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Synthesis and acidity of conformationally constrained 1,3-oxathiane S-oxides

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ABSTRACT

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1. Introduction

Physical and chemical properties of compounds like structure, stability, and reactivity are significantly influenced by stereoelectronic, dipole, charge, and steric effects.¹ We have investigated stereoelectronic interactions in α -anions of sulfides, sulfoxides, and sulfones,² where the stability is ruled by interaction of the anionic lone pair with S-C and S=O bonds. These effects are favorably investigated in derivatives of conformationally fixed 1,3-dithianes.3-5 These have a rigid conformation and the antiperiplanar orientation of bonds and the lone pairs favor possible stereoelectronic interactions. In fact, a carbanion is best stabilized, when the lone pair is in an antiperiplanar orientation to a C-S bond or - even better - to an S=O bond of a sulfoxide, allowing for an $n_C \rightarrow \sigma^*_{S-C}$ or an $n_C \rightarrow \sigma^*_{S-O}$ interaction, respectively. Nevertheless, in dithiane Soxides a possible $n_C \to \sigma \ast_{S\text{-}O}$ interaction might be countervailed by two $n_C \rightarrow \sigma^*_{S-C}$ interactions, what makes an independent investigation of these effects difficult. We thus considered the corresponding 1,3-oxathianes to be more suitable for the examination of these effects since an $n_C \rightarrow \sigma^*_{O-C}$ stereoelectronic effect is small as compared with the respective $n_C \rightarrow \sigma^*_{S-C}$ interaction.^{6,7} The compounds of interest **1–4** together with dithianes 5–8 and the respective anions are given in Figure 1.

Conformationally constrained 5-*tert*-butyl 1,3-oxathiane was synthesized and oxidation led to the diastereoisomeric sulfoxides and the respective sulfone. Stereoelectronic effects are discussed for these compounds and their corresponding 2-carbanions. pK_a values are calculated for these compounds and compared with the respective 1,3-dithiane-derived sulfide, the sulfoxides, and the sulfone.

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Figure 1. Conformationally constrained 1,3-oxathiane and 1,3-dithiane, their *S*-oxides and the corresponding carbanions.

2. Conformationally constrained 1,3-oxathiane S-oxides

4,6-Dimethyl-substituted 1,3-oxathianes have already been prepared by Juaristi et al. starting with (E)-pent-3-en-2one⁸ and by Pasanen et al. from (E)-pent-3-en-2-ol.⁹ They obtained the desired *cis*-substrate **12**, which could be separated from the two *trans*-isomers **13** and **14** by distillation. We decided to develop a differing protocol starting with 2,4-pentanediol **9** (Scheme 1). Activation of one hydroxyl group as tosylate and substitution with thioacetate yielded a mixture of diastereoisomers **10** and **11**, which was separated by chromatography. Subsequent hydrolysis with 1.4M hydrogen chloride in methanol led to the hydroxythiols, which were reacted with dimethoxymethane yielding the respective oxathianes **12–14**. A high dilution of the hydroxythiols had to be maintained in these reactions to avoid diand polymerization, which was achieved by their slow addition through the reflux condenser (using a syringe pump).

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Determination of the configurations was best made at that stage, since the pattern of the coupling constants in ¹H NMR spectra allowed for an unambiguous assignment, which would have been much more difficult in the respective precursors.



Scheme 1. Synthesis of 4,6-dimethyl-substituted 1,3-oxathianes. a) TsCl, pyridine, CH₂Cl₂, 0 °C to rt, 12 h, 35%; b) KSAc, DMF, 80 °C, 40 min, 53%; c) separation by chromatography (26% 10, 27% 11); d) 1.4M HCl in MeOH, rt, 12 h, then (MeO)₂CH₂, F_3B ·OEt₂, CH₂H₂, Δ , 30 min, 88% 12.

