Enhanced Generation of Hydroxyl Radical and Sulfur Trioxide Anion Radical from Oxidation of Sodium Sulfite, Nickel(II) Sulfite, and Nickel Subsulfide in the Presence of Nickel(II) Complexes

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Electron spin resonance (ESR) spin trapping was utilized to investigate the generation of free radicals from oxidation of sodium sulfite, nickel(II) sulfite, and nickel subsulfide (Ni_3S_2) by ambient oxygen or H_2O_2 at pH 7.4. The spin trap used was 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO). Under ambient oxygen, a solution of sodium sulfite alone generated predominantly sulfur trioxide anion radical ($\cdot SO_3^-$) due to the autoxidation of sulfite. Addition of nickel(II) chloride [Ni(II)] enhanced the $\cdot SO_3^-$ yield about 4-fold. Incubation of sulfite with Ni(II) in the presence of chelators such as tetraglycine, histidine, β-alanyl-3-methyl-L-histidine (anserine), β-alanyl-L-histidine (carnosine), γ-aminobutyryl-L-histidine (homocarnosine), glutathione, and penicillamine did not have any significant effect on that enhancement. In contrast, albumin, and especially glycylglycylhistidine (GlyGlyHis), augmented the enhancing effect of Ni(II) by factors of 1.4 and 4, respectively. Computer simulation analysis of the spin-adduct spectrum and formate scavenging experiment showed that the mixture of sodium sulfite, Ni(II), and GlyGlyHis generated both hydroxyl (•OH) radical and $\cdot SO_3^-$ radical, in the ratio of approximately 1:2. The free-radical spin adduct intensity reached its saturation level in about 5 min. The yield of the radical adducts could be slightly reduced by deferoxamine and very strongly reduced by diethylenetriaminepentaacetic acid (DTPA). Aqueous suspensions of sparingly soluble nickel(II) sulfite in the presence of air and GlyGlyHis generated surface-located $\cdot SO_3^-$ and •OH radicals. The same radicals were generated in Ni_3S_2 suspension in the presence of GlyGlyHis and H_2O_2, indicating sulfite production by oxidation of the sulfide moiety of this compound. In view of the present results, the exceptionally high carcinogenic potential of Ni_3S_2 appears to be due to the ability of both the nickel and sulfide constituents of the molecule to facilitate the generation of genotoxic radicals. — Environ Health Perspect 102(Suppl 3):91–96 (1994)

Key words: hydroxyl radical, sulfur trioxide anion radical, sulfite, nickel(II) sulfite, nickel subsulfide, nickel(II) complexes

Introduction

It has been shown that sulfur dioxide (SO_2) is a major air pollutant (*1*). In aqueous media it exists in equilibrium with the sulfite ion (SO_3^{2-})(*2*). Sulfite appears to have genotoxic effects (*3*). It can act as a mutagen or co-mutagen (*4*) and a co-carcinogen (*5*). The mechanism of sulfite toxicity is believed to be related to sulfite oxidation processes involving sulfur trioxide radical ion ($\cdot SO_3^-$) formation (*1,6–8*). Recent studies have shown that hydroxyl (•OH) radical is also generated in the sulfite oxidation pathway (*9*). This radical may play an important role in sulfite-induced genetic damage. For example, incubation of sulfite with DNA produces 8-hydroxy-2'-deoxyguanosine (8-OH-dG) (*10*), a marker of oxidative DNA damage (*11*). It has been reported that Mn(II) (*12*) and chromate (*9*) enhance sulfite oxidation either as catalysts or as oxidants. However, it has not been clear whether sulfite oxidation can also be enhanced by other transition metal ions, Ni(II) in particular. Ni(II)-enhanced sulfite oxidation would be highly interesting, since nickel in many physicochemical forms is carcinogenic to humans and animals (*13–16*). Among nickel compounds, the crystalline sulfides, especially the subsulfide Ni_3S_2, appear to be the strongest carcinogens (*17*). Ni_3S_2 is potentially genotoxic, causing random polymerization of histones *in vitro* (*18*), formation of DNA-protein crosslinking bonds (*18*), and hydroxylation of 2'-deoxyguanosine (dG) to 8-OH-dG in the presence of ambient oxygen (*19*). The latter reaction can be enhanced by H_2O_2 (*19*). Most importantly, Ni_3S_2 interacts with molecular oxygen and undergoes slow oxidation of both its cationic and anionic constituents to soluble Ni(II) and SO_4^{2-} (*20,21*). Oxidation of the sulfur moiety of Ni_3S_2 is gradual and goes through sulfite as an intermediate (*21*). Thus, it appears that Ni_3S_2 yields two products that are capable of damaging DNA.

