

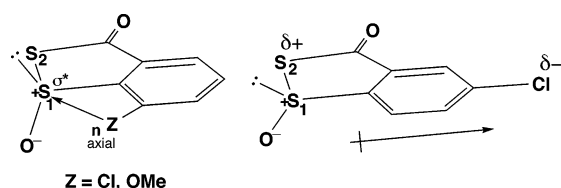
Substituent Effects on the Reactivity of Benzo-1,2-dithiolan-3-one 1-Oxides and Their Possible Application to the Synthesis of DNA-Targeting Drugs

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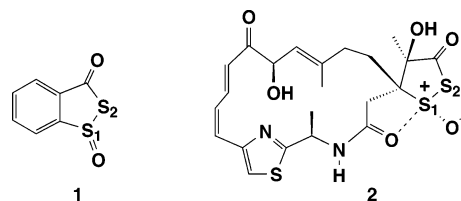
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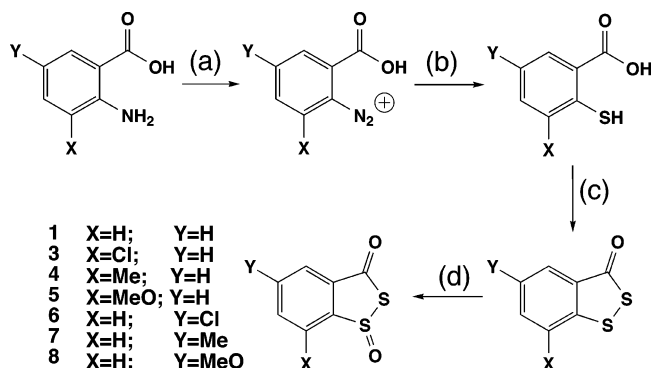
The efficiency of polysulfane product generation has been investigated for *n*-propyl thiol reactions with ortho- and para-substituted benzo-1,2-dithiolan-3-one 1-oxides in acetonitrile–water (7:3) mixtures. The reaction is facilitated by reducing the electron density at the para position or by placing substituents bearing lone pair electrons ortho to the dithiolanone-oxide (S1) reaction center. Through-space and through-bond effects both contribute to the conversion of polysulfane products.

Benzo-1,2-dithiolan-3-one 1-oxide (**1**) contains a thio-sulfinate ester heterocycle¹ and possesses DNA-cleaving activity, albeit reduced, compared to the natural product leinamycin (**2**) (Scheme 1).^{2–5} DNA-cleaving activity^{2–5} and antitumor activity^{6–13} of leinamycin **2** and other dithiolanone-oxide compounds are thought to arise by an

SCHEME 1



SCHEME 2^a



^a Reagents and conditions: (a) HCl, NaNO₂, 5 °C. (b) (i) Na₂S, elemental S₈, NaOH, 5 °C; (ii) Zn, glacial CH₃CO₂H, reflux, 48 h. (c) H₂SO₄, CH₃COSH, 24 °C, 15 min. (d) dimethyldioxirane, 0 °C, 2 h, 20–30%.

initial attack of thiol or another nucleophile onto the dithiolanone-oxide ring system.^{14–16} A structure–activity study in which the structure of the benzene core of **1** is varied by introduction of substituents may provide insight into the factors influencing the thiol reaction with dithiolanone-oxide drugs. We have examined ortho- [X = Cl (**3**), CH₃ (**4**), OCH₃ (**5**)] and para-substituted [Y = Cl (**6**), CH₃ (**7**), OCH₃ (**8**)] 1,2-dithiolan-3-one 1-oxides that contain different substituent groups, which also differ in being nearer to or farther from the sulfinyl sulfur (S1) (Scheme 2). The ortho and para positions are relative to the sulfinyl sulfur (S1) and refer to the 3- and 5-positions of the fused benzene ring.

