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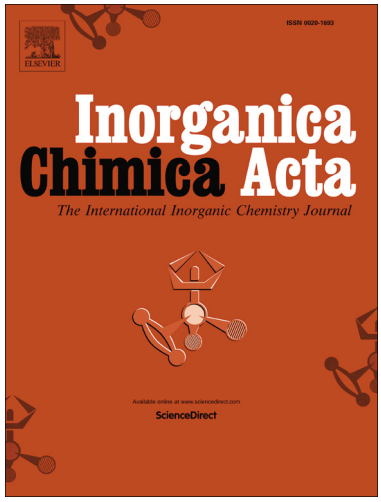

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Synthesis and characterization of new disulfoxides, and their Ru complexes

Elizabeth L.S. Cheu,[a,b] Donald T. T. Yapp,[a,b] Lynsey Huxham,[a,b] Brian O Patrick,[a] Brian R. James [a,*]

[a] *Department of Chemistry, The University of British Columbia, 2036 Main Mall, Vancouver, BC V6T 1Z1, Canada*
[b] *Advanced Therapeutics, British Columbia Cancer Research Centre, Vancouver, BC V5Z 1L3, Canada*

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ABSTRACT

Reported are the syntheses of ten, new disulfoxides, and four known ones, of the type R-S(O)-$CH_2)_n$-(O)S-R (n = 2 or 3, R = alkyl) that were formed by oxidizing the corresponding dithioethers, $RS(CH_2)_nSR$, using acid solutions of DMSO or H_2O_2 as oxidants. The disulfoxides were then reacted with either commercial $RuCl_3 \cdot H_2O$, $K_3(RuCl_6)$, or the so-called Ru 'Blue' or 'Red' solutions, in aqueous or alcohol (MeOH, EtOH) solution from which various S-bonded sulfinyl complexes of the type *cis* or *trans*-$Ru^{II}Cl_2$(disulfoxide)$_2$, $[Ru^{II}Cl_2(disulfoxide)(H_2O)]_2(\mu\text{-}Cl)_2$, and $[Ru_2^{II/III}Cl(disulfoxide)]_2(\mu\text{-}Cl)_3$ were isolated; all three types are well characterized, including X-ray data. One Ru^{III} complex, formulated $RuCl_3(BPhSE)]_2(\mu$–BPhSE) with the bridging disulfoxide 1,2-bis(phenylsulfinyl)ethane, is also synthesized, but less well characterized.

1. Introduction

We reported recently on the synthesis of nine new dithioethers of the type $RS(CH_2)_nSR$, where n = 2 or 3, and R is an alkyl chain [1]; synthesis and data of two known analogues where n = 2 or 3 and R = phenyl, were also presented. The aim was to oxidize these to the corresponding disulfoxide species $RS(O)CH_2)_x(O)SR$, because of the potential biological properties of their Ru complexes; e.g., anti-cancer, radiosensitizer, and hypoxic activities have been reported for some Ru compounds containing sulfoxide or disulfoxide ligands [2,3]. This current paper reports on the syntheses of the disulfoxides, and their reactions with various Ru-precursors to form S-bonded sulfinyl complexes of the type *cis* or *trans*-$Ru^{II}Cl_2$(disulfoxide)$_2$, $[Ru^{II}Cl_2(disulfoxide)(H_2O)]_2(\mu\text{-}Cl)_2$, and $[Ru_2^{II/III}Cl$ (disulfoxide)$]_2(\mu\text{-}Cl)_3$; all types are well characterized, including X-ray data. Some *in vitro* studies on such complexes, such as cell accumulation and toxicity, and binding to DNA [4], will be reported later. This paper is the second of three: the first reported on the dithioethers and some of their Ru complexes [1], and the third will describe later the *in vitro* studies.

*Corresponding author. *E-mail address: brj@chem.ubc.ca (B.R. James).*

2. Experimental section

2.1. General

The dithioethers, required as precursors for oxidation to the corresponding disulfoxide, were prepared and characterized as described [1,3,4]. Table 1 shows the names and abbreviations used for thedisulfoxides; the conversion of the dithioether to the disulfoxide in each case involves a change in the T of the abbreviation (meaning 'thia') to S (meaning sulfinyl), e.g. in Section 2.2.1, BESP is synthesizedfrom BETP. The known 3,6-dithiaoctane, *viz* bis(ethylthio)ethane (BETE), 4,7-dithiadecane, *viz* bis(propylthio)ethane (BPTE), and 1,2 bis(phenylthiol)ethane (BPhTE), were purchased from K & K Laboratories, and were similarly oxidized to the corresponding known disulfoxides, BESE, BPSE, andBPhSE [3,5]. 3,5 Dithiaseptane, *viz* bis(ethylthio)methane (BETM), was synthesized as reported [6].

