[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WASHINGTON UNIVERSITY, ST. LOUIS, MO.]

Conjugative Effects of Sulfur in Several Aromatic Anion-Radicals[1,2]

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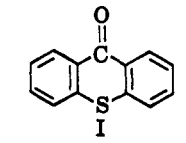
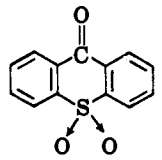
The electron spin resonance spectra of the anion-radicals of thiaxanthone (I), thiaxanthone-5-dioxide (II), thianthrene-5,10-tetroxide (III) and 2,7-dimethylthianthrene-5,10-tetroxide (IV) have been determined and interpreted. The free electron density in the aromatic rings of the anion-radical formed from II which contains a sulfonyl group is much less than that in the aromatic rings of the anion-radical from I which contains a sulfide group. In addition, the radical formed from III possesses an exceptionally narrow and simple spectrum (8.9 gauss wide) indicating considerable delocalization of the odd electron by the sulfonyl group.

Introduction

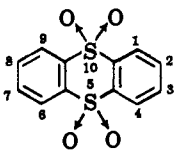
The possibility that sulfur-containing groups can delocalize odd electrons in aromatic systems has been relatively unexplored. With the intention of contributing to the elucidation of the conjugative properties of sulfur, we have determined the e.s.r. spectra of radicals formed by the metallic reduction of thiaxanthone (I), thiaxanthone-5-dioxide (II), thianthrene-5,10-tetroxide (III) and 2,7-dimethylthianthrene-5,10-tetroxide (IV).



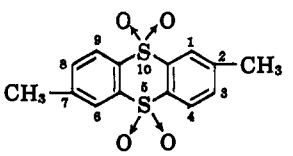
I



II



III



IV

The sulfones were obtained by vigorous oxidation of the respective sulfides with hydrogen peroxide in glacial acetic acid. The aromatic anion-radicals were formed from the sulfur compounds by potassium reduction using 1,2-dimethoxyethane as solvent.[4] Among the anion-radicals studied, only that of II was previously prepared.[5,6]

Experimental

All melting points are uncorrected. Electron spin resonance spectra were recorded immediately after reduction of the sulfur compounds. The radicals investigated were all quite stable even above the temperature of measurement. For example, when reduced II was maintained for several weeks at room temperature, no change in its e.s.r. spectrum was observed.

Materials.—Thiaxanthone was obtained from the Aldrich Chemical Co., and recrystallized from glacial acetic acid; m.p. 208.5–209.5° (lit.[7] 209°).

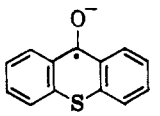
Thiaxanthone-5-dioxide was formed by the oxidation of thiaxanthone in refluxing glacial acetic acid with excess 30% hydrogen peroxide. This sulfone was recrystallized from ethanol; m.p. 186–187° (lit.[8,9] 185.5–186°, 187°).

Thianthrene-5,10-tetroxide was prepared by the oxidation of thianthrene (Eastman Kodak Co.) with excess hydrogen peroxide in glacial acetic acid. Recrystallization was accomplished from glacial acetic acid; m.p. 323–324° (lit.[10] 321°).

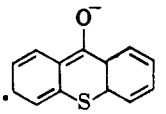
2,7-Dimethylthianthrene-5,10-tetroxide was isolated from the oxidation with excess hydrogen peroxide in glacial acetic acid of 2,7-dimethylthianthrene. Repeated recrystallizations from glacial acetic acid yielded the pure disulfone, m.p. 285–286° (lit.[11] 286°).

Results and Discussion

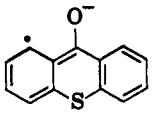
The e.s.r. spectrum of the potassium reduction product of I, which has a total width of 17.3 gauss, shows a major splitting into five groups with separation 3.5 gauss. Each of these groups is further split into 18 lines. (In Table I a total of only 85 lines is listed since lines at either extreme of the spectrum were difficult to count.) This spectrum exhibits qualitative similarity to that of xanthone ketyl[12] and is consistent with a valence-bond picture in which the canonical structures Ia, Ib and Ic are important.