Preparation of dithiolanone-oxides **1** and **3–8** is shown in Scheme 2 where a modification of the method of Beaucage et al.¹⁷ was used. Treatment of a 3- or 5-substituted anthranilic acid with NaNO₂ yielded the diazo compound. Sodium sulfide and elemental sulfur were added to the diazo compound to give the dithiosalicylic acid derivative and, after reduction, thiosalicylic acid. Thiolacetic acid was then added to the thiosalicylic acid, which after oxidation with dimethyldioxirane gave the substituted benzodithiolanone-oxides **3–8** in 20–30% yield (Scheme 2). The synthetic method gave higher yields with structures possessing the methyl (30%) or methoxy groups (25%) compared to the chloro substituent

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TABLE 1. Efficiency of Polysulfane Product Generation (%) Measured for Propyl Thiol Reactions with Substituted Dithiolanone-oxides 1 and 3–8 by NMR Spectroscopy

compd.	substituent ^c	Relative Yields ^{a,b}		
		unsymmetrical ptds.	symmetrical ptds.	overall ptd. yield
1	H	18	16	34
3	o-Cl	63	20	83
4	o-Me	9	2	11
5	o-MeO	51	26	77
6	p-Cl	53	26	79
7	p-Me	5	2	7
8	p-MeO	15	12	27

^a Reaction of compound 1 and ortho- [X = Cl (3), CH₃ (4), OCH₃ (5)] and para-substituted [Y = Cl (6), CH₃ (7), OCH₃ (8)] 1,2-dithiolan-3-one 1-oxides (10 mM) was carried out in the presence of *n*-PrSH (20–40 mM) in 70% CD₃CN–30% D₂O. ^b Relative yields determined by ¹H NMR after 15 min at 25 °C are the average of two runs (see Experimental Section). ^c Ortho or para substituent positions are relative to the sulfinate sulfur (S1) of compounds 1 and 3–8.

(20%). A likely reason is that the generation of the diazo group should depend on electron donation to add stability. Compounds 3–8 were synthesized and characterized as described in Experimental Section.¹⁸ The known dithiolanone-oxide 1¹ was prepared by oxidation of commercially available 3*H*-1,2-benzodithiolan-3-one with dimethyldioxirane.

Experiments to analyze the substituent effect were collected for the reaction of 1 and 3–8 with *n*-propyl thiol in a mixture of CD₃CN and D₂O (Table 1). Thiol was added to 1 and 3–8 in acetonitrile–water (7:3) mixtures. We find that 3 decomposes in the presence of thiol with an 83% conversion, while 7 decomposes to thiol with a 7% conversion. The lower yield of products is caused by a lower rate, not by other reactions. We selected the CD₃CN–D₂O (7:3) mixture for the study because it gave rates such that, after 15 min, products arose in different overall yields and the reactivity and substituent effect could be assessed. No reaction takes place between 1,3–8 and *n*-PrSH over a 3 day period in CD₃CN alone (entry

TABLE 2. Relationship between the CD₃CN–D₂O Ratio for the Reaction of Substituted Benzodithiolanone-oxides 1 and 3–8 with *n*-Propyl Thiol^a

entry	CD ₃ CN–D ₂ O	comment
1	1:0	no reaction (after 3 days)
2	8:2	12 h to reach approximately 50% conversion
3	7:3	2 h to reach approximately 50% conversion
4	1:10	minutes to reach 100% conversion

^a Performed with 10 mM 1 and 3–8 and 30 mM *n*-PrSH.

1, Table 2). The reaction rate increases upon increasing the D₂O content in CD₃CN (entries 2–4) since the acidity of *n*-PrSH is enhanced where *n*-PrS[−] ion can act as a nucleophile; however, substrate solubility becomes a problem at CD₃CN–D₂O 1:10 (entry 4).