Unlike other transition metal ions such as Fe(II), Cu(II) and VO^{2+}, Ni(II) does not cause efficient free radical generation from O_2, H_2O_2 or lipid hydroperoxides. However, recent studies (*22,23*) have shown that reactivity of Ni(II) with those oxygen derivatives can be modulated by chelation, e.g., with certain histidine- and cysteine-containing ligands. We could expect, therefore, that chelation of Ni(II) might also facilitate the stimulatory effect of this cation on sulfite oxidation. Hence, in the present study we investigated free-radical generation during autoxidation of

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sulfite with Ni(II) added in either nonchelated or chelated form. The results show that in the presence of certain chelators, Ni(II) significantly increased $\cdot SO_3^-$ radical generation and, in addition, caused ·OH radical generation from sodium sulfite reacting with ambient oxygen. Aqueous suspensions of sparingly soluble nickel(II) sulfite, under ambient atmosphere, generated surface-bound free radicals only in the presence of a chelator. For Ni_3S_2 suspensions, both a chelator and a stronger oxidant, H_2O_2, were required for the free radical generation. Cooperation of both constituents of Ni_3S_2 in free-radical production may explain the exceptionally high carcinogenic potential of this compound.

Materials and Methods

Nickel(II) chloride hexahydrate ($NiCl_2 \cdot 6H_2O$), iron(II) chloride tetrahydrate ($FeCl_2 \cdot 4H_2O$), potassium dichromate ($K_2Cr_2O_7$), sodium formate (HCOONa), sodium sulfite (Na_2SO_3), and 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO) were purchased from Aldrich Chemical Co. (Milwaukee, WI). Glycylglycylhistidine (GlyGlyHis), tetraglycine (GlyGlyGlyGly), β-alanyl-3-methyl-L-histidine (anserine), β-alanyl-L-histidine (carnosine), γ-aminobutyryl-L-histidine (homocarnosine), L-histidine, glutathione (GSH), penicillamine, albumin, diethylenetriaminepentaacetic acid (DTPA), and deferoxamine were purchased from Sigma Chemical Co. (St. Louis, MO). Nickel(II) sulfite ($NiSO_3$) was purchased from Pfaltz and Bauer, Inc. (Waterbury, CT). Ni_3S_2 (<30 μm particles) was purchased from INCO, Ltd. (Toronto, Canada). Chelex-100 chelating resin was purchased from Bio-Rad Laboratories (Richmond, CA). The phosphate buffer, pH 7.4, used was treated with Chelex-100 to remove possible transition metal ion contaminants. DMPO solutions were purified using activated charcoal until free radical impurities disappeared as verified by ESR spectroscopy.

ESR Measurements

ESR spin-trapping methodology (*24,25*) was employed for detecting short-lived free radical intermediates. All ESR measurements were performed with a Varian E3 ESR spectrometer and a flat-cell assembly. Hyperfine splittings were measured (to 0.1 G) directly from the magnetic field separation using tetraperoxochromate (K_3CrO_8) and 1,1-diphenyl-2-picrylhydrazyl (DPPH) as reference standards. A Bruker ASPECT 2000 computer was used for spectral analyses. Reactants were mixed in test tubes in a total final volume of 250 μl. The reaction mixture was then transferred to a flat cell for ESR measurement. The concentrations given in the figure legends represent final concentrations. All experiments were carried out at room temperature in the presence of air unless otherwise indicated.

