidation chemistry outlined herein extends directly to other sulfur-containing imidazolyl antifungals such as fenbendazole, oxfendazole, and butoconazole. For other alkyl sulfide drugs, similarities are also likely. For formulated alkyl sulfide drugs, for example, information regarding degradation product distribution as a function of formulation pH could be used to infer the structure(s) of the oxidant(s) responsible for drug loss.

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