The nature of the solvent dependence constraining reductive thiol activation reported here may be of importance for dithiolanone-oxide compounds capable of noncovalently associating with DNA.^{19–21} The structure of thiol may also play an important role in the activity of dithiolanone-oxide drugs.^{22,23} Control experiments show that the above dithiolanone-oxide decomposition is a thiol-dependent process. There is no reaction of the benzodithiolanone-oxides in the CD₃CN–D₂O (7:3) mixture over 2 h in the absence of thiol. Each dithiolanone-oxide (1 and 3–8)/*n*-PrSH reaction forms at least five products (Table 1), which are similar to the product distribution observed previously by Gates and co-workers for the reaction of 1 with *n*-PrSH.¹

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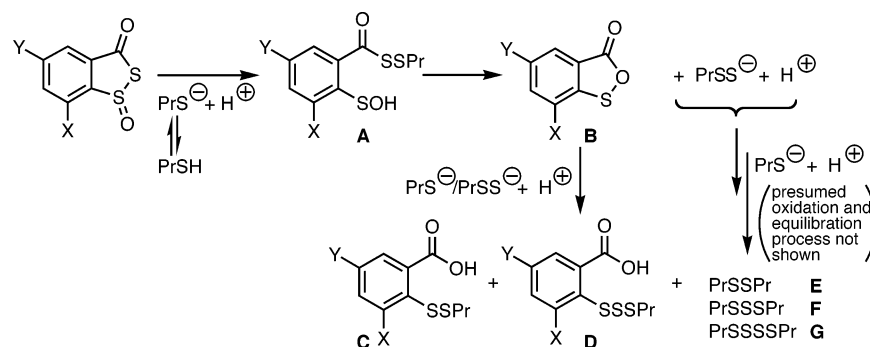
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SCHEME 3

TABLE 3. Calculated Structural Parameters for Substituted Benzo-1,2-dithiolan-3-one 1-Oxides (1 and 3–8)^{a,b}

	substituent		S1–S2	S1–O1	C1–S2	S2–S1–O1	θ^c	NBO charges		
	X	Y						S1	S2	O
1	H	H	2.215	1.497	1.822	113.1	113.1	1.150	0.007	–0.862
3	Cl	H	2.213	1.493	1.815	110.9	104.7	1.155	0.020	–0.853
4	Me	H	2.202	1.499	1.821	111.9	110.1	1.138	0.016	–0.874
5	OMe	H	2.218	1.495	1.817	111.1	105.9	1.159	0.005	–0.862
6	H	Cl	2.217	1.496	1.819	113.1	113.2	1.154	0.017	–0.859
7	H	Me	2.217	1.497	1.822	113.1	112.9	1.150	0.004	–0.863
8	H	OMe	2.222	1.497	1.818	113.1	112.9	1.153	0.007	–0.863

^a Structures optimized at the B3LYP/6-31G(d) level. ^b Distances in Å, angles in degrees. ^c Dihedral angle θ = O1–S1–S2–C1 is positive for a clockwise movement from O1 to C1 as you look down from S1 to S2.

oxathiolane species (**B**) on the reaction surface (Scheme 3). A similar mechanism has been proposed previously by Gates and co-workers for compound **1**.¹ Compounds **A** and **B** are unstable intermediates and are not detected directly in the reaction. Electrophilic oxathiolane **B** can potentially undergo a reaction with PrS^- or PrSS^- to give rise to 3- or 5-substituted 2-propyldisulfuranyl benzoic acid (**C**) and 3- or 5-substituted 2-propyltrisulfuranyl benzoic acid (**D**), respectively. Equilibrium and exchange processes may also contribute to the production of **C** and **D**. The reactive byproduct hydrodisulfide (PrSSH) will likely undergo reactions in the presence of PrSH and O_2 to account for formation of polysulfanes [di-*n*-propyl-disulfane (**E**), di-*n*-propyl-trisulfane (**F**), and di-*n*-propyl-tetrasulfane (**G**)]. Similar thiol-disulfide equilibria (redox) processes have been observed in biological systems.²⁴