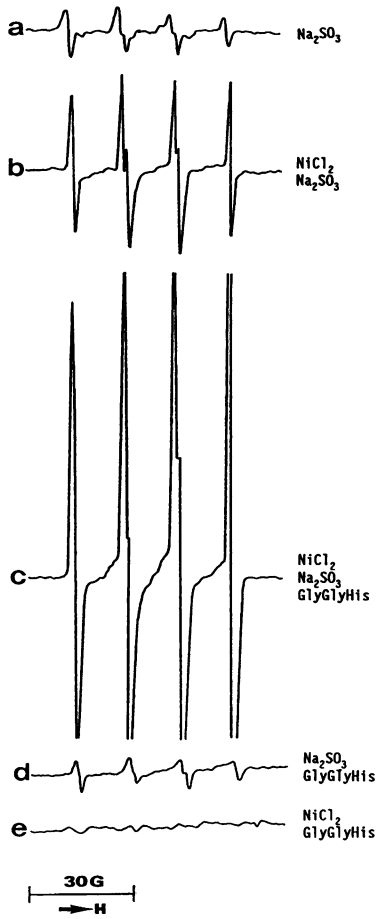

Figure 1. ESR spectra, recorded 3 min after reactions were initiated, from phosphate buffer solutions (pH 7.4) of various combinations of 100 mM DMPO, 2.5 mM Na_2SO_3, 1 mM $NiCl_2$, and 2 mM GlyGlyHis. The ESR spectrometer settings were: receiver gain, 2.0 x 10^5; time constant, 0.3 sec; modulation amplitude, 10 G; scan time, 8 min; magnetic field, 3470 ± 50 G.

Results

Effect of GlyGlyHis and Other Chelators on Ni(II)-mediated Free-Radical Generation in Sodium Sulfite Solution

Figure 1a shows a typical ESR spectrum obtained from an aqueous phosphate buffer solution of 2.5 mM Na_2SO_3 , pH 7.4, under air. The analysis of this spectrum yields the hyperfine splittings of a_N = 14.7 G and a_H = 16.0 G, which are identical to those reported earlier for a

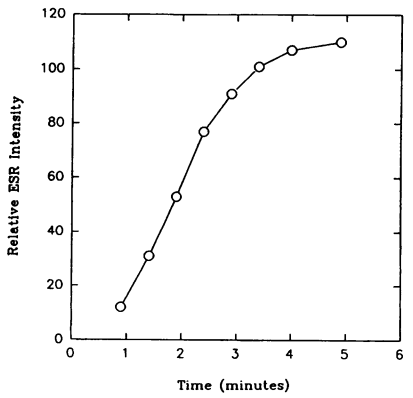

Figure 2. Time course of free radical spin adduct generation from a mixture of 100 mM DMPO, 2.5 mM Na_2SO_3, 1 mM $NiCl_2$, and 2 mM GlyGlyHis. Other experimental conditions were the same as those described in the legend to Figure 1.

DMPO/$\cdot SO_3^-$ adduct produced in various other reaction systems, and thus documents the formation of $\cdot SO_3^-$ radical in sulfite autoxidation (*9,26,27*). When 1 mM Ni(II) was added to this solution, the intensity of the free-radical spin-adduct signal increased by about 4-fold without noticeable change in the spectral hyperfine splittings, indicating that Ni(II) catalyzed the sulfite autoxidation and concomitant generation of $\cdot SO_3^-$ free radical. Addition of 2 mM GlyGlyHis to a mixture of 2.5 mM sulfite and 1 mM Ni(II) increased the signal intensity about 4-fold, compared with that in the absence of GlyGlyHis, and 15-fold versus that obtained by autoxidation of sulfite alone. The time course of free radical generation is shown in Figure 2. Formation of the radicals reached its saturation level in about 5 min, indicating a relatively fast reaction. A sodium sulfite solution containing GlyGlyHis without Ni(II) yielded the free radicals in amounts comparable to those obtained from autoxidation of the sulfite alone (Figure 1d). A mixture of Ni(II) and GlyGlyHis without sulfite did not generate any detectable amounts of free radicals (Figure 1e).

