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STABILITY AND REACTIVITY OF FREE RADICALS: A PHYSICOCHEMICAL PERSPECTIVE WITH BIOLOGICAL IMPLICATIONS

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□ *Several factors control the reactivity of radicals and can provide the strategies to convert highly reactive species into more persistent species that are easier to detect in an experiment. A reaction can only proceed if sufficient mobility and thermodynamic driving force are provided and the reaction is allowed by steric considerations and by electronic states of the reagents and products. A violation of at least one of these conditions can make the radical relatively stable. In certain cases, these factors occur naturally, in other situations, they can be purposefully manipulated to reduce the reactivity of highly reactive radicals, prolonging their lifetime and increasing their concentration. The discussed examples cover a vast range of lifetimes, from 10^{-9} seconds to 10^{9} years, at concentration levels down to 10^{3} radicals per sample (10^{-18} M), and stress that stability and reactivity are not independent notions and are the two sides of the same coin.*

Keywords Unpaired electron, Radical mobility, Electronic stabilization, Spin delocalization, Spin selection rules, Electron spin resonance (ESR), Spectrophotometry, Magnetic field effect

INTRODUCTION

Most molecules have closed electronic shells, and all electrons there sit in coupled "up/down" pairs. Such molecules are relatively stable and

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require activation in order to get involved into a chemical transformation. The breaking of the "up/down" motif creates unpaired electrons and turns the molecule into a radical. As the name implies, the radicals are usually rather reactive species seeking for possibilities to couple their unpaired electrons to something (1). Radicals are created when adding an extra electron to, or removing an electron from, a closed-shell molecule forming radical ions, and upon thermal or photo-induced bond cleavage, the process that is crucial for almost every subfield of chemistry. Radicals also appear naturally when a bond is formed with an odd number of electrons, as is the case with nitric oxides NO and NO_2, in which N contributes three valence electrons while O gives four, so that no closed shell can be formed.

A typical chemical reaction takes breaking an old bond (the "difficult part", *i.e.,* the rate limiting step) and making a new bond (the "easy part"). However, for radicals there is no need to break; the difficult part has already been done, radical reactions are usually barrier-less, and thus radicals must be highly reactive, transient species, readily participating in chemical reactions. While this is indeed normally the case, there are several important situations when the opposite is true: there exist "persistent" radicals that are more stable than the molecules that can form directly from them, and "stable" radicals that live essentially forever. The following sections discuss the factors that govern the reactivity of radicals, and the strategies to convert highly reactive species into more persistent ones that are easier to detect in an experiment.

Stable and Persistent Radicals

In order for two reagents to combine into a product, the reagents need to approach each other, *i.e.,* some form of mobility is required; the reagents need to align with each other in a required way, *i.e.,* the reaction has to be sterically feasible; the product needs to be more stable than the pair of initial reagents, *i.e.,* the reaction has to be thermodynamically driven; and the reaction must be allowed by the electronic states of reagents and products. A violation of at least one of these conditions can make the radical relatively stable.

A typical example of biologic radicals that are stable due to restricted mobility is radiation-generated paramagnetic centers in tooth enamel (Table 1). The enamel is built from prism-shaped scales of hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$, in which 2–3% of PO_4^{3-} are substituted for carbonate CO_3^{2-}. Irradiation of tooth enamel by light or high-energy irradiation produces paramagnetic centers seen by electron spin resonance (ESR) (2). The free electrons produced upon irradiation are trapped by CO_3^{2-} to form several types of carbonate-derived paramagnetic centers, including CO_2^-, CO_3^{3-}, CO_3^-, and CO^-, with the main radiation-induced radical being

