Chemistry of the Phenoxathiins and Isosterically Related Heterocycles. XXXIII [1]. The Influence of Intramolecular Sulfur-Nitro Group Interactions on the Reactivity at Sulfur

Mehul U. Mehta and Gary E. Martin*

Department of Medicinal Chemistry, College of Pharmacy,
University of Houston-University Park, Houston, Texas 77004

Keith Smith

Department of Chemistry, University College of Swansea,
Singleton Park, Swansea SA2 8PP, UK

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Nitro-groups positioned *ortho* to thio-esters have been shown to engage in strong, non-bonded intramolecular interactions between the sulfur atom and one of the nitro-group oxygens. The effect of the sulfur-nitro group oxygen interaction on the chemical reactivity at the sulfur atom of 9-nitro-1-azaphenoxathiin is reported. Conditions which normally produce the sulfone exclusively have been shown to yield the sulfoxide with only a minimal quantity of the sulfone produced. Protracted periods of reflux are required to produce the sulfone from the sulfoxide.

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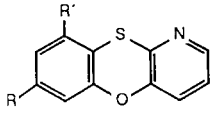
Introduction.

Strong, non-bonded interactions between the oxygen atoms of nitro-groups and *ortho* sulfur atoms have been characterized in the case of a number of thio-ethers [2-4] and sulfur containing heterocycles [5-9]. Electronically, the sulfur-nitro group intramolecular interaction has a pronounced effect on the chemical shift of the carbon atoms bearing the sulfur which is akin to that observed in changing the oxidation level from sulfide to sulfoxide [5-7]. While there have been numerous physical studies on the nature of these sulfur-nitro group interactions, a report of their influence on the chemical reactivity of the sulfur has yet to appear. Therefore, we now wish to detail the results of our preliminary investigations on the oxidation of 9-nitro-1-azaphenoxathiin. This compound exhibits a strong sulfur-nitro group interaction which has been characterized by both X-ray crystallographic [8] and ^{13}C-nmr spectroscopic means [5].

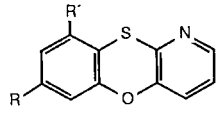
Results and Discussion.

Work by Elliot and co-workers [10] has shown that the 1-azaphenoxathiin system may be readily oxidized to the corresponding 10,10-dioxide by the action of 12% hydrogen peroxide in glacial acetic acid at reflux temperature in about 15 minutes. In order to investigate the chemical effect of a strong sulfur-nitro interaction, we elected to study the peroxide oxidation of two nitro-substituted 1-azaphenoxathiins, the 7- and 9-nitro isomers [11, 5, respectively]. Spectroscopically, the ^{13}C-nmr spectrum of the 7-nitro isomer is unremarkable. Chemical shifts were readily predicted [11] from the incrementation of the established shifts of 1-azaphenoxathiin for substitution with a nitro-group at the 7-position. In contrast, the chemical shifts of 9-nitro-1-azaphenoxathiin were not accurately predicted simply by incrementation for 9-nitro substitution [5]. Rather, the ^{13}C-nmr chemical shifts for this isomer were more accurately predicted when the 1-azaphenoxathiin chemical shifts were incremented for both 9-nitro substitution and for oxidation of the sulfur to the corresponding sulfoxide. This preliminary observation suggested that the sulfur might behave chemically more like a sulfoxide than a sulfide, which prompted our study of the chemical reactivity of these systems.