Analysis of the spectrum in Figure 1c revealed that the hyperfine splittings were different from those shown in Figure 1b. These differences might be due to the trapping of other radicals in addition to $\cdot SO_3^-$. The spectrum in Figure 1c seemed to be a superposition of those from the DMPO adducts of $\cdot SO_3^-$ and ·OH radicals. To test this possibility, we used the well-known reaction of $K_2Cr_2O_7$ with Na_2SO_3 to generate the $\cdot SO_3^-$ radicals (*9,28*). As shown in Figure 3a, this reaction generated the typical DMPO/$\cdot SO_3^-$ adduct, with hyperfine splittings of a_N = 14.7 G and a_H = 16.1 G.

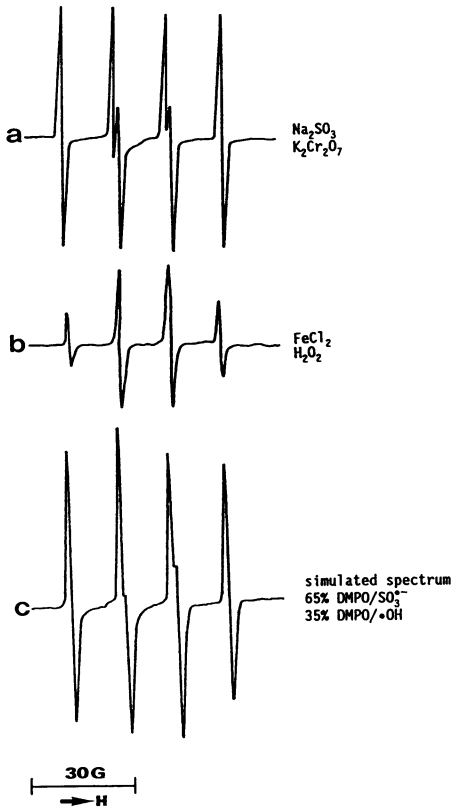

Figure 3. ESR spectra recorded from phosphate buffer solutions (pH 7.4) containing 60 mM DMPO and (a) 1 mM Na_2SO_3 plus 0.1 mM $K_2Cr_2O_7$, (b) 1 mM H_2O_2 plus 0.05 mM $FeCl_2$. (c) Computer-simulated spectrum of 65% DMPO/•SO_3^- and 35% DMPO/•OH. Note that spectrum c closely resembles that in Figure 1c.

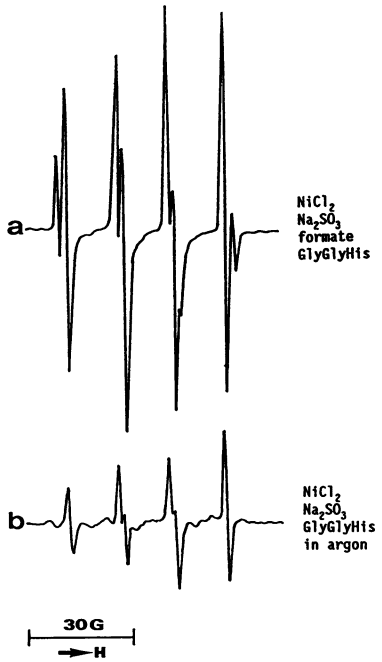

Figure 4. ESR spectra, recorded 3 min after reactions were initiated, from a phosphate buffer solution (pH 7.4) of 100 mM DMPO, 2.5 mM Na_2SO_3, 1 mM $NiCl_2$, 0.6 M sodium formate, and 2 mM GlyGlyHis. (a) Under ambient oxygen, (b) under argon. The ESR spectrometer settings were the same as those described in the legend to Figure 1.