TABLE 1 Representative Radicals and Their Stabilizing Factors

Radical	Source	Stabilizing factors	Half life
Hydroxyl radicals ($OH^{\bullet}$)	Generated by Fenton reaction; metalloenzymes *in vivo*; exposure to high-energy radiation in models	None	Diffusion-controlled reactivity, 10^{-9} to 10^{-6} seconds
Thiyl radicals ($RS^{\bullet}$)	*Intermediate* in enzymatic processes, reactions of thiols with other radicals	None for small thiyl radicals, *e.g.*, glutathione-derived	Nearly diffusion-controlled reactivity with NO, ascorbate; $RS^{\bullet} \rightarrow RC^{\bullet}$ rearrangement in milliseconds
Superoxide radicals ($O_2^{\bullet -}$)	Generation in mitochondrial respiratory chain; autoxidation processes *in vivo*; from donors (*e.g.*, KO_2) in models	None	Diffusion-controlled reactivity, 10^{-6} seconds *in vivo*, 1 second at pH 10
Nitric oxide ($NO^{\bullet}$)	Enzymatic generation *in vivo*; from donors (*e.g.*, SIN-1) in models	Particular electronic structure of the molecule	Milliseconds to seconds depending on available concentration of oxygen, otherwise stable
Semiquinone radicals ($SQ^{\bullet}$)	Generated enzymatically in immune response of insects, used as the electron transport chain in photosynthesis and respiration	Delocalization, additional spin stabilization for ortho-SQ radicals in the presence of metal ions	10^{-4} seconds in aqueous anoxic solution, bimolecular disproportionation with up to diffusion-controlled rates
Tocopheroxyl radicals	Reaction of Vitamin E with radicals	Electrosteric stabilization	5 min. isolated in micelle, reduction with ascorbate at 1/10th of diffusion rate constant
Ascorbate-free radicals ($Asc^{\bullet -}$)	Reaction of Vitamin C with radicals	Resonance (delocalization) stabilization	Seconds in blood/tissues
Peroxyl radicals ($ROO^{\bullet}$) in lipids, DNA, proteins	Reaction of carbon radicals with dioxygen, chain peroxidation processes *in vivo*; exposure to high-energy radiation in model	Restricted mobility	Seconds to hours depending on conditions

Nitroxyl radicals: imidazoline-derived	Artificially introduced as pH-sensitive spin probes	Electronic stability of incorporated NO, steric protection, spin delocalization	Seconds to minutes in blood/tissues, depending on the degree of steric protection
Nitroxyl radicals: piperidine- and pyrrolidine-derived	Produced by spin trapping to artificially introduced precursors	Electronic stability of incorporated NO, steric protection	Minutes to hours in blood/tissues
Triarylmethyl radicals	Artificially introduced as pO_2-sensitive and/or pH-sensitive spin probes	Electronic stability of extended planar π-system, steric protection, spin delocalization	Minutes to hours in blood/tissues
CO_3^{3-}	Irradiation of hydroxyapatitie-rich tissues, *e.g.,* tooth enamel	Blocked mobility	10^9 years
Dioxygen (O_2)	Respiration processes	Kinetically stable in triplet ground state due to spin selection rules	Stable

CO_2^-. However, most interesting is another radical, the stable CO_3^{3-}, which is accumulated and does not disappear from the crystalline structure, having lifetime of about 10^9 years. Here as the centers are trapped in the crystalline structure of the enamel they cannot move to find a partner unless severely heated, and thus their chemical reactivity is completely blocked.

An important class of persistent radicals are nitroxides such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (Figure 1a) or imidazoline-derived imino- and nitronyl-nitroxide type radicals as shown in Figure 1b (3). As pure solids these radicals can be stored for years, and in solutions they also persist for extended periods of time, up to months. The radicals are stable enough to be used as off-the-shelf synthons, *e.g.*, for preparation of stable paramagnetic complexes with metal ions as shown in Figure 1c (4), or to measure local values of pH and thiol content in various biological systems based on the observation of specific chemical reactions of these nitroxides with protons or thiols followed by significant changes in their ESR spectra (5).

