

The Through-Bond Interaction of a Sulfur Lone Pair with Oxygenated Substituents in the Thiacyclohexane Framework

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Low-temperature X-ray crystal structures were determined on a range of derivatives of 4-thiacyclohexanol **5a** of varying electron demand with a view to finding evidence for a through-bond interaction between the sulfur lone pair and the oxygenated substituent. In contrast to earlier suggestions, plots of C–OR bond distance versus pK_a (ROH) showed that any interaction between the sulfur and the OR group is unlikely to be of a through-bond origin. Furthermore, unimolecular solvolysis rate measurements on the nosylate ester derivative **5g** showed that the sulfur actually retards the reaction slightly in comparison with the corresponding sulfur-free analogue **6**.

Manuscript received: 11 March 2005.

Final version: 21 April 2005.

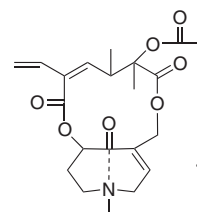
Introduction

Interactions between donor and acceptor groups within molecules can have a huge impact on both their ground state and reactivity properties. The interactions can occur directly through space, by transmission through the carbon framework (through bond), or sometimes by a combination of the two.^[1,2] For example, a through-space interaction between the nitrogen lone-pair and the transannular carbonyl group in clivorine^[3] **1** (Scheme 1) results in a close contact between the amino nitrogen and the carbonyl carbon. On the other hand, a through-bond interaction between the nitrogen lone pair and the developing carbocation orbital is believed to be responsible for the hugely different reactivities of the bicyclic chlorides **2** and **3** (Scheme 2) towards unimolecular solvolysis.^[4]

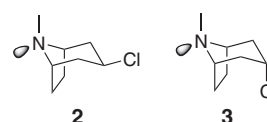
Whichever of the above type of interaction occurs, a strong dependence of the magnitude of the interaction upon the relative orientation of the donor and acceptor fragments is observed. The results of these interactions are often referred to as stereoelectronic effects, a description which reflects their electronic basis and recognizes their dependence upon stereochemistry.

The present study was prompted by a theoretical investigation into the mechanism of the carboxyl transfer reaction, which in living systems is facilitated by the coenzyme biotin **4** (Scheme 3).^[5]

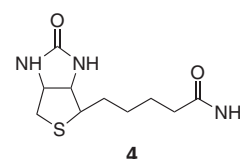
It was suggested that a through-bond interaction develops between the sulfur p-type lone pair and the ureidyl moiety when the biotin molecule is twisted towards a transition-state geometry.^[6] This interaction, which results in donation of electron density from the sulfur atom towards the ureidyl moiety would be expected to increase the nucleophilicity of the urea nitrogen, and therefore, improve the efficiency of the carboxyl transfer step.



Scheme 1.



Scheme 2.



Scheme 3.

As part of our general interest in the structural effects of donor–acceptor interactions,^[7] particularly as they manifest themselves in the cyclohexane framework, we chose to investigate whether a through-bond interaction between the sulfur lone pair and the σ_{C-O}^* orbital in ester and ether derivatives of thiacyclohexanol **5** (Fig. 1) leads to any observable effects on the ground state structures or reactivity of these derivatives.

Such an interaction might be expected to result in the lengthening of the C–OR bond distance in comparison to similar model compounds that lack the interaction and also lead to increased rates of unimolecular solvolysis. A powerful

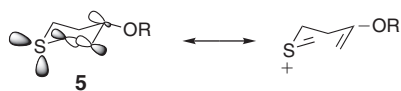
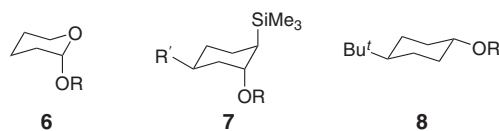


Fig. 1. The through-bond $ns-\sigma^*_{C-O}$ interaction.



Scheme 4.