Ia



Ib



Ic

The spectrum of reduced II was very different from that of I. Not only was the spectrum of the former radical 2.8 gauss narrower, but also at −30° some 70 evenly spaced lines were found with a splitting of 0.21 gauss. Since a major line was not observed at the center of resonance, it seems probable that potassium splitting of an otherwise odd-numbered line spectrum is involved. In this regard the spectrum resembles that of benzophenone ketyl.[13]

The decreased total width of the spectrum of reduced II compared to I implies a lower spin density in the aromatic rings of the sulfonyl radical. A description of the radical should include contributions from the resonance structures IId and IIe involving the sulfonyl group, as well as from structures IIa, IIb and IIc.[14]

When III was reduced with potassium, a very simple spectrum of only 8.9 gauss width with a g-value of *ca.* 2.002 was observed. The narrow width of this spectrum is indicative of low spin density in the aromatic rings resulting from delocalization of the odd electron by the sulfonyl group as in the case of the thiaxanthone-5-dioxide free radical. Five lines were seen (splitting 2.1 gauss) with an intensity ratio of 1:4:6:4:1, demon-

(1) Grateful acknowledgment is made to the donors of the Petroleum Research Fund for support of this research.

(2) Presented in part at the 142nd National Meeting, American Chemical Society, Atlantic City, N. J., September, 1962.

(3) George Washington University, Washington, D. C.

(4) D. E. Paul, D. Lipkin and S. I. Weissman, *J. Am. Chem. Soc.*, **78**, 116 (1956). In this paper the reduction of aromatic compounds by sodium to the anion-radicals is described. Our potassium reductions were carried out in an entirely analogous manner.

(5) H. Heymann, *ibid.*, **71**, 260 (1949). The polarographic reduction of II to the anion-radical was investigated.

(6) G. Vincow, Abstracts of the American Physical Society Summer Meeting, *Bull. Am. Phys. Soc.*, **II-7**, 475 (1962); G. Vincow, *J. Chem. Phys.*, **37**, 2484 (1962). These recent reports on the e.s.r. spectrum of the anion-radical of II appeared during the preparation of our manuscript. The radical was formed in Vincow's work by atmospheric oxidation of thiaxanthenol-5-dioxide in alkaline solution and also by reduction of II with sodium dithionite.

(7) E. G. Davis and S. Smiles, *J. Chem. Soc.*, **97**, 1290 (1910).

(8) E. A. Fehnel, *J. Am. Chem. Soc.*, **71**, 1065 (1949).

(9) F. Ullman and O. von Glenke, *Chem. Ber.*, **49**, 2509 (1916).

(10) F. Krafft and R. E. Lyons, *ibid.*, **29**, 435 (1896).

(11) H. Baw, G. M. Bennett and P. Dearns, *J. Chem. Soc.*, 680 (1934).

(12) Private communication from N. Hirota and Professor S. I. Weissman.

(13) N. Hirota, *J. Chem. Phys.*, **37**, 1884 (1962).

(14) Vincow, ref. 6, reports proton hyperfine splittings at positions 1 and 3 which are considerably stronger than those at positions 2 and 4. This assignment is in accord with the above picture for the sulfonyl radical in which resonance structures IIb and IIc are important. Furthermore, Vincow has made calculations which verify the application of Moffitt's theory of 3d-sulfur orbital expansion to this case of conjugation in a sulfone. *Cf.* H. P. Koch and W. E. Moffitt, *Trans. Faraday Soc.*, **47**, 7 (1951).