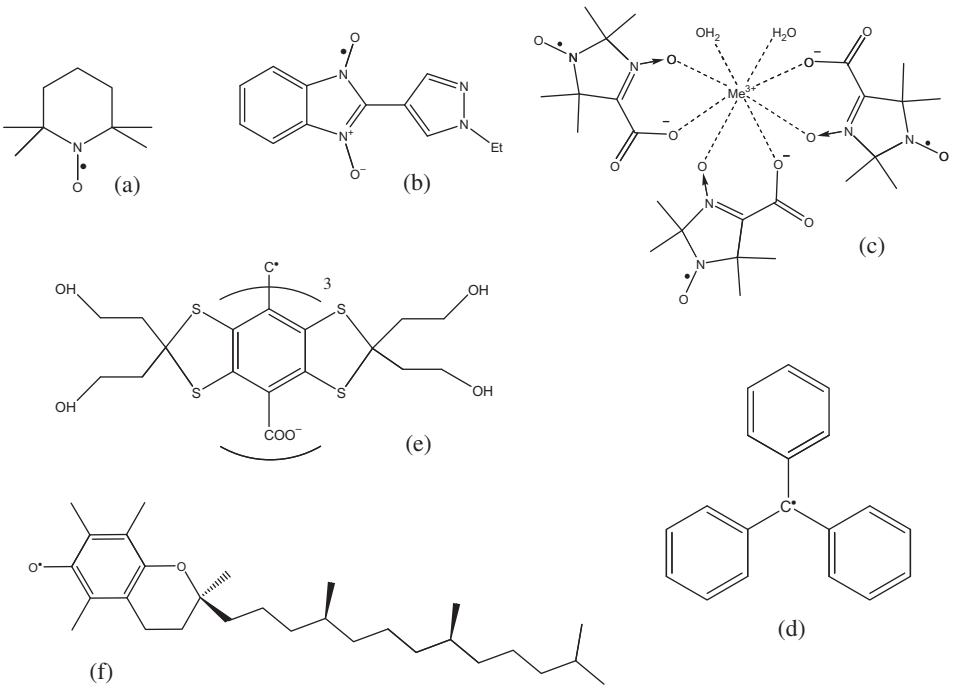

FIGURE 1 The persistent radicals: (a) TEMPO – a typical piperidine-derived nitroxide; (b) an imidazoline-derived nitronyl nitroxide; (c) persistent radicals coordinated to a trivalent lanthanide ion in a stable triradical complex; (d) triphenylmethyl radical; (e) a commercially available triarylmethyl radical, OX063; (f) tocopheroxyl radical.

These radicals inherit their stability from nitric oxide (NO) that is the main carrier of the unpaired electron here, and is additionally sterically protected by four guarding methyl groups or more bulkier substituents. Nitric oxide itself is so stable that its concentration in exhaled air is routinely used as a reliable biomarker in diagnosing lung status (Table 1) (6), and its coupling into at first sight plausible dimeric form ON-NO is possible only under extreme conditions, *e.g.,* when reductively catalyzed by certain transition metal complexes that mimic the natural enzyme NO reductase (7). The biological importance of persistent nitroxides is that by using suitable precursors highly reactive and thus directly inaccessible naturally occurring radicals such as hydroxyls and peroxyls can be converted into more stable nitroxides that can be further detected.

Another epitomic sterically and electronically stabilized persistent radical is triphenylmethyl radical (Figure 1d) and its descendants, triarylmethyl (trityl) radicals, TAMs. Although the less sterically loaded diarylmethyl radicals readily combine to form tetraarylethane, the corresponding hexaarylethane is too sterically overcrowded to form the central C-C bond. Even more sterically hindered TAMs that further have no magnetic nuclei in the vicinity of the spin and thus give a single very narrow ESR line are purposefully produced for ESR oxymetry (8) and are commercially available, such as OX063 (Figure 1e) from Nycomed Innovations Co. (Malmo, Sweden). The half-life of such a spin probe in whole blood is about 20 min., with the rate of clearance by excretion about 0.040 $min.^{-1}$ (9). Continuous infusion following a bolus injection of the probe was found to be effective to obtain stable plasma concentration as well as image intensity to permit reliable pO_2 estimates in animal models.