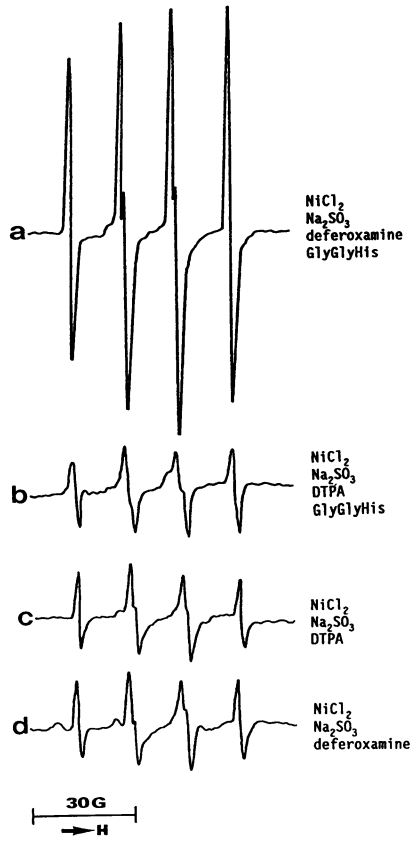

Figure 5. ESR spectra, recorded 3 min after reactions were initiated, from phosphate buffer solutions (pH 7.4) of various combinations of 100 mM DMPO, 2.5 mM Na_2SO_3, 1 mM $NiCl_2$, 2 mM GlyGlyHis, 2 mM deferoxamine, and 2 mM DTPA. The ESR spectrometer settings were the same as those described in the legend to Figure 1.

We also used the Fenton reagent to generate authentic DMPO/•OH adduct, with hyperfine splittings of $a_N = a_H = 14.9$ G (Figure 3b). An ASPECT 2000 computer was used to combine various percentages of the DMPO/•SO_3^- and DMPO/•OH adduct spectra. The profile in Figure 3c, which corresponded most closely with the spectrum in Figure 1c, was a combination of 65% DMPO/•SO_3^- and 35% DMPO/•OH. To ascertain whether •OH radicals were indeed produced in the sulfite oxidation in the presence of Ni(II) and GlyGlyHis, formate was used as an •OH radical scavenger. It was added to a mixture containing 2.5 mM sodium sulfite, 1 mM Ni(II) and 2 mM GlyGlyHis at concentrations of up to 0.8 M. The resulting spectrum is shown in Figure 4a. Formate caused the appearance of DMPO/•COO^- adduct, suggesting that •OH radical was indeed being produced in the mixture of sodium sulfite, Ni(II), and GlyGlyHis.

An experiment carried out under argon showed a significant decrease in the overall spectral intensity (Figure 4b). Thus, the free radical generation from the mixture of sodium sulfite, Ni(II), and GlyGlyHis required molecular oxygen. The residual free radical generation observed under argon may be due to remnants of oxygen dissolved in the reaction mixture.

Figure 5a shows the ESR spectrum obtained from a mixture containing 1 mM Ni(II), 2.5 mM sulfite, 2 mM GlyGlyHis, and 2 mM deferoxamine. The latter caused only a slight decrease in the overall spectral intensity (compare Figures 5a and 1c). Moreover, upon addition of deferoxamine, the second peak of the spectrum exhibited a doublet, similar to that in Figure 3a. This indicates that the major spin adduct obtained in this case was DMPO/•SO_3^-. Hence, deferoxamine inhibited •OH generation to a greater degree than •SO_3^- generation. Addition of DTPA sharply reduced the spectral intensity (Figure 5b). In the absence of GlyGlyHis, deferoxamine and DTPA decreased the enhancing effect of Ni(II) on free radical generation from autoxidation of sulfite alone (compare Figures 5c and 5d with Figure 1b).