Though the preference of the diequatorial over the respective flipped diaxial conformation in dimethyl-substituted sixmembered rings was reported to be higher than in the respective tert-butyl-substituted compounds,10 the conformational rigidity in the latter is more than sufficient for the aimed investigations.¹¹ Since the synthesis of 5-tert-butyl-1,3-oxathianes is simpler than that of the dimethyl derivatives (especially since separation of the isomers turned out to be easier to achieve) we decided to continue our investigations with 5-tert-butyl-substituted substrates. The hydroxythiole 15, whose synthesis was reported previously,¹² was reacted with dimethoxymethane furnishing oxathiane 1 (Scheme 2) with quantitative yield. Oxidation with one equivalent sodium periodinate yielded a mixture of sulfoxides 2 and 3 (79:21), which could be separated by column chromatography. These sulfoxides could be further oxidized with potassium permanganate to the respective sulfone 4, which was similarly obtained in one step from the sulfide using two equivalents of an oxidizing agent like sodium periodinate, potassium permanganate, or Oxone.



Scheme 2. Synthesis of 5-*tert*-butyl-substituted 1,3-oxathiane S-oxides. a) (MeO)₂CH₂, $F_3B \cdot OEt_2$, CHCl₃, Δ , 30 min, quant.; b) 1 eq. NaIO₄, THF/H₂O (1:1), rt, 12 h, 62% 2 + 16% 3; c) 2 eq. NaIO₄ or KMnO₄ or Oxone (92%); d) KMnO₄, acetone/H₂O (1:1), rt, 48 h, 68% (from 2).

3. Acidity of 1,3-oxathiane and 1,3-dithiane S-oxides

The relative orientation of the S=O bonds has a crucial influence on the compounds' properties. Stereoelectronic interactions with participation of an axial S=O bond lead to a weakening of the axial C2–H bond ($\sigma_{C-H} \rightarrow \sigma^*_{S-O}$) and to a stabilization of an axial anionic lone pair in the respective deprotonated species ($n_C \rightarrow \sigma^*_{S-O}$). Similar interactions are significantly less relevant in the equatorial sulfoxide. The weakening of the axial C–H bond and the stabilization of an axial lone pair can be observed, e.g., in NMR spectra (smaller ${}^1J_{C-H}$ coupling constants),¹³ in IR spectra, via their structural parameters (longer C–H bonds), and especially by comparison of the p K_a values. We calculated p K_a values of oxathianes 1–4, both for deprotonation of the axial and the equatorial proton, respectively, and compared the obtained values with those of the