The radical derived from α-tocopherol, or Vitamin E (Figure 1f), provides a biologically relevant example of an electrosterically stabilized radical (10). The radical scavenging functionality of tocopherol is provided by its phenol-type head, as phenols readily donate the hydrogen of their hydroxyl group to neutralize a free radical creating the corresponding phenoxyl radical stabilized by delocalization of spin density into the aromatic system. However, the O-H bond in tocopherol is further weakened and the phenoxyl radical derived from it is further stabilized due to the presence of the oxygen atom that is para to the OH group and has its lone pair in favorable orientation with respect to the benzene ring. The p orbital of this oxygen couples into the π-system, thus augmenting it and stabilizing the phenoxyl radical by conjugative electron delocalization. The rates of Vitamin E oxidation by peroxyl radicals to form the tocopheroxyl radical are much higher than the rates of the back reaction between the tocopheorxyl radical and alkyl hydroperoxides, with typical values for the respective rate constants of the order of 3×10^6 $M^{-1}s^{-1}$ and 3×10^{-1} $M^{-1}s^{-1}$, demonstrating the seven orders of magnitude difference (11). Normally,

the tocopheroxyl radical is regenerated back to tocopherol by companion antioxidants such as Vitamin C to produce ascorbate free radicals, and when the latter are not available can, due to their persistence, cause more damage than they cure, creating a pool of latent radicals.

Going from macroscopic thermodynamic considerations to the elementary step of a chemical reaction, an important factor governing the reactivity of species with unpaired electrons is the conservation of the total electronic spin throughout the reaction step leading from reagents to products. A radical has electronic spin of $^1/_2$, and therefore its reaction with a normal closed-shell molecule having total spin 0 must also produce a spin-$^1/_2$ species, *i.e.,* a radical. The radical is thus "indestructible" and cannot disappear in reactions with normal molecules, although it can convert into a different type of radical, as was the case with the peroxyl/tocopheroxyl pair above. In order to disappear the radical must meet either another radical – two spins $^1/_2$ can combine into total spin 0, *i.e.,* two radicals can recombine into a closed-shell molecule – or a redox-active metal center that can change its valence and thus spin state. Two spins $^1/_2$ can also combine into total spin 1, thus offering a distinctly different reaction channel leading to a triplet product. The latter is usually thermodynamically less favorable, and thus the total spin state of the pair of reacting radicals plays the role of the switch that determines which route, singlet or triplet, the reaction will take, and whether it will proceed at all.

An important example of the controlling effect of the electronic spin is the intrinsic stability and inertness of dioxygen, the ubiquitous oxygen molecule (Table 1) (12). The ground state of oxygen is a triplet, $^3\Sigma^-_g$, so formally dioxygen is a biradical having two unpaired electrons. Furthermore, dioxygen-utilizing reactions involve the cleavage of the oxygen-oxygen bond and are very energetically favorable, and dioxygen is small enough to avoid any sterical hindrance. However, the dioxygen is very stable kinetically towards reactions with closed-shell molecules: as the total electronic spin of such a pair of reagents is $1 + 0 = 1$, the product must also form in a triplet state that for most molecules is an excited state, and such a reaction involves a high energy barrier leading to low rate constants. Some form of activation is thus required for reaction to proceed.

The oxygen molecule can be converted into the lowest singlet excited state, $^1\Delta_g$, lying 22.4 kCal above the ground state, producing the highly reactive "singlet oxygen" that lacks the spin barrier for further reactions. Oxygen can be converted to its singlet state with light in the presence of a triplet photosensitizer (PS), a molecule that upon absorption of light forms a metastable triplet excited state , ^{3}PS*, followed by spin- and energy-allowed combination of two triplets into singlet excited oxygen, $^3O_2 + {}^3PS^* \rightarrow {}^1O_2* + {}^1PS$. Another option is adding an electron to form the superoxide anion: $^3O_2 + {}^2e^- \rightarrow {}^2O_2{}^-$. The latter is an ordinary radical with spin $^1/_2$ and can

participate in radical recombination reactions, *e.g.,* it readily reacts with NO to form closed-shell peroxynitrite: $^2O_2^- + {}^2NO \rightarrow {}^1 ONOO^-$ with nearly diffusion-controlled rate constant of $(1.6 \pm 0.3) \times 10^{10}$ $M^{-1}s^{-1}$ (13). The $^2O_2^-$ is also redox-active and can act both as an efficient donor and acceptor of electrons. The next way to remove the spin barrier is reacting $^3O_2$ with a radical ^2R to form another radical, *e.g.,* converting an alkyl radical into a peroxyl radical: $^3O_2 + {}^2R \rightarrow {}^2RO_2$. All these forms of activation produce one of the well-known "reactive oxygen species."

