Supplementary Material Available: Full characterization data for products listed in Table I, for compounds **12**, **14**, **15**, **17**, and **18**, and for complexes **5**, **6**, **7**, and **16** are available (8 pages). Ordering information is given on any current masthead page.[14,15]

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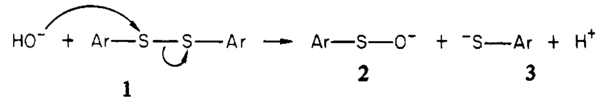
Received May 15, 1980

Oxidative Decomposition of a Mononitrobenzenesulfenate Ion in 15.3 M Potassium Hydroxide via a Stable Meisenheimer Complex

Sir:

A sulfenate ion, 3-carboxylato-4-nitrobenzenesulfenate ($ArSO^-$, **2**), is formed quantitatively by attack of hydroxide ion on the aromatic disulfide, 5,5′-dithiobis(2-nitrobenzoic acid) (Ellman's reagent, ArSSAr, **1**) in 3.0 M NaOH at 25 °C as shown in eq 1.[1] Under these conditions, the red sulfenate ion (**2**) is stable



$$HO^- + Ar—S—S—Ar \rightarrow Ar—S—O^- + {}^-S—Ar + H^+ \quad (1)$$

except for slow oxidation by O_2 to give the corresponding colorless sulfinate ion ($ArSO_2^-$).[1a] We report here an oxidative loss of sulfur from the sulfenate ion **2** in concentrated alkali (15.3 M KOH). Further, these experiments provide the first example of a stable Meisenheimer complex of a *mononitro* derivative of benzene.[2]

The reaction of hydroxide ion with the disulfide **1** [6.1×10^{-5} M] to produce the sulfenate **2** (eq 1) has a calculated half-life of ~0.1 s in 15.3 M KOH at 25 °C.[1b] However, under these conditions, the initial red color due to the sulfenate ion **2** fades within 10 s, and the absorbance of the product mixture in the region ~400-450 nm increases for many minutes; eventually, a stable final spectrum is obtained. The thiophenoxide ion (**3**, eq 1) is stable under these conditions, and subtraction of its absorption spectrum (Figure 1A) from that of the final product mixture produces a difference spectrum (Figure 1B) with a λ_{max} of 425 ± 2 nm. This spectrum identifies the major product of decomposition (64%) of the sulfenate **2** as 3-carboxylato-4-nitrophenoxide ion (**4**, Scheme I), by comparison with the spectrum of an authentic sample (Figure 1C).[3] A similar yield of sulfite ion was obtained.[4] A minor product with a λ_{max} of 475 nm is also formed (Figure 1D).

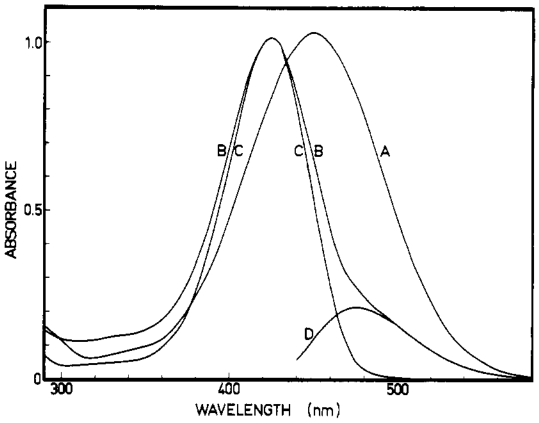


Figure 1. Final products of decomposition of 6.1×10^{-5} M 5,5′-dithiobis(2-nitrobenzoic acid) (**1**) in 15.3 M KOH at 25 °C. Oxygen was supplied as described in Figure 2. (A) Spectrum of 6.1×10^{-5} M 3-carboxylato-4-nitrothiophenoxide ion (**3**). (B) Calculated difference spectrum (final reaction mixture less spectrum A). (C) Spectrum of 3.9×10^{-5} M 3-carboxylato-4-nitrophenoxide ion (**4**). (D) Calculated difference spectrum (spectrum B less spectrum C).