X-ray structural technique for detecting the presence of interactions between donor groups and oxygenated substituents is known as the variable oxygen probe.^[8] The variable oxygen probe was first introduced by Kirby and coworkers who established that the C—O bond distance in the C—OR fragment increases as the electron demand of the OR substituent increases, and thereby, reflects an increasing contribution of the $C^+ -OR$ valence bond form to the ground state structure. If the electron demand of a substituent (OR) is quantified as the pK_a value for the parent acid (ROH), then a plot of C—OR bond distance versus $pK_a(ROH)$ will be linear, and the slope of the resultant plot will be sensitive to the effects of electron donation into the C—OR σ^* antibonding orbital. The presence of good donor orbitals vicinal and antiperiplanar to the C—O bond results in a strong response of the C—OR distance to the electron demand of OR, and is reflected by the increased stabilization of the cation part of the valence bond form $C^+ -OR$. For example, plots of C—OR bond distance [Å] versus $pK_a(ROH)$ constructed for **6**,^[9] **7**,^[10] and **8**^[11] (Scheme 4) gave the following relationships (Eqns 1–3):

$$6 \quad r_{C-O} = 1.493 - 6.49 \times 10^{-3} pK_a(ROH) \quad R^2 = 0.985 \quad (1)$$

$$7 \quad r_{C-O} = 1.502 - 5.30 \times 10^{-3} pK_a(ROH) \quad R^2 = 0.986 \quad (2)$$

$$8 \quad r_{C-O} = 1.48 - 2.77 \times 10^{-3} pK_a(ROH) \quad R^2 = 0.976 \quad (3)$$

A strong response of C—OR bond distance to the electron demand of OR is demonstrated for **6**, which has an oxygen lone pair (n_O) orbital antiperiplanar to the OR substituent (this is the basis of the well known anomeric effect).^[12] A strong response is also observed for **7**, which has a C—Si bond antiperiplanar to the OR substituent (this is the basis of the silicon β -effect).^[13] However, a weaker response is obvious in **8**, which has a σ_{C-C} bonding orbital, and is the result of a weaker donor orbital being situated antiperiplanar to the OR bond. Thus, the slope of the plot of C—OR bond distance versus the $pK_a(ROH)$ for **5a** and its derivatives was expected to provide a measure of the extent of the through-bond interaction between the sulfur lone pair and the oxygenated substituent.

Results and Discussion

Alcohol **5a** was prepared from thiocyclohexanone and converted into the crystalline ester and ether derivatives **5b–g** (Scheme 5) covering the pK_a range +16 to –3.18. As the *m*-nitrobenzoate **5c** and *p*-nitrobenzoate **5d** derivatives surprisingly crystallized with the cyclohexane ring adopting a conformation in which the ester groups were axial,^[14] they



- 5a** R = H
5b R = *p*-NO₂C₆H₄
5c R = *m*-NO₂C₆H₄CO
5d R = *p*-NO₂C₆H₄CO
5e R = *o*-NO₂C₆H₄CO
5f R = 2,4-NO₂C₆H₃CO
5g R = *p*-NO₂C₆H₄SO₂

Scheme 5.

could not be used in this study because they do not meet the stereoelectronic requirements for through-bond interaction with the sulfur lone pair.

The X-ray structures of **5a**, **5b**, and **5e–g** were determined at 130 K to minimize the unwanted effects of thermal motion. Selected bond distances are presented in Table 1 and a thermal ellipsoid plot for one of the structures (**5g**) is presented in Fig. 2.