A possible through-space effect emerges²⁵ with substituents bearing lone pair electrons positioned near the dithiolanone-oxide sulfinat sulfur (S1). *ortho*-Chloro- (**3**) and -methoxy-substituted dithiolanone-oxides (**5**) yield higher concentrations of polysulfane products (**C–G**) compared to **1**, **4**, **7**, and **8**, which may be explained by intramolecular S1–Cl or S1–O_(methoxy) dipole–dipole interactions that enhance the ease of ring opening of the heterocycle. According to B3LYP/6-31G(d) calculations, the 1,4-S–X interaction (X = Cl, OMe) influences the

structure of dithiolanone-oxide **3** and **5** (Table 3). The calculated S2–S1–O1 bond angle in **3** (110.9°) and **5** (111.1°) is less than that in other dithiolanone-oxides **1** (113.1°), **4** (111.9°), **6** (113.1°), **7** (113.1°), and **8** (113.1°).²⁶ The 1,4-S–X interaction [X = Cl (**3**), OMe (**5**)] influences the S1–O1 and C1–S2 bond distances but has little or no effect on the S1–S2 bond distance. We observe decreases in the S1–O1 and C1–S2 bond distance when comparing **3** and **5** with **1**, **4**, and **6–8**. The S–X interaction also influences the calculated dihedral angle (θ = O1–S1–S2–C1). The torsion angle θ in **3** (104.7°)

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and **5** (105.9°) is reduced compared with that in **1** (113.1°), **4** (110.1°), **6** (113.2°), **7** (112.9°), and **8** (112.9°).

The *para*-chloro substituent in **6** yielded an unexpected influence on product generation. A reason for the enhanced reactivity of **6** is a suggested thiol attack at S2, which should depend on electron-withdrawing through-bond effects in ortho or para positions to enhance reactivity. There is a small reduction of electron density at S2 when comparing the NBO positive charge in **3** (0.020) and **6** (0.017) with that in compounds **1** (0.007), **4** (0.016), **5** (0.005), **7** (0.004), and **8** (0.007) (Table 3). We believe that the destabilizing substitution of chlorine in the ortho or para position accounts for the increase in the rate of thiol activation. Finally, a chemical consequence from the perturbation of the sulfinyl center in **3** could be accounted for by combined through-space S–Cl interaction and an electron-withdrawing substituent effect responsible for increased product formation (Table 1). This is shown in **3**, where unlike others in the series, the through-bond and through-space effects both contribute in the same direction to product conversion.

In conclusion, mechanistic evidence points to an electron-withdrawing chlorine substituent in the para position or a neighboring group interaction involving lone pair electrons on methoxy or chlorine substituents as factors that enhance benzodithiolanone-oxide reactivity toward thiol. Successful attempts to quantify substituent effects have been made using an acetonitrile–water 7:3 solvent mixture, but up to now the only substrates considered have had limited water solubility. The relationship between the substituent effect in thiol activation of the dithiolanone-oxide heterocycle may be dramatic in vivo because of substrate–DNA noncovalent associations where dipolar aprotic and aqueous solvent environments are both contributors. Using remote and nearby functional groups as a mechanistic tool enables one to bias the yield of the polysulfane products **C–G**. Polysulfane autoxidation and subsequent Fenton chemistry can take place. Oxygen radicals such as OH radical are produced in a trace metal-dependent Fenton reaction previously reported for the oxidative DNA cleavage by the antitumor antibiotic leinamycin and synthetic dithiolanone-oxide analogues.^{2,4,5,27,28} However, unlike compounds **1** and **3–8**, leinamycin **2** can also act as a DNA-alkylating agent because of an intramolecular reaction of an alkene moiety on the oxathiolane heterocycle.^{6,8,9,11–13,16,29}