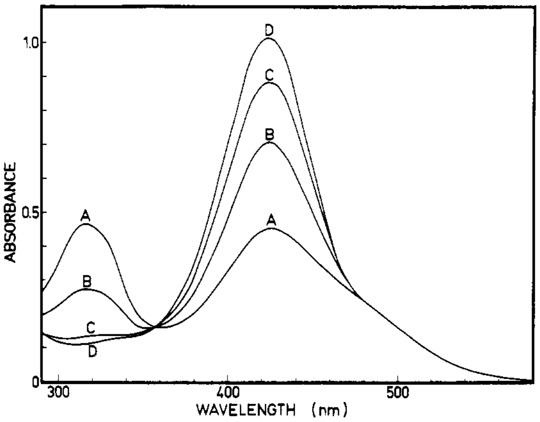
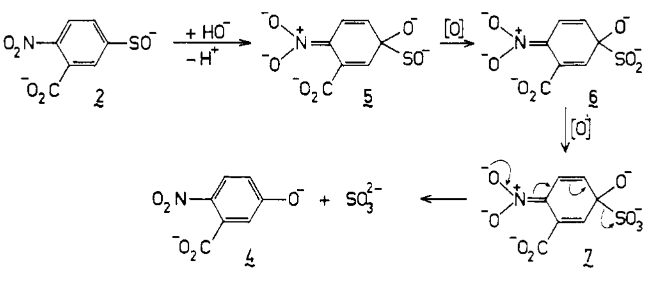


Figure 2. Formation of 3-carboxylato-4-nitrophenoxide ion (**4**) from 6.1×10^{-5} M 5,5′-dithiobis(2-nitrobenzoic acid) (**1**) in 15.3 M KOH at 25 °C. Calculated difference spectra [reaction mixture less 6.1×10^{-5} M 3-carboxylato-4-nitrothiophenoxide ion (**3**), (Figure 1A)]. (A) Scanned at 1.5-4.5 min. (B) Scanned at 9-12 min. (C) Scanned at 17-20 min. (D) Scanned at 60 min (Figure 1B). The solution was bubbled with O_2 for 3 min after scan A and after scan B and for a total of 15 min between scans C and D.

Scheme I



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[1] (a) Blakeley, R. L.; Riddles, P. W.; Zerner, B. *Phosphorus Sulfur* **1980**, in press. (b) Riddles, P. W.; Blakeley, R. L.; Zerner, B. *Anal. Biochem.* **1979**, *94*, 75-81.

[2] (a) Crampton, M. R. *Adv. Phys. Org. Chem.* **1969**, *7*, 211-257. de Boer, Th. J.; Dirkx, I. P. "The Chemistry of the Nitro and Nitroso Groups"; Zeuer, H., Ed.; Interscience: New York, 1970; Part 1, pp 487-612. Hall, T. N.; Poranski, C. F., Jr. *Ibid.* Part 2, pp 329-384. Strauss, M. J. *Chem. Rev.* **1970**, *70*, 667-712. (b) A transient Meisenheimer adduct of hydroxide ion with a mononitro derivative of benzene occurs in the quantitative conversion of 2-nitrobenzoic acid to 2-nitroso-5-hydroxybenzoic acid in 15.8 M KOH: Treston, A.; Blakeley, R. L.; Zerner, B. *J. Chem. Soc., Chem. Commun.* **1980**, 394-395. (c) The crystalline triethylammonium salt of the 1,1-Meisenheimer complex of diethyl malonate carbanion with 2,4-dinitro-1-fluorobenzene is stable in dry DMF (λ_{max} 510 nm) but decomposes rapidly in the presence of water to give diethyl 2-(2,4-dinitrophenyl)malonate: Baudet, P. *Helv. Chim. Acta* **1966**, *49*, 545-551. In alkaline 70% Me_2SO-30% water, *N*,*N*′-dimethyl-*N*-(2,4-dinitrophenyl)ethylenediamine is in a rapidly attained equilibrium with its corresponding spiro Meisenheimer complex [λ_{max} 525 nm (ϵ_{max} 2.1×10^4 M^{-1} cm^{-1})]: Bernasconi, C. F.; Terrier, F. *J. Am. Chem. Soc.* **1975**, *97*, 7458-7466.

[3] Species **4** was prepared as the free acid by Ag_2O oxidation of 2-nitro-5-hydroxybenzaldehyde and recrystallized from toluene, ethylene dichloride, and dilute HCl to give off-white crystals: mp 169.5-171 °C dec, lit. (Beyer, P. H. *Recl. Trav. Chim. Pays-Bas* **1921**, *40*, 621-631) mp 171.5-172 °C: *m*/*e* 183 ($M^{+\cdot}$, 32%); pK_a' 6.98; λ_{max} (nm), ϵ_{max} (M^{-1} cm^{-1}) at 25 °C: 0.1 M NaOH (397.5, 1.73×10^4), 10 M LiCl/0.1 M NaOH (399.5, 1.67×10^4), 3.1 M KOH (402, 1.84×10^4), 10 M NaOH (411, 2.06×10^4), 15.8 M KOH (425, 2.59×10^4). The identity of the final reaction product as **4** was confirmed by the spectral shift which occurred when KOH in the product mixture was diluted from 15.3 to 3.1 M.