Examination of the distances in Table 1 shows that (a) there is excellent agreement between those bonds which are related by the approximate local plane of symmetry defined by S, C4, and O1; and (b) there is a clear relationship between the C1—O1 bond distance and the electron demand of the oxygen substituent [as estimated by the $pK_a(ROH)$]. In particular, the C1—O1 bond distance increases as the electron demand of the oxygen substituent increases. Thus, the C4—O1 bond distance in the weakly electron demanding alcohol **5a** is 1.431(2) Å and increases to 1.487(2) for the strongly electron demanding nosylate derivative **5g**. This data is presented graphically in Fig. 3 and gives rise to the following relationship (Eqn 4):

$$r_{C-O} = 1.48 - 2.76 \times 10^{-3} pK_a(ROH) \quad R^2 = 0.99 \quad (4)$$

This relationship is essentially identical to that obtained for the derivatives of cyclohexanol **8** (Eqn 3) above, which suggests that the proposed through-bond interaction between the sulfur lone pair and the oxy substituent is either not present, or is simply too small to be detected by this method. Stereoelectronic effects on ground states of molecules are relatively small in comparison to the effects on transition states. Therefore, in order to magnify the effects of the proposed through-bond interaction we determined the rate of unimolecular solvolysis of the nosylate derivative **5g** so that this could be compared with that which has been previously reported for the equatorial cyclohexyl nosylate derivative **6** (Scheme 6).^[15] The relative reactivities of **5g** and **6** would provide a measure of the relative stabilities of the carbenium ion intermediates **7** and **8**, and hence, provide a measure of the through-bond stabilization of **8** by the sulfur lone pair.

The solvolysis of **5g** was carried out in 97% CF₃CD₂OD/D₂O in the presence of 2,6-lutidine at 40°C using the NMR method reported by Creary and Jiang.^[16] Absolute and relative rates of solvolysis of **5g** and **6** are presented in Table 2.

Surprisingly, nosylate **5g** underwent solvolysis at a rate of more than one order of magnitude slower than the corresponding sulfur cyclohexyl ester **6**. Thus, the presence of sulfur appears to destabilize the intermediate carbenium ion **8** in comparison to **7**. This result suggests that there is either no

Table 1. Selected bond distances for compounds **5a**, **5b**, and **5e–g**

Compound	p <i>K</i> _a	S–C2	S–C6	C2–C3	C3–C4	C4–C5	C5–C6	C4–O1
5a ; M1	16	1.792(2)	1.798(2)	1.516(3)	1.510(3)	1.504(3)	1.521(3)	1.442(3)
M2	–	1.803(2)	1.799(2)	1.523(3)	1.512(3)	1.505(3)	1.526(3)	1.428(3)
M3	–	1.796(2)	1.793(2)	1.500(3)	1.513(3)	1.500(3)	1.520(3)	1.423(3)
5b	7.15	1.809(3)	1.810(3)	1.526(4)	1.513(4)	1.513(4)	1.524(4)	1.460(3)
5e	2.17	1.809(2)	1.810(2)	1.526(2)	1.515(2)	1.516(2)	1.530(2)	1.470(2)
5f	1.4	1.801(3)	1.800(3)	1.527(4)	1.517(4)	1.504(4)	1.520(4)	1.471(3)
5g	–3.8	1.808(2)	1.806(2)	1.525(2)	1.517(2)	1.519(2)	1.524(2)	1.487(2)

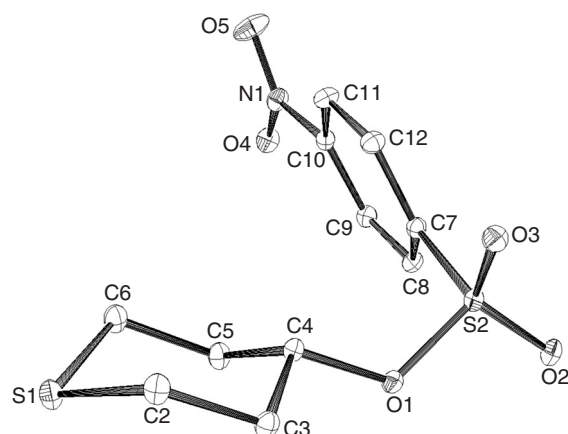


Fig. 2. Thermal ellipsoid plot for ester **5g**. Ellipsoids are at the 20% probability level. The numbering scheme for the thiacyclohexane ring is employed for all structures.