1a R = NO_2, R′ = H

1b R = H, R′ = NO_2



2a R = NO_2, R′ = H, X = SO_2

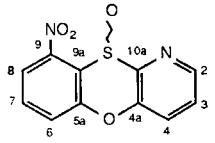
2b R = H, R′ = NO_2, X = SO

2c R = H, R′ = NO_2, X = SO_2

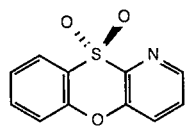
Using the general procedure of Elliott and co-workers [10] 7-nitro-1-azaphenoxathiin (**1a**) was treated with 12% hydrogen peroxide in glacial acetic acid at reflux temperature. After 15 minutes of reflux, 7-nitro-1-azaphenoxathiin 10,10-dioxide (**2a**) was isolated as the exclusive product of the reaction. This result confirms the observations of Elliott and co-workers [10]. In contrast, treatment of 9-nitro-1-azaphenoxathiin (**1b**) under identical conditions gave a relatively major product (88% isolated yield) and a minor product (8% isolated yield). Both products were identified by mass spectrometry, the major product as 9-nitro-1-azaphenoxathiin 10-oxide (**2b**), the minor pro-

Table I

^{13}C-NMR Chemical Shift Assignments of 9-Nitro-1-azaphenoxathiin 10-Oxide (**2b**) and 9-Nitro-1-azaphenoxathiin 10,10-Dioxide (**2c**) at 25.2 MHz in Hexadeuteriodimethyl sulfoxide at 30°



2b



2c

Position	δ ^{13}C **2b** Method A [a]	Method B	obs. **2b**	δ ^{13}C **2c** Method A	Method B	obs. **2c**
2	138.8	151.4	147.11	146.3	147.1	147.31
3	128.5	128.7	129.34	129.2	129.4	130.20
4	132.0	130.7	127.42	127.8	126.5	128.33
4a	148.2	147.5	145.60	147.9	147.2	146.38
5a	151.2	151.1	149.15	150.3	150.2	151.25
6	130.5	130.4	125.71	124.4	124.3	125.00
7	134.1	133.0	133.91	135.4	134.3	135.32
8	112.9	115.5	121.94	118.4	121.0	121.74
9	150.6	148.1	143.47	145.5	142.8	147.60
9a	116.4	123.4	121.01	120.8	127.8	119.03
10a	145.7	144.5	147.85	140.3	139.1	140.10

[a] The baseline values for 1-azaphenoxathiin 10-oxide are themselves calculated using the values for 1-azaphenoxathiin [16] and adding incrementations for the incorporation of a 9-nitro substituent.

duct as 9-nitro-1-azaphenoxathiin 10,10-dioxide (**2c**). Thus, the sulfur-nitro group oxygen interaction indeed appeared to have caused the sulfur atom to behave like a sulfoxide. In the interest of seeing if the sulfur-nitro group interaction could be overcome, we subjected a sample of the pure 10-oxide, **2b**, to prolonged reflux with 12% hydrogen peroxide in glacial acetic acid. Refluxing for 60 hours gave approximately a 70% conversion of **2b** into the corresponding 10,10-dioxide, **2c**. That the conversion of **2b** to **2c** should occur so slowly presumably reflects the necessity in this reaction for disruption of the sulfur-nitro group interaction and concomitant twisting of the nitro group out of the plane of the ring in order for the oxidation from the 10-oxide to the 10,10-dioxide to occur.

The ^{13}C-nmr chemical shift assignments for **2b** and **2c** are contained in Table I along with values calculated by two alternative methods: A) incrementation of the shifts for 1-azaphenoxathiin 10-oxide or 10,10-dioxide for the introduction of a 9-nitro substituent; B) incrementation of the shifts for 9-nitro-1-azaphenoxathiin by the values required for the introduction of a 10-oxide or 10,10-dioxide group [12,13].

As can be seen from the Table, Method B gives a reasonable fit for the C9a resonance of compound **2b** whereas Method A gives a poor fit for the chemical shift of the C9a resonance. By contrast, for compound **2c**, Method A gives a reasonable fit whereas Method B gives a poor fit for C9a. These observations are readily understood in terms of the presence of a strong sulfur-nitro group interaction in compound **2b** and also in 9-nitro-1-azaphenoxathiin itself (**1b**), but the absence of such an interaction in **2c**. Thus, for **2b**, Method B is appropriate since the calculation is based on **1b** which has the same type of interaction as **2b**. However, Method A is inappropriate because the model system used for the calculation (1-azaphenoxathiin 10-oxide) lacks the type of interaction which occurs in **2b**. On the other hand, for **2c**, which itself lacks the sulfur-nitro goup interaction, this method is appropriate; Method B which assumes and interaction by use of **1b** as the model, breaks down because the sulfur-nitro group interaction is absent in **2c**.