Table 1. Names and abbreviations used for the synthesized R-S(O)-$CH_2)_n$-(O)S-R disulfoxides; the first 5 (in italics) are known compounds (see Section 3.1, Table 2).

n	R	Name	Abbreviation
2	methyl	1,2-bis(methylsulfinyl)ethane	*BMSE*
2	ethyl	1,2-bis(ethylsulfinyl)ethane	*BESE*
2	propyl	1,2-bis(propylsulfinyl)ethane	*BPSE*
2	phenyl	1,2-bis(phenylsulfinyl)ethane	*BPhSE*
3	methyl	1,3-bis(methylsulfino)propane	*BMSP*
2	n-butyl	1,2-bis(butylsulfinly)ethane	BBSE
2	*n*-hexyl	1,2-bis(hexylsulfinyl)ethane	BHSE
2	cyclohexyl	1,2-bis(cyclohexylsulfinyl)ethane	BCySE
2	*n*-pentyl	1,2-bis(pentylsulfinyl)ethane	BPeSE
3	ethyl	1,3-bis(ethylsulfinyl)propane	BESP
3	*n*-propyl	1,3-bis(propylsulfinyl)propane	BPSP
3	*i*-propyl	1,3-bis(*i*-propylsulfinyl)propane	B^{i}PSP
3	*n*-butyl	1,3-bis(butylsulfinyl)propane	BBSP
3	*n*-pentyl	1,3-bis(pentylsulfinyl)propane	BPeSP
3	phenyl	1,3-bis(phenylsulfinyl)propane	BPhSP

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in Section 2.2.1, BESP is synthesized from BETP. The known 3,6-dithiaoctane, *viz* bis(ethylthio)ethane (BETE), 4,7-dithiadecane, *viz* bis(propylthio)ethane (BPTE), and 1,2 bis(phenylthiol)ethane (BPhTE), were purchased from K & K Laboratories, and were similarly oxidized to the corresponding known disulfoxides, BESE, BPSE, and BPhSE [3,5]. 3,5 Dithiaseptane, *viz* bis(ethylthio)methane (BETM), was synthesized as reported [6].

Common chemicals and solvents used were at least of reagent grade, and were purchased from Fisher Scientific, and used as provided; deuterated solvents $CDCl_3$, D_2O were purchased from MSD Isotopes. $RuCl_3 \cdot 3H_2O$ was donated by Colonial Metals Inc.; $K_3[RuCl_6]$ and *cis*-$RuCl_2(DMSO)_4$ were made as reported [7]; the so-called "Ru-blue solution" [8] was generated by refluxing a MeOH solution of $RuCl_3 \cdot 3H_2O$ under H_2 for ~4 h; and the so-called "Ru-red solution" [9] was made by heating, under reflux in air for ~2 h, an EtOH solution of $RuCl_3 \cdot 3H_2O$ in the presence of HCl acid.

Syntheses of the disulfoxides are described in Section 2.2. All samples (products and solvents) were stored in air, and all syntheses and measurements were carried out in air, unless noted otherwise. Syntheses of Ru^{II} and dinuclear Ru_2^{II} complexes, a dinuclear Ru^{II}/Ru^{III} complex, and a dinuclear Ru_2^{III} complex, are described in Sections 2.3, 2.4, 2.5 and 2.6, respectively. The complex, *trans*-$RuCl_2(BMSE)_2$ was made via the Ru-blue solution as reported [3].

Elemental analyses (EA) were performed in the UBC chemistry department on a Carlo Erba 1106 instrument, with data having an accuracy of ±0.3%. Melting points (M.p., given in ºC) were obtained using a Fisher-Johns apparatus and are uncorrected.

Unless stated otherwise, NMR spectra were obtained in $CDCl_3$ solutions of the compounds using a Bruker AC-200E (200 MHz) instrument. The proton shifts, indicated by d = doublet, t = triplet; quin = quintet; m = multiplet, br = broad, are given with reference to the residual $CHCl_3$ solvent peak (δ 7.24) as the internal standard, relative to TMS. IR spectra (reported in cm^{-1}) were obtained using an ATI Mattson Genesis Series FTIR instrument, solid pellet samples being prepared by mixing the compound with KBr. UV-visible data were measured on a Hewlett-Packard 8452A diode array spectrophotometer, λ_{max} being given in nm, followed by an extinction coefficient given as log ε. Mass spectra were measured using +LSIMS on a KRATOS Concept IIHQ.

Determination of the μ_{eff} and number of unpaired electrons for paramagnetic Ru^{III} complexes was performed at room temperature (r.t. ~20 ˚C) using a Johnson-Matthey Mk1 Magnetic Susceptibility Balance. Molar conductance measurements, reported as Λ_M ($\Omega^{-1}cm^2mol^{-1}$), were carried out at r.t. at

~10^{-3} M concentrations using a Thomas Serfass conductivity bridge, and a cell from Yellow Springs Instrument Company, the cell constant being determined as 1.016 cm^{-1}. Thermal gravimetric data were collected using a TGA 51 Analyzer fitted with a quartz furnace tube with a temperature range from ambient to 1200 ºC. Column chromatography was performed on Merck silica TLC Al sheets (silica gel 60F254). Photochemical experiments were carried out at r.t. using an Ace-Hanovia 450Watt high pressure Hg vapour lamp (cat. #7825-34, Ace Glass Inc.).