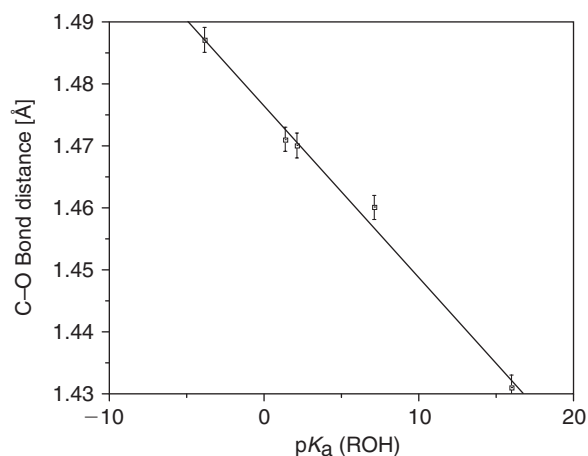
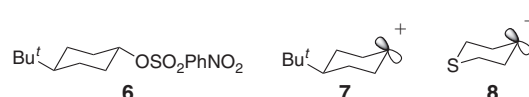


Fig. 3. $r(\text{C–O})$ versus $\text{p}K_{\text{a}}(\text{ROH})$ relationship for the derivatives **5a**, **5b**, and **5e–g**.

through-bond interaction between the sulfur lone pair and the carbenium ion p-orbital, or that perhaps it is more than compensated for by an unfavourable inductive or field effect of the sulfur atom. Evidence for through-bond participation during solvolysis reactions can be provided by analysis of the reaction products. For example, solvolysis of the bicyclic amine **2** leads exclusively to products derived from the iminium ion **9** (Scheme 7), and indicates the participation of the nitrogen lone pair in the displacement of the chloride ion.

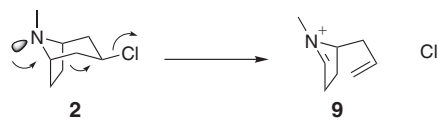
In contrast, solvolysis of **5g** leads exclusively to 4-thiacyclohexene **10** (Scheme 8) through a simple E1 elimination. This provides no evidence that the sulfur lone pair is involved in the reaction, but rather, that the intermediate



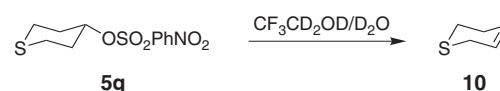
Scheme 6.

Table 2. Solvolysis rates for **5g** and **6**

Compound	<i>k</i> [s ^{–1}]	<i>k</i> (rel)
5g	1.5×10^{-6}	1.0
6	approx. 1.9×10^{-7}	ca. 0.1



Scheme 7.



Scheme 8.

carbenium ion **8** prefers to be stabilized by hyperconjugation with the neighbouring axial hydrogens.

Conclusions

We have examined the through-bond interaction between a sulfur lone pair and oxygenated substituents in the unstrained thiacyclohexane framework in terms of both ground state and reactivity effects. Our data provides evidence that biotin is unlikely to facilitate the carboxyl transfer reaction by a through-bond interaction.

Experimental

General experimental details have been published elsewhere.^[11]

General Procedure for the Preparation of Ester Derivatives **5e–g**

To a solution of tetrahydrothiopyran-4-ol (0.102 g, 0.87 mmol) in pyridine (1.5 mL) was added 4-nitrobenzenesulfonyl chloride (0.222 g, 1.00 mmol). Upon completion of the reaction (formation of salts), the mixture was quenched with a few drops of water, extracted with EtOAc (3 × 20 mL), and washed with NaHCO₃ (10 mL). The organic layer was then evaporated to give **5g**, which was crystallized from pentane, mp 121–123°C. δ_{H} (CDCl₃) δ 8.41 (2H, d, *J* 9.0), 8.12 (2H, d, *J* 9.0), 4.75–4.69 (1H, m), 2.84–2.78 (2H, m), 2.55–2.48 (2H, m), 2.14–2.07 (2H, m), 2.04–1.96 (2H, m). δ_{C} (CDCl₃) 150.6, 143.0, 128.9, 124.5, 80.8, 33.2, 25.0.