The internal consistency of these nmr data with the experimental finding that compound **2b** is difficult to oxidize lends further support to the notion that the calculated chemical shift abberation observed for C9a in **1b** [5] is indeed caused by the strong sulfur-nitro group interaction. Further support for the lack of an interaction in **2c** is given by the x-ray crystal structure of this compound. In the crystal, the nitro group has no interaction with the sulfur and is, in fact, forced out of planarity with the benzene ring [14]. Compound **2b** does, however, show an interaction between the nitro group and the sulfur in the crystald [14].

Conclusion.

In conclusion, sulfur-nitro group intramolecular interac-

tions have a pronounced effect on the reactivity of the sulfur atom toward oxidation. In one previous report [5], a sulfur-nitro group interaction was postulated to influence the outcome of the reaction. The present case, however, is the first example where such an interaction has clearly been demonstrated to influence the chemical reactivity markedly. It will be of interest to examine other reactions involving systems capable of interaction between sulfur or other Group VIa elements and various oxygen containing functional groups (*e.g.* aldehydes [15]) for the occurrence of untoward reaction products which may be accounted for on the basis of the sulfur-substituent interactions. Efforts in this direction will serve as the basis of future reports. We are also presently engaged in the determination of the X-ray crystal structures of **2b** and **2c**, the results of these studies to be reported elsewhere (see [14]).

EXPERIMENTAL

Melting points were determined in open capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were obtained as potassium bromide pellets using a Perkin Elmer Model 283 spectrophotometer. The nmr spectra were recorded using a Varian XL-100-15 spectrometer equipped with a Nicolet 1180 data system and operating at observation frequencies of 100.060 and 25.158 MHz for ^1H and ^{13}C, respectively, in the Fourier transform mode. Standard instrument parameters were: pulse width = 10 μsec (22 μsec = 90° pulse); interpulse delay = 4 sec, sweep width = 5 KHz (quadrature); digitization = 4K for ^1H-decoupled spectra and 8K for ^1H-spin coupled ^{13}C spectra acquired using the gated decoupling routine; lock internally to the hexadeuteriodimethyl sulfoxide solvent which was also employed as a chemical shift reference, the central line of the multiplet taken as 39.6 ppm downfield of tetramethyl silane; 0.6 Hz apodization was uniformly employed.

Oxidation of 9-Nitro-1-azaphenoxathiin (**1b**) to Afford 9-Nitro-1-azaphenoxathiin 10-Oxide (**2b**) and 9-nitro-1-azaphenoxathiin 10,10-Dioxide (**2c**).

To 0.246 g (0.001 mole) of 9-nitro-1-azaphenoxathiin (**1b**) prepared according to the procedure of Turley and Martin [5] in 6 ml of glacial acetic acid, 1 ml of 12% hydrogen peroxide was added. The reaction mixture was heated to reflux temperature, the bright orange starting material dissolving during the heating. During the course of the reaction, the color of the solution went from orange to pale yellow. After fifteen minutes the solution was allowed to cool and poured into 10 ml of distilled water. The mixture was cooled to 0° for two hours, whereupon a crystalline material separated. This was removed by filtration and allowed to dry in air. Thin layer chromatography (silica gel) of this material showed a major and minor component to be present. The crystalline material was then dissolved in 35 ml of boiling methanol which yielded a crop of pale yellow needles on cooling, 0.23 g (88% yield) mp 211-212°. Concentration of the mother liquor and cooling yielded a second crop of crystals, 0.022 g (8% yield) mp 192.5-193.5°.

