Synthesis and Structure of a Chiral Sulphinamidocobalt(III) Complex derived from (*R*)-Cysteine

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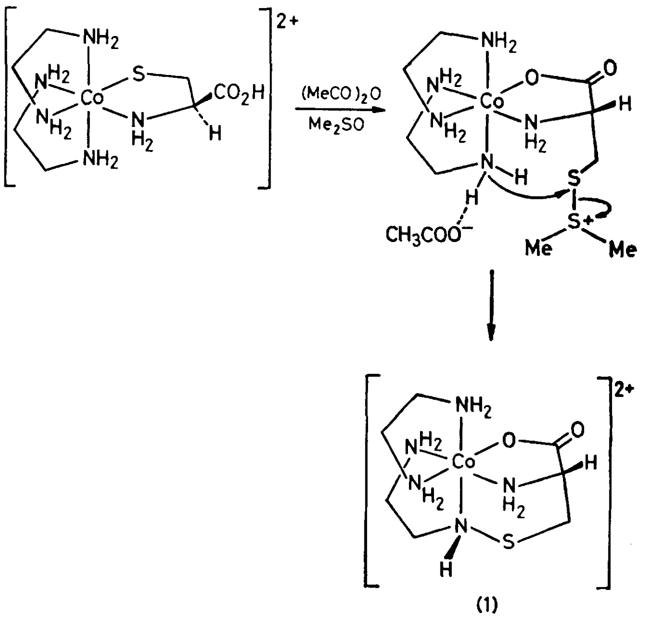
Summary Co-ordinated chiral sulphinamides, prepared by the stereoselective oxidation of a sulphenamidocobalt(III) complex, are shown to be stable to inversion except in 3 M HCl; the crystal and molecular structure and absolute configuration of a sulphinamido-complex derived from (*R*)-cysteine are reported.

Sulphenamides ($RSNH_2$) and sulphinamides [$RS(O)NH_2$] are uncommon classes of organosulphur compounds. Recently, sulphenamides[1,2] derived from (*R*)-cysteine and ethylenediamine were prepared by a remarkable reaction between a nucleophilic, metal-bound amido-ion and an electrophilic sulphur centre, both generated *in situ* (Scheme 1). Routes to oxidized forms of these sulphenamides are now reported, namely to sulphinamides and the more common class of organic sulphur compounds, sulphonamides [equation (**1**)].

$$R^1SNHR^2 \xrightarrow{[O]} R^1SONHR^2 \xrightarrow{[O]} R^1SO_2NHR^2 \qquad (1)$$

The orange sulphenamide complex (**1**) [Δ(*R*,*S*)-isomer, perchlorate salt], when treated with *N*-bromosuccinimide (NBS, 1·0 equiv.) in water (20 °C), rapidly yielded (< 1 min) a pink–orange solution from which crystals of the $ZnCl_4^{2-}$ salt of complex (**2**) were isolated in 95% yield (Scheme 2).†



Scheme 1.

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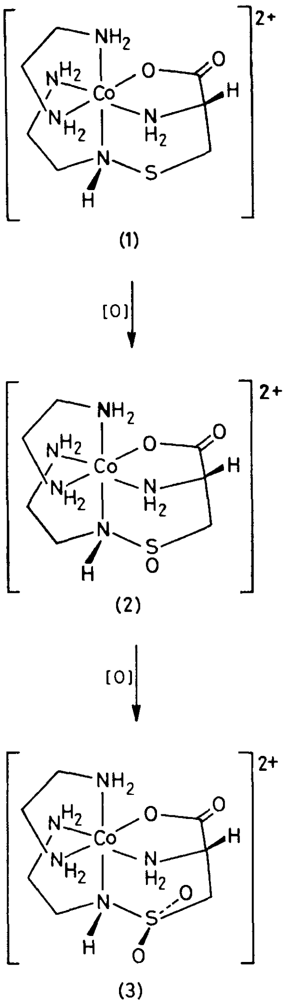
† All the salts of complex (**2**) gave satisfactory elemental analyses.