4-Thiacyclohexyl 2,4-Dinitrobenzoate **5f**

From diethyl ether/pentane, mp 101–103°C. δ_{H} (CDCl₃) 8.81 (1H, d, *J* 2.0), 8.54 (1H, dd, *J* 8.4 and 2.2), 7.95 (1H, d, *J* 8.2), 5.18–5.12 (1H, m),

2.83–2.77 (2H, m), 2.69–2.62 (2H, m), 2.29–2.22 (2H, m), 2.05–1.97 (2H, m). δ_{C} (CDCl₃) 162.9, 148.9, 148.0, 133.0, 131.3, 127.5, 119.6, 74.3, 31.9, 25.6.

4-Thiacyclohexyl 2-Nitrobenzoate **5e**

From diethyl ether/pentane, mp 93–95°C. δ_{H} (CDCl₃) 7.93–7.90 (1H, m), 7.75 (1H, dd, J 7.5 and 1.7), 7.71–7.62 (2H, m), 5.16–5.10 (1H, m), 2.25–2.18 (2H, m), 2.04–1.96 (2H, m). δ_{C} (CDCl₃) 164.6, 148.3, 132.9, 131.8, 129.9, 127.8, 123.9, 73.0, 32.0, 25.7.

4-Thiacyclohexyl *p*-Nitrophenyl Ether **5b**

To a solution of tetrahydrothiopyran-4-ol (0.100 g, 0.85 mmol) in THF (5 mL) was added NaH (50%, 0.05 g, 1.04 mmol) at 0°C and the mixture was stirred for 45 min at room temperature. *p*-Fluoronitrobenzene (0.125 g, 0.89 mmol) was then added and the mixture was stirred overnight. The resultant mixture was subsequently treated with H₂O (20 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with H₂O (2 × 10 mL), dried (Na₂SO₄), filtered, and concentrated to give the desired compound as an oil which slowly crystallized. Recrystallization from MeOH gave **5b**, mp 116–118°C. δ_{H} (CDCl₃) 8.19 (2H, d, J 9.5), 6.94 (2H, d, J 9.2), 4.53–4.48 (1H, m), 2.95–2.89 (2H, m), 2.64–2.57 (2H, m), 2.27–2.20 (2H, m), 2.10–2.02 (2H, m). δ_{C} (CDCl₃) 162.3, 141.4, 126.0, 115.3, 73.8, 32.1, 25.2.

Kinetics

2,6-Lutidine was stirred over KOH for 24 h before distillation from CaH₂ under nitrogen. [D₄]Trifluoroethanol and D₂O were used without purification.

The method used was based on that reported by Creary and Jiang.^[17] The substrate (1.5 × 10^{−5} mol) was dissolved in a solution of 0.04 M 2,6-lutidine in 97% [D₄]trifluoroethanol/D₂O (0.5 mL). The solution was maintained at 40°C using a Laude constant temperature bath, and ¹H NMR spectra were measured every 5–6 h over a period of several days. The reaction was essentially complete after 24 days, as at this stage the only species present were the lutidinium nosylate salt and signals at δ_{H} 2.30 (2H, m), 2.70 (2H, t), 3.10 (2H, m), and 5.87 (2H, m), which correspond to 4-thiacyclohexene.^[17]

Crystallography

Intensity data were collected with a Bruker SMART Apex CCD detector using MoK α radiation (graphite crystal monochromator, λ 0.71073).^[18] Data were reduced using the program *SAINT* and corrected for absorption where appropriate (*SADABS*). Structures were solved by direct methods and difference Fourier synthesis using the *SHELX*^[19] suite of programs as implemented by the *WINGX*^[20] software. Crystallographic information files (CIFs) for compounds **5a**, **5b**, and **5e–g** have been deposited at the Cambridge Crystallographic Data Centre, CCDC numbers 258422–258426; www.ccdc.cam.ac.uk/data_request/cif.