The major component of the reaction was identified as 9-nitro-1-azaphenoxathiin 10-oxide (**2b**) on the basis of its mass spectrum, m/z = 262 (17.6%), 154 (30), 153 (90), 140 (30), 125 (20), 123 (100), 113 (25) and 95 (28) and the elemental analysis. The ^{13}C-nmr data for **2b** are contained in Table I.

Anal. Calcd. for $C_{11}H_6N_2O_4S$: C, 50.38; H, 2.29; N, 10.68. Found: C, 50.41; H, 2.31; N, 10.63.

The minor component of the reaction mixture was identified as 9-nitro-1-azaphenoxathiin 10,10-dioxide (**2c**) on the basis of its mass spectrum, m/z = 278 (100), 262 (25), 156 (39), 153 (28), 140 (43), 123 (32), 114 (20), 113 (33), 109 (24) and 95 (20) and the elemental analysis. The ^{13}C-nmr data for **2c** are contained in Table I.

Anal. Calcd. for $C_{11}H_6N_2O_5S$: C, 47.48; H, 2.16; N, 10.07. Found: C, 47.41; H, 2.18; N, 10.01.

In order to maximize the yield of **2c**, a reaction of **2b** was carried out with excess hydrogen peroxide under reflux for 60 hours. Work up as described above provided **2c** in 70% yield.

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REFERENCES AND NOTES

[1] This paper also represents Part **29** in the series Novel Heterocyclic Compounds.

[2a] J. C. Ricci and I. Bernal, *J. Chem. Soc.*, 806 (1970); [b] J. D. Korp, I. Bernal, R. F. Miller, J. C. Turley, L. Williams and G. E. Martin, *J. Cryst. Molec. Struct.*, **8**, 127 (1978).

[3] M. Kimura, S. H. Simonsen, S. R. Caldwell and G. E. Martin, *J. Heterocyclic Chem.*, **18**, 469 (1981).

[4] V. M. Lynch, S. H. Simonsen, R. F. Miller, J. C. Turley and G. E. Martin, *Acta Cryst.*, **C41**, 1240 (1985).

[5] G. E. Martin and J. C. Turley, *J. Heterocyclic Chem.*, **15**, 609 (1978).

[6] J. C. Turley and G. E. Martin, *Spectroscopy Letters*, **11**, 681 (1978).

[7] J. C. Turley and G. E. Martin, *J. Heterocyclic Chem.*, **18**, 431 (1981).

[8] M. B. Hossain, C. A. Dwiggins, D. van der Helm, P. K. Sen Gupta, J. C. Turley and G. E. Martin, *Acta Cryst.*, **B38**, 881 (1982).

[9] W. W. Lam, G. E. Martin, V. M. Lynch, S. H. Simonsen, C. M. Lindsay and K. Smith, *J. Heterocyclic Chem.*, **23**, 747 (1986).

[10] A. J. Elliott, N. Eisenstein and L. L. Iorio, *J. Med. Chem.*, **23**, 333 (1980).

[11] G. E. Martin, J. C. Turley, L. Williams, M. L. Steenberg and J. P. Buckley, *J. Heterocyclic Chem.*, **14**, 1067 (1977).

[12] O. M. Sejiny and G. E. Martin, *J. Heterocyclic Chem.*, **17**, 1741 (1980).

[13] M. S. Chauhan and I. W. J. Still, *Can. J. Chem.*, **53**, 2880 (1975).

[14] This work will be reported separately: M. Kimura, S. H. Simonsen, M. U. Mehta, G. E. Martin and K. Smith, manuscript in preparation.

[15] R. Close, D. Cagniant, G. Le Coustumer, C. G. Andrieu and Y. Mollier, *J. Chem. Res. (S)*, 4 (1978).

[16] G. E. Martin, J. C. Turley and L. Williams, *J. Heterocyclic Chem.*, **14** 1249 (1977).