Several other Ni(II) chelators, such as GlyGlyGlyGly, histidine, anserine, carnosine, homocarnosine, GSH, penicillamine, and albumin at 2 mM concentrations were also tested for their effect on 1 mM Ni(II)-mediated free radical generation from 2.5 mM sodium sulfite at pH 7.4. Of these chelators, only albumin had a significant enhancement effect. Albumin doubled the peak intensity of the free radical adducts compared with the intensity produced in the mixture of Na_2SO_3 and $NiCl_2$. For comparison, under the same condition, 2 mM GlyGlyHis increased the intensity by a factor of 6.

Effect of GlyGlyHis on Free Radical Generation in Nickel(II) Sulfite Suspension

Figure 6 shows a spectrum obtained from sparingly soluble $NiSO_3$ (50 mg/ml) suspended in phosphate buffer (pH 7.4) in the presence of 2 mM GlyGlyHis. The spectral intensity reached its saturation level in about 4 min. Without GlyGlyHis, $NiSO_3$ suspension did not generate any significant amounts of free radicals. The broad peaks in the spectra obtained (Figure 6a, 6b) suggest that the majority of the free

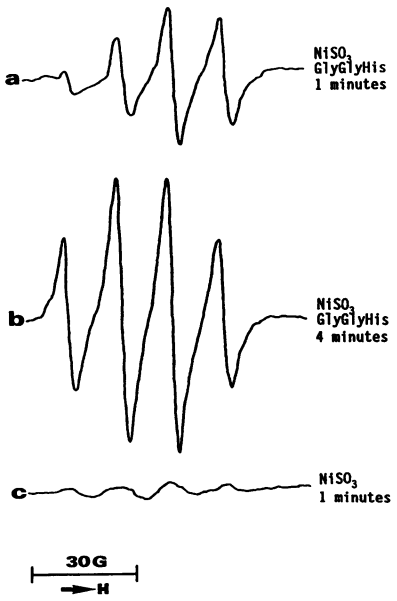

Figure 6. ESR spectra, recorded from phosphate buffer solutions (pH 7.4) of 100 mM DMPO, 50 mg/ml $NiSO_3$ and 2 mM GlyGlyHis. (a) Spectrum recorded 1 min after reaction initiation; (b) spectrum recorded 4 min after reaction initiation. (c) Same as (a) but without GlyGlyHis. The ESR spectrometer settings were the same as those described in the legend to Figure 1.

radicals generated were surface-located and had a limited motion in the $NiSO_3$ suspension (*29*). Since the spectrum consisted of only four peaks, it can be assigned to a combination of DMPO/$\cdot SO_3^-$ and DMPO/•OH as discussed in the previous section. However, the broadness of the peaks made it difficult to determine the ratio of DMPO/$\cdot SO_3^-$ to DMPO/•OH.

Effect of GlyGlyHis on Free Radical Generation in Nickel Subsulfide Suspension

Figure 7a and 7b shows the spectra obtained from a suspension of 50 mg/ml Ni_3S_2 in phosphate buffer (pH 7.4) in the presence of 2 mM GlyGlyHis and 5 mM H_2O_2. These spectra were recorded at time intervals of 1 min and 3.5 min, respectively. The DMPO free radical adducts shown in Figure 7b were present in solution, as indicated by the relatively narrow spectral peaks (compared with Figure 6b). Like that in Figure 6b, the spectrum in Figure 7b can be assigned to a combination of DMPO/$\cdot SO_3^-$ and DMPO/•OH. The control reaction of Ni(II) and GlyGlyHis with H_2O_2 also generated a relatively strong spin adduct signal (Figure 7c). Computer analysis indicated that this signal consisted of 50% DMPO/superoxide radical ($\cdot O_2^-$) adduct with hyperfine splittings of a_N = 14.2 G, a_H = 11.4 G and a_H^- = 1.3 G and DMPO/•OH adduct with hyperfine splittings of $a_N = a_H$ = 14.9 G, in concordance with those reported earlier (*30*). Since the spectrum in Figure 7b consisted of only four peaks, it appeared that in contrast to the case for Ni(II), no detectable amount of O_2^- was produced from H_2O_2 by Ni_3S_2 in the presence of GlyGlyHis. Ni_3S_2 suspension containing GlyGlyHis or H_2O_2 alone did not generate any significant amounts of free radicals (Figure 7d, e).