Crystal Data for **5a**

C₅H₁₀SO, M 118.19, T 130.0(1) K, λ 0.71069, monoclinic, space group $P2_1/c$, a 6.492(1), b 16.408(3), c 17.390(3) Å, β 90.637(4)°, V 1852.3 Å³, Z 12, D_{c} 1.271 mg M^{−3}, μ (MoK α) 0.401 mm^{−1}, $F(000)$ 768, crystal size 0.05 × 0.05 × 0.01 mm³, 9283 reflections measured, 3257 independent reflections (R_{int} 0.07), the final R was 0.0393 [$I > 2\sigma(I)$] and $wR(F^2)$ was 0.0825 (all data).

Crystal Data for **5b**

C₁₁H₁₃NO₃S, M 239.28, T 130.0(1) K, λ 0.71069, monoclinic, space group Cc , a 6.541(1), b 23.824(4), c 7.240(1) Å, β 92.451(3)°, V 1127.1(3) Å³, Z 4, D_{c} 1.410 mg M^{−3}, μ (MoK α) 0.278 mm^{−1}, $F(000)$ 504, crystal size 0.3 × 0.15 × 0.05 mm³, 3856 reflections measured, 2238 independent reflections (R_{int} 0.0386), the final R was 0.0437 [$I > 2\sigma(I)$] and $wR(F^2)$ was 0.0871 (all data).

Crystal Data for **5e**

C₁₂H₁₃NO₄S, M 267.29, T 130.0(1) K, λ 0.71069, triclinic, space group $P\bar{1}$, a 6.891(2), b 7.887(2), c 11.711(3) Å, α 75.111(4), β

79.971(4), γ 86.087(4)°, V 605.5(3) Å³, Z 2, D_{c} 1.466 mg M^{−3}, μ (MoK α) 0.273 mm^{−1}, $F(000)$ 280, crystal size 0.3 × 0.3 × 0.15 mm³, 5520 reflections measured, 2708 independent reflections (R_{int} 0.0228), the final R was 0.0410 [$I > 2\sigma(I)$] and $wR(F^2)$ was 0.1082 (all data).

Crystal Data for **5f**

C₁₂H₁₂N₂O₆S, M 312.30, T 130.0(1) K, λ 0.71069, orthorhombic, space group $Pbca$, a 7.4594(15), b 8.921(2), c 40.313(9) Å, V 2682 Å³, Z 8, D_{c} 1.547 mg M^{−3}, μ (MoK α) 0.272 mm^{−1}, $F(000)$ 1296, crystal size 0.3 × 0.2 × 0.2 mm³, 17813 reflections measured, 2365 independent (R_{int} 0.0874), the final R was 0.0476 [$I > 2\sigma(I)$] and $wR(F^2)$ was 0.1346 (all data).

Crystal Data for **5g**

C₁₁H₁₃NO₅S₂, M 303.34, T 130.0(1) K, λ 0.71069, triclinic, space group $P\bar{1}$, a 6.8688(7), b 10.059(1), c 10.294(1) Å, α 113.164(2), β 96.939(2), γ 91.788(2)°, V 646.6(1) Å³, D_{c} 1.558 mg M^{−3}, μ (MoK α) 0.427 mm^{−1}, $F(000)$ 316, crystal size 0.4 × 0.2 × 0.1 mm³, 4637 reflections measured, 2900 independent reflections (R_{int} 0.0555), the final R was 0.0362 [$I > 2\sigma(I)$] and $wR(F^2)$ was 0.0966 (all data).

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