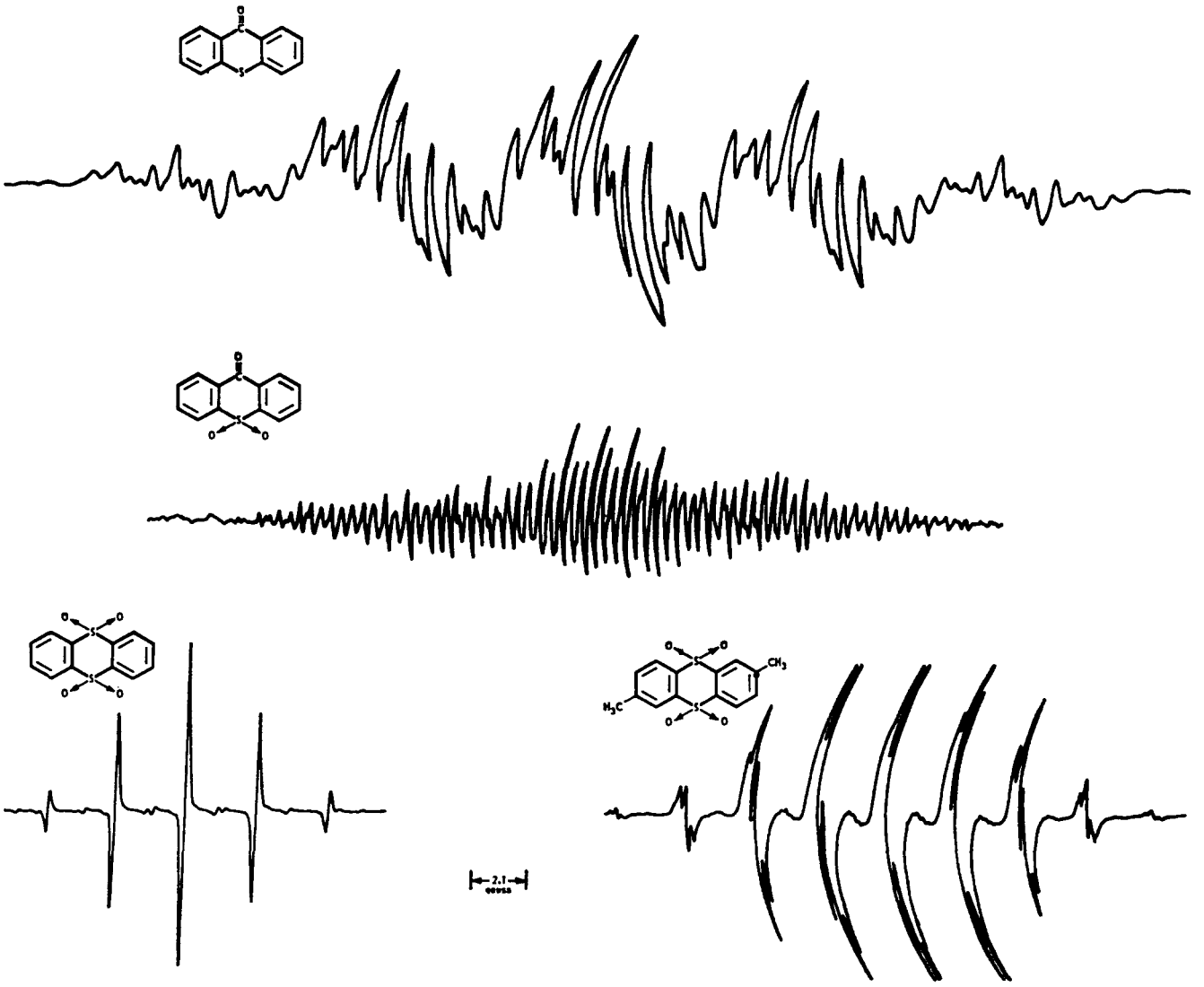
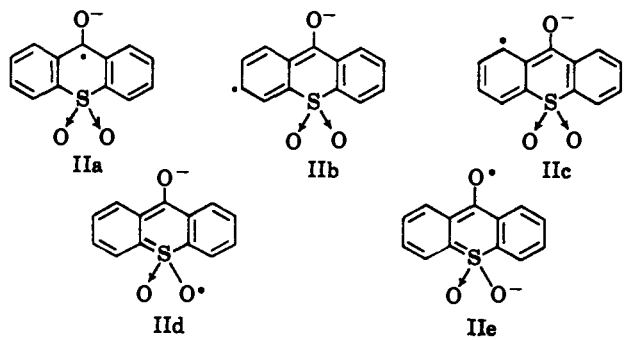


Figure 1.

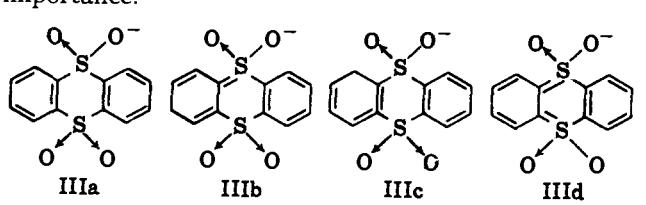
strating a splitting by four equivalent protons. In the case of this radical, we have shown by a labeling experiment employing methyl groups to determine the positions of maximum spin density that resonance



IIa IIb IIc

IId IIe

structures IIIb and IIIc are very unequally weighted. Indeed, it appears that IIIc makes little contribution to the structure of the radical and that IIIb is of primary importance.