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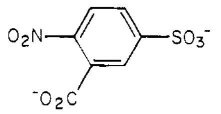
The formation of 3-carboxylato-4-nitrophenoxide ion (**4**) was monitored as a growing absorption peak at 425 nm in difference spectra during the course of the reaction (Figure 2A–D). The rate of formation of **4** was increased when oxygen was bubbled through the solution, but the final yield of **4** is essentially independent of whether or not oxygen has been deliberately provided.

In the first few minutes of the reaction, the difference spectrum also displayed an absorption maximum at ~315 nm (Figure 2A). When oxygen was not deliberately supplied by bubbling, this peak decayed very slowly as the product nitrophenoxide ion **4** was formed. When oxygen was bubbled through the solution for 3-min periods, the peak at ~315 nm was markedly diminished, and the nitrophenoxide peak at 425 nm was markedly enhanced (Figure 2B, C). With sufficient oxygen treatment, the peak at 315 nm was totally abolished, and the product spectrum became stable (Figure 2D).

These facts may be understood in terms of Scheme I, in which hydroxide ion very rapidly attacks the sulfenate ion **2** to form a Meisenheimer complex. The pK_a' of the hydroxyl group of this complex would be less than the H_- of the solvent (~18).[5] Thus, the complex would exist predominantly as its conjugate base (**5**). A two-electron oxidation involving O_2 would produce the Meisenheimer complex **6**, and the absorption maximum near 315 nm is due to **5** and/or **6**.[6] The oxygen sensitivity of this absorption is due to a further two-electron oxidation of **6** to the Meisenheimer complex **7** which undergoes rapid loss of sulfite ion[4] to give the product nitrophenoxide ion **4**.[7-9]

The species **7** is *formally* a deprotonated Meisenheimer complex of hydroxide ion with 3-carboxylato-4-nitrobenzenesulfonate ion (**8**). The decomposition of the sulfonate **8** in 15.3 M KOH is first order with a k_{obsd} of 1.12×10^{-3} s^{-1} at 25 °C.[10] The products are stable and consist of the nitrophenoxide ion **4** in 50% yield (presumably formed by way of **7**) and a new species[11] with λ_{max} of 362 ± 2 nm (ϵ_{max} 15600 M^{-1} cm^{-1}). No significant absorption in this region is produced during the decomposition of the disulfide **1** in 15.3 M KOH (Figures 1 and 2). *This establishes that the sulfonate **8** is not produced at any stage in the decomposition of the disulfide **1** in 15.3 M KOH.*



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Although stable Meisenheimer complexes of trinitro[2a] and dinitro[2c] derivatives of benzene are well-known, Meisenheimer complexes of mononitro derivatives of benzene have heretofore been identified only as transient intermediates.[2a,b] The stability of **5** and/or **6** is presumably associated with lack of a good nucleofuge by virtue of loss of a proton in the highly basic medium.

Acknowledgment. We thank Tony Treston for competent technical assistance and Dr. P. W. Riddles for helpful comments. This work was supported by the Australian Research Grants Committee and the University of Queensland.

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(4) (a) The reaction mixture (13 mL) was diluted and acidified with H_3PO_4 (net concentration 2.2 M). Sulfur dioxide was distilled at gentle reflux in a stream of nitrogen into a tetrachloromercurate solution and then determined by the pararosaniline technique (Method B) of Scaringelli et al.[4b] Control experiments established a recovery of 65–70%. The corrected ratio $[SO_2]_\infty/[\text{3-carboxylato-4-nitrophenoxide}]_\infty$ was 0.8. (b) Scaringelli, F. P.; Saltzman, B. E.; Frey, S. A. *Anal. Chem.* **1967**, *39*, 1709–1719. Scaringelli, F. P.; Norris, D.; Hochheiser, S. *Ibid.* **1970**, *42*, 1818–1820.

(5) Yagil, G. *J. Phys. Chem.* **1967**, *71*, 1034–1044.

(6) The apparent value of ϵ_{315} is $(1.3 \pm 0.2) \times 10^4$ M^{-1} cm^{-1}. Similar values have been reported for 2,5-cyclohexadienones: Baird, R.; Winstein, S. *J. Am. Chem. Soc.* **1963**, *85*, 567–578.

(7) The final step (**7** → **4**) is analogous to the elimination of sulfite which occurs when 2,4,6-trinitrobenzenesulfonate reacts with amines to form the corresponding 2,4,6-trinitroaniline derivative (Fields, R. *Methods Enzymol.* **1972**, *25*, 464–468) and to the elimination of phosphate which occurs when 4-nitrophenyl phosphate reacts with dimethylamine (Kirby, A. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1965**, *87*, 3217–3224).

(8) Roughly 50% of the final [**4**] is produced in the first 3 min as oxygen initially present in the system is depleted. Subsequent conversion of **5** and/or **6** to **4** is much slower unless oxygen is supplied. The reproducibility and light insensitivity of these reactions render unlikely the possibility that aromatic radical mechanisms are involved.