Finally, the reaction of triplet oxygen with singlet substrate can be catalyzed by a transition metal ion that can shuttle between different valence and thus spin states – this is the route chosen by nature in numerous oxygen-utilizing enzymes, *e.g.,* heme-containing oxygenases (12), in which to promote the reaction dioxygen is coordinated to the heme iron. Here the triplet-spin barrier is removed due to the presence of the third spin-carrying species acting as a "spin buffer" allowing to change the total spin state of the pair of reacting molecules from triplet to singlet.

Approaching Unstable and Reactive Radicals

The discussed factors that reduce the reactivity of radicals are directly useable for devising approaches for the study of highly reactive radicals. The concentrations of biologically relevant radicals are often too low for direct observation due to their high reactivity, and to build up the concentration either the mobility has to be reduced, or the radical can be converted into a more stable radical that is already accessible in experiment. Another option for boosting the concentration of radicals in model studies is using pulsed high energy irradiation to create extremely high momentary concentrations of radicals and then follow them by optical absorption spectroscopy, magnetic resonance, or other suitable techniques. Pulse radiolysis or photolysis in aqueous environments offers the way to study reactive short-lived species produced in living organisms (14), such as hydroxyl, peroxyl, thiyl, and semiquinone radicals, while radiolysis in non polar media can reproduce the conditions of the hydrophobic biologic media such as inner parts of membranes. It should be kept in mind though that the reactivity of *in vivo* radicals is very much dependent on the environment, and conclusions drawn from studies in model systems should not be unconditionally transferred to naturally occurring systems, *e.g.,* stability of a radical towards reduction by ascorbate mimicking the reductive environment of whole blood in a model system does not guarantee its stability *in vivo*. Finally, the spin selectivity of radical recombination reactions offers approaches to not only study radicals at intrinsically low concentrations (fluorescence-based spin chemistry methods are quite comfortable with steady-state concentration of tens-to-hundreds of radicals

per sample, aiming at the "single-molecule" target), but to study the "difficult" radicals, *e.g.,* having short spin relaxation times or unstable towards monomolecular decay, even in the absence of reaction partners.

An example of literally "freezing" the radicals is observation of O_2^- at 95K in EtOH (15). The radical anion is generated by vacuum-UV photolysis of oxygenated ethanolic solutions, and is directly identified by its optical absorption spectrum and low-temperature ESR spectrum. Just three seconds of irradiation followed by rapid freezing in liquid nitrogen produced the stable concentration of 130 μM of O_2^- in the sample – more than enough to yield an ESR spectrum.

Another approach to visualize superoxide and other reactive radicals in ESR is using the spin-trapping methodology: converting an unstable radical into a more stable persistent radical, usually a nitroxyl, by addition to or oxidation of a suitable precursor molecule – the "spin trap." The popular addition-type spin traps are nitrones that produce specific ESR spectra of the adducts allowing the reconstruction of the identity of the added radical (Figure 2a). An advanced trap 5-(diethoxyphosphoryl)-5-methyl-1-pyrroline