IIIa IIIb IIIc IIId

On reduction of IV with potassium, a spectrum which was 17.2 gauss wide, consisting of nine major groups of lines split into approximately five hyperfine lines each, was observed. The appearance of nine major lines in the e.s.r. spectrum shows that the unpaired electron interacts with the magnetic moments of eight equivalent protons which must be the six methyl protons at positions 2 and 7 and the two aromatic protons at 3 and 8.[15] This indicates that IVb and IVb′ are important resonance contributors.[16] The occurrence of five hyperfine lines per major group results from weak splitting by the four aromatic protons at positions 1, 4, 6 and 9. Since there is only weak splitting by these four protons, contributions from structures IVc and IVc′ are relatively unimportant. Thus, it is clear that a satisfactory interpretation of the e.s.r. spectrum of reduced IV requires that the greatest observable spin density be located at the β-carbon atoms with much less at the α-positions of the thianthrene-5,10-tetroxide ring system.[17]

(15) The accidental magnetic equivalence of the methyl and aromatic protons that this implies is quite common. For instance, it has been noted for semiquinone free radicals. *Cf.* D. J. E. Ingram, "Free Radicals as Studied by Electron Spin Resonance," Butterworths Scientific Publications, London, 1958, p. 163.

(16) In referring to these structures we also include their mirror images.

(17) We have found that the spectra of anion-radicals of various oxides of thianthrene, *e.g.*, *cis*-thianthrene-5,10-dioxide, *trans*-thianthrene-5,10-dioxide, as well as thianthrene-5,10-tetroxide, differ markedly and can be interpreted in terms of the structures of the parent compounds and their stereochemistry (D. H. Eargle, Jr., and E. T. Kaiser, to be published).

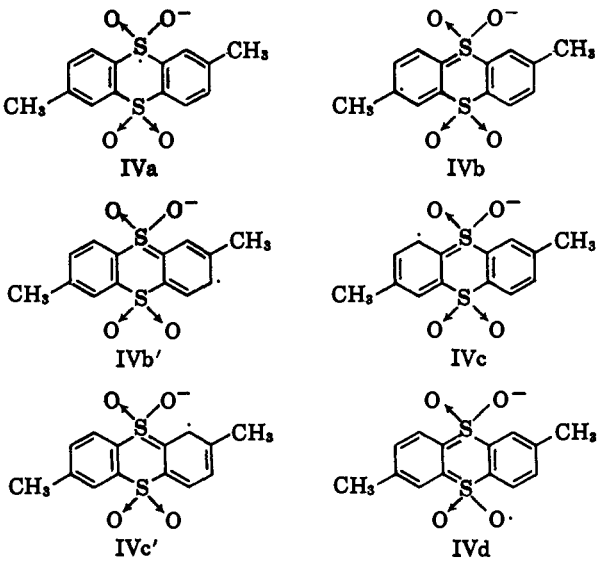
TABLE I

SUMMARY OF E.S.R. MEASUREMENTS[a]

Anion-radical of compound	Color of radical	No. of major lines/splitting (gauss)[c]	Approx. no. fine lines	Total width of absorption, gauss
I	Blue	5/3.5	85	17.3
II	Blue	...	35[b]/70	14.5
III	Pale blue	5/2.1	5	8.9
IV	Pale blue	9/2.1	45	17.2

[a] Measurements were carried out at −30° on the potassium reduction products. The e.s.r. spectra are shown in Fig. 1. All radicals were stable indefinitely at the temperature of measurement. [b] Thirty-five lines of 0.41 gauss splitting were observed at 25°. [c] Peroxylamine disulfonate was the standard.

There is therefore no evidence for any interconversion of the different oxidation states of thianthrene under the conditions of our experiments. This behavior contrasts with that reported for thianthrene and its oxides in sulfuric acid. The positive ion-radicals of several of these compounds possess a common spectrum which has been interpreted as indicating that they have a common structure. *Cf.* J. M. Hirshon, D. M. Gardner and G. K. Fraenkel, *J. Am. Chem. Soc.*, **75**, 4115 (1953); J. E. Wertz and J. L. Vivo, *J. Chem. Phys.*, **23**, 2193 (1955); A. Fava, P. B. Sogo and M. Calvin, *J. Am. Chem. Soc.*, **79**, 1078 (1957); W. C. Needler, Ph.D. Thesis, University of Minnesota, 1961, University Microfilms, Inc.; H. J. Shine and L. Piette, *J. Am. Chem. Soc.*, **84**, 4798 (1962). The last two references cite evidence from the e.s.r. spectra of the positive ion-radicals of substituted thianthrenes which indicates that positions 2, 3, 7 and 8 of the thianthrene skeleton have the greatest spin density just as we have found for the anion-radicals of III and IV. We thank Professor Shine for the opportunity to read his manuscript prior to publication.