Figures 6b and 7b show that the intensities of the two spectra, representing $NiSO_3$ and Ni_3S_2, respectively, are comparable but the linewidth of the former is very broad. Since the integration of the spectrum represents the amount of free radicals generated, the relative yield of free radical production by Ni_3S_2 was much lower than that by $NiSO_3$.

Discussion

It has been known that Ni(II) does not easily react with oxidants to produce free radical species (*31,32*). However, its reactivity toward molecular oxygen, H_2O_2, and lipid hydroperoxides can be greatly enhanced by coordination with certain chelating agents, including GlyGlyHis (*22,23,30,32,33*). Likewise, the results obtained in the present study show that while Ni(II) can increase $\cdot SO_3^-$ radical generation from sulfite to some extent, Ni(II) chelated with the oligopeptide GlyGlyHis is far more effective. Most importantly, in addition to $\cdot SO_3^-$ radical, chelated Ni(II) markedly enhances generation of •OH radicals in this system. Unlike GlyGlyHis, other histidyl chelators, including anserine, carnosine, homocarnosine, and histidine itself, as well as some thiol-containing chelators such as GSH and penicillamine, did not affect the Ni(II)-enhanced free radical generation from sodium sulfite. It is noteworthy that all these chelators have been shown to enhance Ni(II)-mediated free radical generation from model lipid hydroperoxides, cumene hydroperoxide and *t*-butyl hydroperoxide (*22,23*). Similarly, GlyGlyGlyGly, which appeared to lack any effect on Ni(II) action in the present study, has been reported to enhance Ni(II)-promoted free radical generation from H_2O_2 (*30*). It appears, therefore, that the enhancing effect of various Ni(II) chelates on free radical production in the case of oxidation of different substrates depends on the chemistry of those substrates.

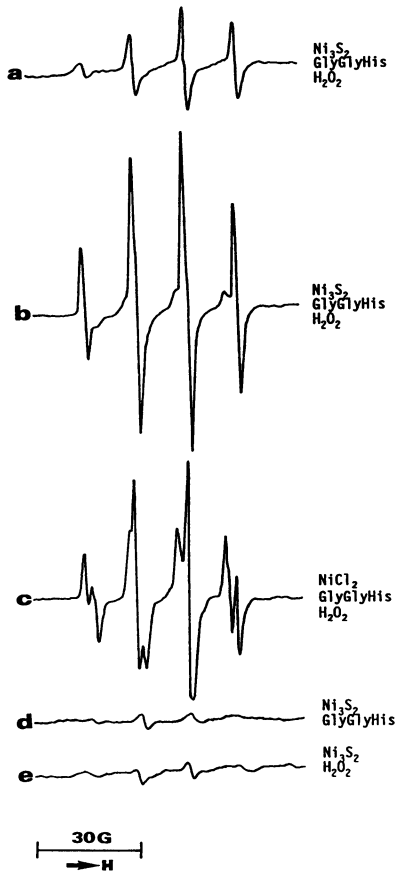

Figure 7. ESR spectra, recorded 1 min after the reactions were initiated, from phosphate buffer solutions (pH 7.4) of 100 mM DMPO and (a) 50 mg/ml Ni_3S_2, 5 mM H_2O_2, and 2 mM GlyGlyHis, (b) Same as (a) but the spectrum was recorded 4 min after the reaction was initiated. (c) Same as (b) but 1 mM $NiCl_2$ used in place of Ni_3S_2. (d) Same as (a) but without H_2O_2. (e) Same as (b) but without GlyGlyHis. The spectrometer settings were the same as those in the legend to Figure 1.