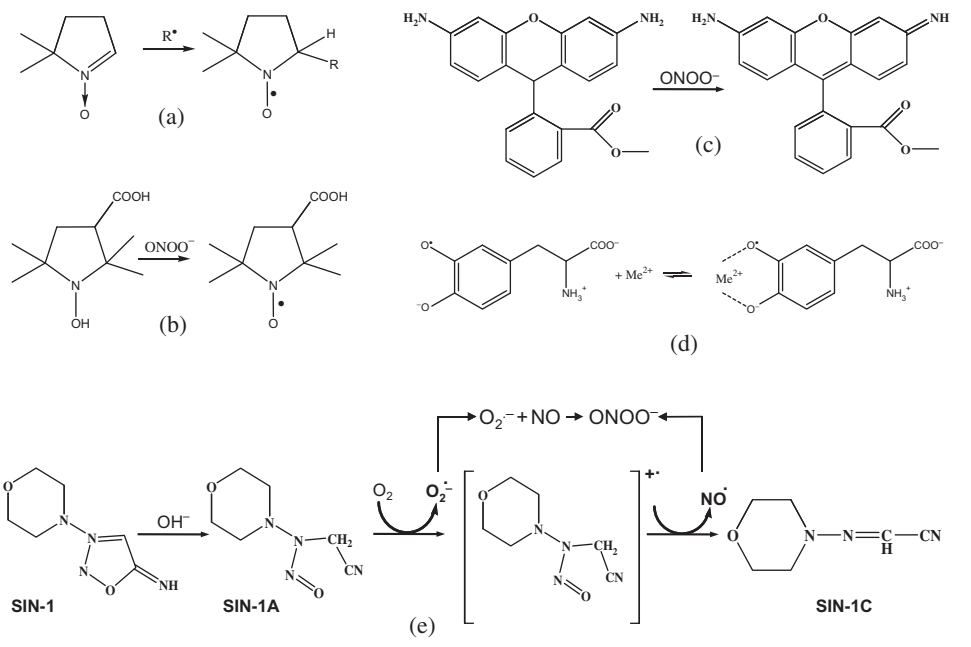

FIGURE 2 Converting highly reactive species into more persistent species: (a) spin trapping by a cyclic nitrone to produce a persistent nitroxide; (b) oxidation of a cyclic hydroxylamine CP-H into a persistent nitroxide CP; (c) oxidation of dihydrorhodamine-123 (DHR-123) into a specifically colored persistent rhodamine-123 (RH-123); (d) spin stabilization of a DOPA-semiquinone radical by a divalent metal ion; (e) a model system of SIN-1 for generation of a pair of superoxide anion and nitric oxide that recombine into peroxynitrite.

N-oxide (DEPMPO) (16) reacts with O_2^- with rate constant of 0.53 $M^{-1}s^{-1}$ to form adduct DEPMPO-OOH having lifetime of 890 seconds at pH 7. The persistence of the adduct can be further improved by sterically protecting the formed radical, *e.g.,* addition of methylated cyclodextrins (CD) to the DEPMPO/superoxide system increases the lifetime of the DEPMPO-OOH adduct to 96 min. by forming an inclusion complex of adduct with CD, in which the radical center is safely tucked inside the CD bucket (17).

A popular redox-type spin trap is CP-H (Fig. 2b), 1-hydroxy-3-carboxy-pyrrolidine (18), a sterically hindered hydroxylamine that is oxidized by O_2^- with rate constant 3.2×10^3 $M^{-1}s^{-1}$ and by $ONOO^-$ with a rate constant of 4.5×10^9 $M^{-1}s^{-1}$ by losing the hydrogen of its hydroxyl group to form a persistent nitroxyl radical, CP. This trap was used, *e.g.,* to study the formation of reactive oxygen species in hemolymph and hemocytes of *Galleria mellonella* and *Dendrolimus superans sibiricus* larvae by ESR spectroscopy in an attempt to clarify the role of superoxide radical and 3,4-dihydroxyphenylalanine (DOPA)-derived quinones/semiquinones in the immune response of insects (19). An important "intrinsic spin trap" that is naturally present in biological systems is dinitrosyl iron complexes (DNIC) that bind NO, increasing its stability and ensuring effective targeting of NO to organs and tissues (20). The complexes also turn the ESR-silent NO into observable spin-$^1/_2$ paramagnetic species with the ESR spectrum being specific enough to serve as the basis of identification of the compound. Figure 2c shows a related "optical trapping" system: peroxynitrite oxidizes nearly colorless dihydrorhodamine-123 (DHR-123) into a persistent colored rhodamine-123 (RH-123) having a characteristic absorption band with $\lambda_{max} = 500$ nm, $\varepsilon = 74500$ $M^{-1}cm^{-1}$. The yield of RH-123 in this process is 40-44% by the amount of peroxynitrite and strongly depends on such experimental conditions as pH, sample composition, temperature, *etc.* (21).