Experimental Section

Materials and Instrumentation. Reagents and solvents [2-amino-3-methylbenzoic acid, 2-amino-3-methoxybenzoic acid, 2-amino-3-chlorobenzoic acid, 2-amino-5-methylbenzoic acid, 2-amino-5-chlorobenzoic acid, 2-amino-5-methoxybenzoic acid, 1,3,5-trimethoxybenzene, sodium nitrate, sodium sulfide, elemental sulfur (S₈), sodium hydroxide, sodium bicarbonate, zinc dust, hydrochloric acid solution (12 M), sulfuric acid solution (1 M), glacial acetic acid, thiolacetic acid, magnesium sulfate, potassium bromide, acetone, ethanol, CHCl₃, CDCl₃, CH₃CN, CD₃CN, hexane, propyl thiol] were obtained commercially and used as received. Proton and carbon NMR data were acquired on a Bruker 400 MHz NMR spectrometer. Mass spectrometry data were collected on one of two GC/MS instruments, a Hewlett-Packard GC/MS instrument consisting of a 6890 series GC and a 5973N series mass selective detector, or a Hewlett-Packard GC/MS instrument consisting of a 5890 series GC and a 5988A series mass selective detector. IR data were collected on a Nicolet

Magna FI-IR 760 spectrometer. UV data were collected on a Hitachi V-2001 spectrometer.

Dithiolanone-oxide Synthesis. The synthesis involved adding a 3- or 5-substituted anthranilic acid (6.6 mmol) to a 4 mL water solution of 2 mL of concentrated HCl and NaNO₂ (6.6 mmol) at 5 °C to generate the diazo compound. A separate solution was prepared by mixing Na₂S (7.3 mmol) with elemental sulfur (7.3 mmol) at 24 °C, which was heated and made alkaline by the addition of 10 M NaOH. Mixing the two solutions resulted in a precipitate upon addition of HCl. The sulfuration gave the dithiosalicylic acid derivative, which after purification was then mixed and Zn dust in glacial acetic acid and refluxed, yielding thiolsalicylic acid. Thiolacetic acid (0.110 mol) was added to thiosalicylic acid (0.005 mol) in concentrated H₂SO₄ at 24 °C. Oxidations of the benzo-substituted dithiolanone-oxides were carried out with dimethyldioxirane.

Reaction of Thiol with Substituted Dithiolanone-oxides. Reactions of **1** and **3–8** (10 mM) were carried out in the presence of *n*-PrSH (20–40 mM) in 70% CD₃CN–30% D₂O. The volume of the reaction mixture was 5 or 10 mL, and the internal standard was 1,3,5-trimethoxybenzene (4 mM). The percent yield of products was determined after 15 min at 25 °C. Reaction of **3** or **5** with *n*-propyl thiol in a CD₃CN–D₂O (1:10) solvent mixture gave products too rapidly to discern a possible substituent effect by NMR spectroscopy. ¹H NMR data on the dithiolanone-oxide (**1**, **3–8**)–*n*-PrSH reaction provided evidence for the formation of unsymmetrical and symmetrical sulfane products similar to that observed previously by Gates for the **1**–*n*-PrSH reaction.¹ The assignment of unsymmetrical products [3- or 5-substituted-2-propyl disulfanyl benzoic acid (**C**) and 3- or 5-substituted-2-propyl trisulfanyl benzoic acid (**D**)] is based on two sets of triplets; a downfield set at about δ 2.8 ppm (2H, SCH₂) and a downfield set at about δ 2.9 ppm (2H, SCH₂), respectively. The chemical shifts for β-methylene and methyl protons are often obscured by reagent peaks. Downfield chemical shifts of polysulfane neighboring protons with higher numbers of sulfur atoms have been reported previously.^{30–32} In the case for the reaction of **1** with *n*-PrSH, we utilized GC/MS data of the polysulfane mixture to corroborate this method of analysis by ¹H NMR spectroscopy. The percent yields of **C** and **D** were determined by analysis of products in the respective reaction mixtures.

Acknowledgment. We thank Cliff Soll of the Hunter College Mass Spectrometry Facility for help in determining the masses of some of the compounds and Edlaine Lucien for synthetic work conducted in an early phase of the project. The City University of New York and PSC-CUNY provided financial support for this work. We wish to dedicate this paper to the late Professor Christopher S. Foote (1935–2005) who was as an inspirational figure to us.

Supporting Information Available: Characterization data for **1**, **3–8**, **3C–8C**, **3D–8D**, and **E–G** and computational data for **1** and **3–8**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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