The present study also shows that besides assisting Ni(II) in the enhancement of free radical production by autoxidation of the sulfite anion in solution, GlyGlyHis could as well increase radical production from sparingly soluble $NiSO_3$ particles in aqueous suspension. In contrast, Ni_3S_2 suspension, alone or in the presence of GlyGlyHis, did not generate a detectable amount of free radicals under ambient oxygen. Free radicals could be detected in the Ni_3S_2/GlyGlyHis system only after the addition of H_2O_2. Unlike in the suspension of $NiSO_3$ in which $\cdot SO_3^-$ and •OH radicals were associated mainly with the particle surface (broad ESR peaks), the same radicals generated in the Ni_3S_2 system were detectable in the solution (narrow peaks). The reason for this difference is not clear. It may be due to the different physicochemial properties of the two sys-

tems, e.g., different distribution of Ni(II) and sulfite between the aqueous and the solid phases and the presence of H_2O_2. Apparently, H_2O_2 functioned as a Ni_3S_2 oxidant to produce Ni(II) and sulfite, a mixture facilitating generation of $\cdot SO_3^-$ and ·OH, especially in the presence of GlyGlyHis, as discussed above. It also seems possible that Ni(II), derived from Ni_3S_2 and chelated with GlyGlyHis, reacted with H_2O_2 to yield ·OH and $\cdot O_2^-$ radicals, as described elsewhere (*30*). Both, ·OH and $\cdot O_2^-$ could, in turn, react with sulfite to produce $\cdot SO_3^-$ radicals (*34,35*). However, no DMPO/$\cdot O_2^-$ adduct was detected, which argues against but does not exclude the second scenario.

It is now generally believed that $\cdot SO_3^-$ radical can cause many adverse effects while reacting with biological molecules. These include oxidation of methionine (*36*), diphosphopyridine nucleotides (*37*), and lipids (*38*); destruction of β-carotene (*8*) and tryptophan (*36*); addition to double bonds in unsaturated fatty acids (*39*); and modification of nucleic acids (*7,40*). Some of these effects are potentially genotoxic and may contribute to carcinogenesis (*3–5*). The genotoxicity of ·OH radical, also generated by sulfite oxidation, is well recognized (*41*). For example, the ·OH radical generated by sodium sulfite autoxidation was reported to be capable of producing promutagenic 8-OH-dG in DNA (*10*). The observed enhancement of ·OH radical production from sulfite by Ni(II) chelated with GlyGlyHis and albumin may be involved in the mechanism(s) of carcinogenesis by nickel(II) sulfides, the strongest nickel carcinogens. Both Ni(II) and sulfite are derived from oxidative dissolution of Ni_3S_2 and crystalline NiS (*20, 21*). Albumin and other proteins having metal binding sites of the GlyGlyHis type are major tissue Ni(II) carriers (*42*). All these reagents, together with H_2O_2 may thus act in concert to generate genotoxic radicals from nickel sulfides. H_2O_2 may originate from cellular metabolic or pathogenic processes; e.g., sulfides of nickel and cadmium induce H_2O_2 formation by polymorphonuclear leukocytes (*43*). In concordance with this assumption, in the presence of molecular oxygen, Ni_3S_2 was found to cause hydroxylation of dG to 8-OH-dG in vitro. The yield of 8-OH-dG was greatly enhanced by H_2O_2 (*19*). Ni_3S_2 and $NiSO_3$ were also found to produce another potentially mutagenic effect, i.e., deamination of 5-methyl-2'-deoxycytidine to thymidine (*44*). $NiSO_3$ was much more active in this reaction than the well-known deaminating agent, sodium bisulfite. Thus, the exceptionally high carcinogenic potential of Ni_3S_2 compared to other nickel derivatives (*17*) may be due to the ability of both the metal and sulfide constituents of the molecule to enhance generation of genotoxic free radicals.

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