In conclusion, we have shown that sulfonyl groups can participate in the delocalization of odd electrons in aromatic systems. Furthermore, sulfonyl groups are more effective in this regard than sulfide groups.

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[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, HARVARD MEDICAL SCHOOL, BOSTON 15, MASS.]

Proton Magnetic Resonance of Purine and Pyrimidine Derivatives. X. The Conformation of Puromycin

BY OLEG JARDETZKY

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An analysis of the 60 Mc. high resolution proton resonance spectrum of puromycin is presented. It is concluded that the conformation of the ribose ring in this compound corresponds to the previously discussed C'_3-endo form and that the entire molecule exists in a folded configuration.

1. Introduction

The antibiotic puromycin (6-dimethylamino-9-[3-deoxy-3-(*p*-methoxy-L-phenylalanylamino)-β-D-ribofuranosyl]-β-purine) is thought to inhibit the assembly of the protein chain in the ribosomes by virtue of its structural similarity to the terminal 3′-aminoacyladenylate on the transfer RNA.[1] Since the process of protein synthesis is highly stereospecific and since it appears that different ribonucleosides and ribonucleotides possess different conformations, as well as considerable conformational rigidity,[2-6] it is to be expected that the conformation of puromycin will be of importance for the molecular mechanism of its action. Some inferences concerning this conformation on the basis of the high-resolution proton magnetic resonance (p.m.r.) spectra of puromycin have proved feasible.

2. Results and Discussion

The 60 Mc. p.m.r. spectrum of 0.1 *M* puromycin in D_2O, obtained with the Varian V-4300B-HR spectrometer, is shown in Fig. 1. The peak assignments are based on previous nucleotide and amino acid work[6-8] and on measurements of line intensities. (All shifts, measured as described before,[2-7] are in c.p.s. referred to benzene as an *external* standard.) The spectrum shows several remarkable features, when compared to the spectra of other structurally similar compounds. (1) The coupling constant between the protons on the first two ribose carbons, $J_{1'2'} = 2.5$ c.p.s., which is considerably smaller than generally found in purine derivatives.[2-7] (2) The C'_5 protons are shifted to higher fields by approximately 45 c.p.s. *and are non-equivalent*, in contrast to other ribosides, while C'_4H is shifted to lower fields by ~10 c.p.s. (Table I). (3) The peaks attributable to the aliphatic protons of phenylalanine are only slightly shifted to lower fields compared to their position in the free amino acid,[8] but the coupling constant between them is small and the peaks are broad (this feature is not entirely obvious from Fig. 1, but becomes clearly apparent when the HDO peak is shifted to lower fields by the addition of acid). (4) The aromatic peaks of phenylalanine are likewise broadened by comparison to either the free amino acid, or to other *p*-substituted phenyl derivatives at comparable concentrations in D_2O,[9,10] while the relaxation times of the adenine peaks are not changed. The magnitude

(1) M. B. Yarmolinsky and G. L. De la Haba, *Proc. Natl. Acad. Sci., U. S.* **45**, 1721 (1959).
(2) C. D. Jardetzky, *J. Am. Chem. Soc.*, **82**, 229 (1960).
(3) C. D. Jardetzky, *ibid.*, **84**, 62 (1962).
(4) R. U. Lemieux, *Can. J. Chem.*, **39**, 116 (1961).
(5) O. Jardetzky and C. D. Jardetzky, to be published.
(6) O. Jardetzky, to be published.
(7) C. D. Jardetzky and O. Jardetzky, *J. Am. Chem. Soc.*, **82**, 222 (1960).
(8) O. Jardetzky and C. D. Jardetzky, *J. Biol. Chem.*, **233**, 383 (1958).
(9) O. Jardetzky, *ibid.*, in press.
(10) N. Weiner, P. Pappas and O. Jardetzky, *Biochem. Pharmacol.*, **8**, 115 (1961).