The chloride, ClO_4^-, and $S_2O_6^{2-}$ salts of (**2**) were also obtained and the elemental analyses in each case corresponded to the addition of one oxygen atom to the cation (**1**). A similar reaction between (**1**) and excess of NBS or Cl_2 afforded a different (pink) complex (**3**) in high yield, and analysis indicated the addition of two oxygen atoms. Purity was established by ion-exchange chromatography under conditions where complexes (**1**)—(**3**) separate readily.‡ Salts of deprotonated forms of (**2**) and (**3**) {crystallised from H_2O–tris [tris = $(CH_2OH)_3NMe$]} were also characterized, and the strongly pH-dependent visible absorption spectra indicated deprotonation at the NHS moiety. The trend in pK_a values for the moieties R^1SNHR^2 (**1**), 9·3[3] > R^1SONHR^2 (**2**), 2·3[4] > $R^1SO_2NHR^2$ (**3**), *ca.* 0 is consistent with the sequential addition of oxygen to sulphur in these reactions.



Scheme 2.

We were particularly interested in the specificity of the first oxidation step $R^1SNHR^2 \rightarrow R^1SONHR^2$ since a chiral sulphur centre is generated. In preliminary studies we found no evidence (chromatography, ^1H n.m.r. and 15 MHz ^{13}C n.m.r. spectroscopy) for the existence of the two expected epimers and it appeared that the reaction was stereospecific. A single-crystal *X*-ray study of complex (**2**) was carried out to confirm the sulphinamide structure and to determine the absolute configuration at the sulphur centre. The structural result (Figure) confirmed the presence of a single oxygen atom attached to sulphur. Remarkably, however, the oxygen was found to be disordered between the two tetrahedral sulphur sites. The diffraction data were consistent with the two epimeric sulphinamides [(*R*)-form, 78% and (*S*)-form, 22% (shaded oxygen atoms)] being randomly distributed throughout the crystal. There are no close intramolecular contacts to either O(31) or O(32).§

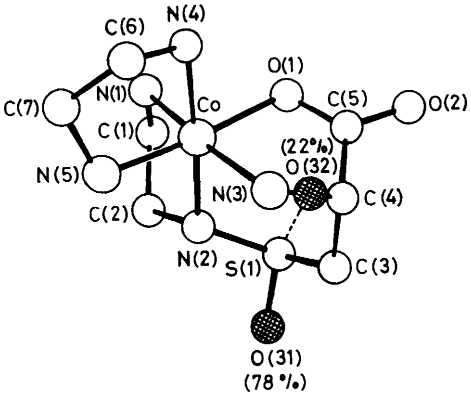


Figure. Molecular structure of the sulphinamide complex dication (**2**) as its $ZnCl_4^-$ salt. Bond lengths: N(2)–S(1), 1·765(7); S(1)–O(31), 1·742(10); S(1)–O(32), 1·476(36); Co–N(1,4,5), ave. 1·954(7); Co–N(2), 1·997(7); and Co–N(3), 1·982(7) Å; Bond angle: O(31)–S(1)–O(32), 126(1)°.

The chiralities of the cobalt, carbon, and nitrogen centres have been determined to be Δ, (*R*), and (*S*), respectively, as in the parent sulphenamide complex (**1**).[1] The structures of complexes (**1**) and (**2**) are remarkably similar; indeed, their $ZnCl_4^{2-}$ salts are isomorphous. Five crystal structures of sulphenamide and related[2] complexes are now known and in each case the six-membered ring adopts the chair conformation.

A 69 MHz ^{13}C n.m.r. spectrum of (**2**) resolved the two diastereoisomers (3 : 1) not resolved in the lower resolution (15 MHz) spectrum. Furthermore the two pure isomers have now been isolated *via* ion-exchange chromatography at pH 4·5 (utilizing the small difference in pK_a between them). We have shown that mixtures of any composition co-crystallize as their $ZnCl_4^{2-}$ or $S_2O_6^{2-}$ salts even though the molecular structures are different. The 78 : 22 ratio found in the *X*-ray study of the $ZnCl_4^{2-}$ salt merely reflects the

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‡ Chromatography on Dowex 50WX2 (H^+-form) cation-exchange resin, 2 M HCl eluant.