The stability of the *o*-semiquinone-type transient radical can be increased without changing its chemical identity using the "spin stabilization" methodology (Figure 2d) by forming a bidentate chelate complex with divalent metal ions using the two oxygens in para position to benzene ring that carry substantial spin density (22), *e.g.,* the reported effect of complexation of DOPA semiquinone radical with Zn^{2+} is cutting the rate constant of bimolecular disproportionation of two radicals from 2.5×10^8 $M^{-1}s^{-1}$ down to 1.1×10^4 $M^{-1}s^{-1}$ at pH 5. Spin stabilization with Mg^{2+} was used to assess the formation of DOPA-derived highly reactive intermediates via reactive oxygen species during melanization in hemolymph of insects using ESR spectroscopy (23). The formation of superoxide here was not detected due to reaction of DOPA with superoxide having estimated rate constant of 5×10^5 $M^{-1}s^{-1}$ and producing the

detected DOPA-semiquinone radicals. Comparative studies in hemolymph of intact insects and insects infected by fungal infection suggested the importance of DOPA-semiquinone production in the immune status of insects.

Nitric oxide and superoxide can be generated simultaneously by decomposition of 3-morpholinosydnonimine (SIN-1) (24), yielding the two radicals that further recombine with nearly diffusion-controlled rate constant to form peroxynitrite. As shown in Figure 2e, in oxygenated aqueous solutions the molecule of SIN-1 transforms into intermediate product SIN-1A, transfers an electron to a dioxygen molecule to form O_2^- and then decomposes producing NO and a non radical end product SIN-1C. Figure 3 shows two experimental approaches to determine peroxynitrite