(9) When the spectrum of **4** present at each stage (based on A_{425}) is subtracted from the difference spectra in Figure 2A–D, a new difference spectrum is obtained with λ_{max} 475 ± 5 nm [ϵ_{475} $(1.0 \pm 0.1) \times 10^4$ M^{-1} cm^{-1}] (Figure 1D). This difference spectrum is essentially stable with respect to time and independent of oxygenation. It is postulated to be due to 3-carboxylato-5-sulfinato-2-nitrophenoxide ion or the corresponding sulfonate, produced by addition of hydroxide ion ortho to the nitro group of the sulfenate **2** [in parallel to para addition (Scheme I)] followed rapidly by the equivalent of hydride transfer to O_2 and oxidation of the sulfur. Loss of the hydrogen atom may involve transition-metal ion impurities which are present at ~0.1 mM in 15.3 M reagent grade KOH.

(10) (a) Species **8** was produced by performic acid oxidation[10b] of 5,5′-dithiobis(2-nitrobenzoic acid). The dried solid[10c] had a λ_{max} of 263 nm at pH 7.0. Kinetics of decomposition in 15.3 M KOH were monitored at 263, 360, and 425 nm. (b) Moore, S. *J. Biol. Chem.* **1963**, *238*, 235–237. (c) Silverstein, R. M.; Hager, L. P. *Biochemistry* **1974**, *13*, 5069–5073.

(11) This species is tentatively identified as the 3-carboxylato-5-sulfonato-2-nitrosophenoxide ion, which would be expected to form on this time scale by addition of hydroxide ion ortho to the nitro group followed by proton abstraction.[2b]

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Received April 28, 1980

Photochemistry of 4-Hydroxybenzothiazole: A Model for Pheomelanin Photodegradation

Sir:

The melanin pigments occurring in the hair and skin of most mammals are divided into two major classes, the brown-black eumelanins and the red-brown pheomelanins. Melanins are the major photoprotective pigments present in the epidermis.[1] However, compared to eumelanin, pheomelanin is exceptionally photolabile,[2] and it has been suggested that this photolysis contributes to the well-documented hypersensitivity to sunlight and susceptibility to chronic solar damage exhibited by fair-skinned individuals[3] whose epidermis contains pheomelanin. It is necessary to have further information on the mechanism(s) of pheomelanin photolysis to obtain a better understanding of these effects. Herein we report on the primary photochemical steps leading to photoionization of both pheomelanin (PM) and a model compound, 4-hydroxybenzothiazole (BTH).

Aerobic irradiation of red-brown pheomelanins has been shown to result in formation of the superoxide anion, $O_2^{-}\cdot$.[2b,c] Although the pigment consists of approximately 13% chromophore and 87% protein,[2b] photochemical production of $O_2^{-}\cdot$ has been shown to be a consequence of absorption of light by the chromophore and not the protein.[2c] The chromophore is believed to be a polymer incorporating the 4-hydroxybenzothiazole (BTH) moiety as the basic unit (structure **1**).[4] Problems with homogeneity and solubility have thus far frustrated attempts to investigate in detail the mechanism(s) of pheomelanin photolysis, and, thus, we have turned to BTH[5] as a model compound.

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(1) Pathak, M. A.; Fitzpatrick, T. B. In "Sunlight and Man"; Fitzpatrick, T. B., Ed.; University of Tokyo Press: Tokyo, 1974; pp 725–750.

(2) (a) Chedekel, M. R.; Post, P. W.; Deibel, R. M.; Kalus, M. *Photochem. Photobiol.* **1977**, *26*, 651–653. (b) Chedekel, M. R.; Smith, S. K.; Post, P. W.; Vessell, D. L. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 5395–5399. (c) Chedekel, M. R.; Agin, P. P.; Sayre, R. M. *Photochem. Photobiol.* **1980**, *31*, 553–555.

(3) Agin, P. P.; Sayre, R. M.; Chedekel, M. R. *Photochem. Photobiol.* **1980**, *31*, 359–362.

(4) Prota, G.; Thomson, R. H. *Endeavour* **1976**, *35*, 32–38.

(5) BTH was prepared as follows: 2-amino-4-methoxybenzothiazole, prepared by the method of Erlenmeyer and Uberwasser,[6] was first converted to 4-methoxy-benzothiazole[7] whereupon the methoxy group was removed.[6]

(6) Erlenmeyer, H.; Uberwasser, H. *Helv. Chim Acta* **1942**, *25*, 515–520.

(7) Chedekel, M. R.; Sharp, D. E.; Jeffery, G. A. *Synth. Commun.* **1980**, *10*, 167–173.

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