§ *Crystal data:* $C_7H_{20}CoN_5O_3S\cdot ZnCl_4$, $M = 520\cdot4$; orthorhombic, space group $P2_12_12_1$; $a = 16\cdot073(1)$, $b = 17\cdot139(1)$, $c = 6\cdot3427(8)$ Å; $U = 1752\cdot7$ Å^3; $D_m = 1\cdot96(5)$, $D_c = 1\cdot97$ g cm^{-3} for $Z = 4$; $\mu(\text{Cu-}K_\alpha) = 162\cdot2$ cm^{-1}, $\lambda(\text{Cu-}K_\alpha) = 1\cdot5418$ Å. Unique data with $\theta < 57\cdot1°$ were collected on a Hilger and Watts Y290 diffractometer. Full-matrix least-squares refinement using 1071 independent, absorption-corrected reflections with $I > 3\sigma(I)$ converged with $R = 0\cdot041$ (see text). Full details of the *X*-ray work will be published later. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

kinetic distribution of the NBS oxidation reaction, and we have confirmed this by direct chromatography of the total products. The epimers can also be separated by fractional crystallization of the $S_2O_6^{2-}$ salts of their deprotonated forms. Both isomers give a common sulphonamide product (**3**) on oxidation with Cl_2 (Scheme 2).

It is apparent that the chiral sulphur centre of the sulphinamides in both the protonated (at nitrogen) and deprotonated forms is optically stable. However, in strong acid (3 M HCl) slow mutarotation occurs. The mechanism (Scheme 3) is probably akin to that for the acid-catalysed racemization of sulphoxides.[5] Approached from either side

$$\begin{array}{rcl} (S)\text{-}R^1SONHR^2 + H^+ & \rightleftharpoons & (S)\text{-}R^1S^+(OH)NHR^2 \\ & & \quad \upharpoonleft\!\downharpoonright H_2O \\ (R)\text{-}R^1SONHR^2 & \rightleftharpoons & R^1S(OH)_2NHR^2 + H^+ \\ & & \text{symmetrical} \end{array}$$

Scheme 3.

the equilibrium distribution of isomers is *ca.* 95% (*R*), 5% (*S*); the specificity is obviously substantial.

The sulphinamides [and the sulphonamide (**3**)] do not invert about the cobalt atom, even in base. They are at least 10^5-fold less reactive than the corresponding sulphenamides in this respect.[1,6]

This study has established that both the kinetically and thermodynamically preferred oxygen orientations at sulphur are equatorial. Simple conformational arguments would predict the equatorial disposition in a six-membered chair ring as being the more stable, and it is interesting that the kinetic isomer distribution also reflects this preference, although to a lesser extent (95:5 *vs.* 75:25). Hydrogen peroxide oxidation of (**1**) also gives both sulphinamides, with the equatorial oxygen epimer predominating. The product ratio is different from that for the NBS oxidation. Moreover the H_2O_2 oxidation is acid-catalysed and the epimer ratio appears to be different for both the acid-dependent and acid-independent pathways.

Finally, we note the thermal stability of the sulphinamido- and sulphonamido-complexes. For example, they strongly resist hydrolysis (S–N cleavage) in aqueous acid or base. Furthermore the sulphinamides do not disproportionate, and this may be contrasted with the behaviour of the unco-ordinated organic species.[7] The metal-ion stabilization of the organic moiety is consistent with that reported[8] for sulphenates (RSO^-) which, in the free state, are even less stable than sulphinamides. The sulphenamides[1,2] and the present sulphinamide complexes are active bacteriostats and their biochemistry is under scrutiny.

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