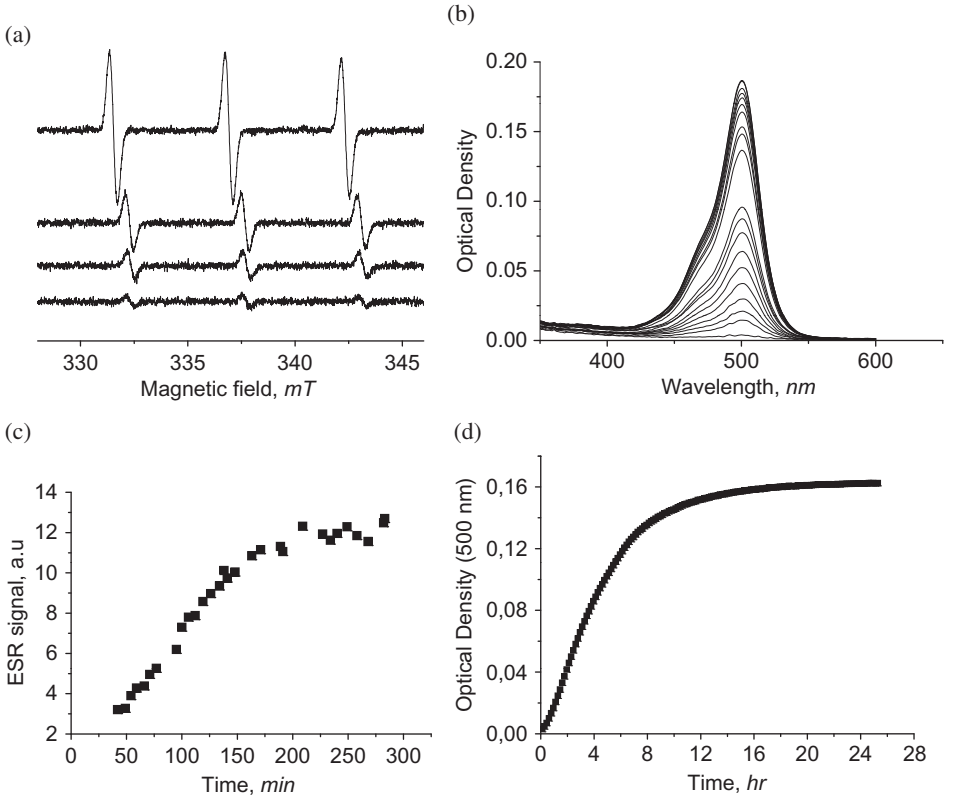

FIGURE 3 Two approaches to determine peroxynitrite generated by decomposition of SIN-1 (Figure 2e), 50 mM phosphate buffer solution at pH 7.6, room temperature: (a) oxidation of CP-H into CP (Figure 2b) with ESR detection of the produced radical, C(SIN-1) = 1 mM, C(CpH) = 1 mM; (b) oxidation of DHR-123 into RH-123 (Figure 2d) with spectrophotometric detection of the produced dye, C(SIN-1) = 0.05 mM, C(DHR-123) = 0.05 mM, optical density measured in a 1 mm cuvette; (c) kinetics of accumulation of the ESR from CP (as per Figure 3a); (d) kinetics of accumulation of optical absorption at 500 nm from RH-123 (as per Figure 3b).

that is generated in this process, oxidation of CP-H into CP followed by ESR detection of the produced persistent CP radical (Figure 3a), and oxidation of DHR-123 into RH-123 followed by spectrophotometric detection of the characteristically colored persistent RH-123 dye in its absorption maximum at 500 nm (Figure 3b). The two lower panels show the kinetics of accumulation of the observed product, either persistent radical (Figure 3c) or persistent dye (Figure 3d). As can be seen, "optical trapping" in this particular case gives much better sensitivity and is preferred if accurate determination of peroxynitrite are needed, provided the background processes have been understood and taken into account.

The system of SIN-1 allows the generation of two radicals (NO and superoxide) as a pair and have them recombine into a detectable product (peroxynitrite), and this opens a possibility to apply the pair-oriented "spin chemistry" methodology (25) to probe these elusive radicals. Exploiting spin correlation in a pair offers an important alternative to conventional magnetoresonance methods of detecting radicals: as already noted, in a pair of reacting radicals the mutual alignment of their spins controls, whether the recombination reaction proceeds or not, and the spins are, tiny magnets that can be manipulated by applying external magnetic fields. A representative pair-oriented technique is our recently developed magnetically affected reaction yield (MARY), or level-crossing spectroscopy, providing magnetic and kinetic parameters of radical ions living as short as nanoseconds at stationary concentrations as low as 10^3 radicals per 1 mL sample (about 10^{-18} M), as opposed to a minimum of about 100 ns and 10^{11}, respectively, for X-band ESR. Thus, the radical cation of neat warm *n*-alkanes were found to have lifetimes varying from 1 ns for *n*-pentane to 33 ns for *n*-hexadecane (26).

Magnetic and spin effects in radical pairs are well studied in photo- and radiation-generated chemical systems involving spin-correlated radical pairs, and were shown to mediate magnetic effects (MFE) in several biologically relevant systems. The MFE in the system of SIN-1 was recently studied by comparing the efficiency of peroxynitrite production in exposed and otherwise identical control samples (27). NO has extremely short relaxation time in solution, about 10^{-12} s, and the MFE approach is currently the only direct way of detecting free NO in liquid as radical, *i.e.,* by sensing its spin.

CONCLUSIONS

Many factors control the reactivity of species with unpaired electrons, the radicals, which cover a vast range of lifetimes, from 10^{-9} seconds to 10^9 years and at concentration levels down to 10^{-19} M (Table 1). The stability and reactivity of radicals are not independent notions, and a

reactive radical is reactive because it is unstable, either thermodynamically or kinetically, and *vice versa*. A stable or persistent radical is non reactive either for kinetic reasons, because there is no suitable partner close enough to react or because the reaction is forbidden by spin selection rules, or due to thermodynamic consideration, when the radical itself is sufficiently stabilized by delocalization of unpaired electron and favorable geometry that it can assume.

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