respective dithiane derivatives (Table 1). For this we used a method described previously.¹⁴ All structures were optimized with the B3LYP¹⁵/6-311G++(d,p)^{16,17} basis set and single point calculations were performed at the B3LYP/AUG-cc-pVTZ level¹⁸ using des Gaussian 09 package.¹⁹ We considered dimethyl sulfoxide as solvent using the CPCM-SCRF method.²⁰ As expected the acidity of the oxathianes substantially increases from the sulfide via the sulfoxides to the sulfone derivatives. A comparison of sulfoxides 2 and 3 is more meaningful: The axial sulfoxide 3 is 3.7 pK_a units more acidic than the respective equatorial sulfoxide 2 and a deprotonation of the axial (antiperiplanar) proton in 3 is significantly favored over an equatorial deprotonation ($\Delta p K_a = 1.5$). This can mainly be explained by the mentioned $n_C \to \sigma \ast_{S\!-\!O}$ interaction, which is highest, when S=O bond and anionic lone pair are in an antiperiplanar orientation. The $(\sigma_{C-H} \rightarrow \sigma^*_{S-O})$ stereoelectronic effect stabilizing the protonated species is significantly smaller and thus has a vanishing effect on the pK_a value. Hardly any stereoelectronic stabilizing is possible involving the equatorial S=O bond in sulfoxide 2. An $n_C \rightarrow \sigma^*_{S-C}$ interaction is possible especially with an equatorial lone pair making the deprotonation of the equatorial hydrogen in 2 more likely. Since this stabilizing effect is less significant, the difference in the acidities of the axial and the equatorial protons is $(\Delta p K_a = 0.5)$ smaller. The significant difference for the deprotonation of the equatorial protons in compounds 2 and 3 is quite astonishing, since a similar $n_C \rightarrow \sigma^*_{S-C}$ interaction would be expected in both cases. Nevertheless, it has been observed previously⁴ that this interaction is more pronounced, when the sulfur bears an axial oxygen as compared to an S(Oeq)-C bond. Furthermore, we have shown previously that an $n_C(eq) \rightarrow \sigma^*_{S-O(ax)}$ stereoelectronic effect is significant, while an $n_C(eq) \to \sigma \ast_{S \text{-}O(eq)}$ interaction is close to zero.⁴ No systematic influence of the carbanions' dipole momentums on the acidity of the respective compounds is obvious from the calculated values. A comparison with previously investigated dithiane derivatives⁴ supports these conclusions: $n_C \rightarrow \sigma^*_{S-C}$ interactions to both of the sulfur atoms significantly stabilize an equatorial lone pair²¹ and make the respective mode of deprotonation in the equatorial sulfoxide 6 much more relevant ($\Delta p K_a = 3.2$). These interactions are countervailed by a significant $n_C \to \sigma \ast_{S\!-\!O}$ stereoelectronic effect possible in the axial sulfoxide 7. Deprotonations of the equatorial and the axial proton, respectively, are similarly possible; the difference in the pK_a values here is only 0.6. The preferential equatorial deprotonation in dithianes (e.g. 5) without interfering oxygen atoms has been calculated and explained repeatedly.^{4,14,21}

Table 1. Calculated pK_a values of oxathiane and dithiane and of their *S*-oxides

Oxathiane	p <i>K</i> _a ^[a]	μ [D] ^[a,b]	Dithiane	p <i>K</i> _a ^[a]	$\mu_{[a,b]}$ [D]
$1 \rightarrow 1 anion_{ax}$	46.9	13.2	5→5anion _{ax}	41.7	12.6
$1 \rightarrow 1$ anion _{eq}	45.3	16.1	$5 \rightarrow 5 anion_{eq}$	36.9	15.0
$2{\rightarrow}2anion_{ax}$	40.1	15.3	6→6anion _{ax}	34.8	14.4
$2{\rightarrow}2anion_{eq}$	40.6	17.4	6→6anion _{eq}	31.6	16.2
$3 \rightarrow 3 anion_{ax}$	36.4	13.3	$7 \rightarrow 7 anion_{ax}$	31.7	12.9
$3 \rightarrow 3anion_{eq}$	37.9	16.3	$7 \rightarrow 7 anion_{eq}$	31.1	15.1
4→4anion _{ax}	33.3	14.4	$8{\rightarrow}8anion_{ax}$	28.4	13.9
4→4anion _{eq}	31.9	16.9	$8 {\rightarrow} 8anion_{eq}$	24.8	15.9

^a B3LYP/AUG-cc-pVTZ//B3LYP/6-311G++(d,p) with CPCM-SCRF (solvent=DMSO). The results for these compounds were put into relation with calculated and measured values for fluorene. The pK_a values must not be taken as absolute numbers; only their relative differences are meaningful c.f. Ref. 14.

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^bDipole moments of the respective carbanions.

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Supplementary Material

Supplementary data associated with this article (experimental procedures, spectroscopic data, archive entries for all calculated minimum structures) can be found, in the online version, at http://dx.doi.org/

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Highlights

- Rigid oxathianes allow for the investigation of Accepting stereoelectronic effects

- Acidity of sulfoxides is strongly influenced by the

- orientation of the functional group
- Anionic lone pairs are stabilized by interaction

with antiperiplanar S=O bonds

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