2.2. Synthesis of Disulfoxides

2.2.1. 1,3-Bis(ethylsulfinyl)propane (BESP)

A stirred solution of 3,7-dithianonane (BETP), 10 mL, 60 mmol), DMSO (9.5 mL, 120 mmol) and conc. HCl (200 μL) was heated at 85 ºC for 8 h. A cooling of the solution to 0 ºC precipitated a white, crystalline product that was collected, and washed with acetone to remove excess DMSO and dimethyl sulphide. The filtrate was re-heated for a further 4 h, and gave more product. The disulfoxide was recrystallized from EtOH (50 mL) three times, and then dried under vacuum Yield 7.8 g (65 %). Anal. Calc. (found) for $C_7H_{16}O_2S_2$: C, 42.83 (43.1); H, 8.21 (8.2) %. ^{1}H-NMR: δ2.90 (m, 8H, CH_2S(O)CH_2), 2.45 (m, 2H, $CH_2CH_2CH_2$), 1.35 (t, 6H, CH_3). IR ν_{SO}: 1016, 1047. M.p.:127-130.

2.2.2. 1,3-Bis(propylsulfinyl)propane (BPSP)

BPSP was prepared according to the procedure given in Section 2.2.1, but using 4,8-dithiaunadecane (BPTP, 10 mL, 52 mmol), DMSO (8 mL, 100 mmol) and conc. HCl (200 μL). Yield 8.9 g (77 %). Anal. Calc. (found) for $C_9H_{20}O_2S_2$: C, 48.18 (48.1); H, 8.98 (9.1) %. ^{1}H-NMR: δ 3.00 (m, 4H, CH_2CH$_2$CH_2), 2.90 (m, 4H, CH_2S(O)), 2.20 (m, 2H, $CH_2CH_2CH_2$), 1.80 (m, 4H, $CH_2CH_2CH_3$), 1.07 (t, 6H, CH_3). IR ν_{SO}: 1021, 1075. M.p.: 140-143.

2.2.3. 1,3-Bis(i-propylsulfinyl)propane (B^{i}PSP)

B^{i}PSP was prepared basically via the Section 0 procedure, but using 2,8-dimethyl-3,7-dithianonane (B^{i}PTP, 10 mL, 52 mmol), DMSO (8 mL, 100 mmol) and conc. HCl (200 μL). The white disulfoxide precipitated when the reaction mixture was cooled to 0ºC, after the sides of the flask were scratched and Et_2O (30 mL) was added. Yield 2.3 g (20 %). Anal. Calc. (found) for $C_9H_{20}O_2S_2$: C, 48.18 (48.3); H,

8.98 (9.1) %. ^{1}H-NMR: δ2.75 (m, 6H, CHS(O)$CH_2CH_2CH_2$S(O)CH), 2.35 (m, 2H, $CH_2CH_2CH_2$), 1.35 (d, 12H, $(CH_3)_2$). IR ν_{SO}: 1016.

2.2.4. 1,3-Bis(butylsulfinyl)propane (BBSP)

BBSP was prepared as above, but using 5,9-dithiatridecane (BBTP, 10 mL, 45 mmol), DMSO (7 mL, 90 mmol) and conc. HCl (200 μL). Yield 9.9 g (87 %). Anal. Calc. (found) for $C_{11}H_{24}O_2S_2$: C, 52.34 (52.4); H, 9.58 (9.6) %. ^{1}H-NMR: δ2.80 (m, 8H, CH_2S(O)CH_2), 2.40 (m, 2H, $CH_2CH_2CH_2$), 1.75 (quin, 4H, $CH_3CH_2CH_2$), 1.50 (brs, 4H, CH_3CH_2), 0.95 (t, 6H, CH_3). IR ν_{SO}: 1021. M.p: 146-148.

2.2.5. 1,3-Bis(pentylsulfinyl)propane (BPeSP)

BPeSP was prepared as in Section 0, but using 6,10-dithiapentadecane (BPeTP, 10 mL, 40 mmol), DMSO (6 mL, 80 mmol) and conc. HCl (200 μL). Yield 3.3 g (29 %). Anal. Calc. (found) for $C_{13}H_{28}O_2S_2$: C, 55.67 (55.5); H, 10.06 (10.1) %. ^{1}H-NMR: δ2.70 (m, 8H, CH_2S(O)CH_2), 2.25 (m, 2H, $CH_2CH_2CH_2$), 1.68 (quin, 4H, $CH_3CH_2CH_2CH_2$), 1.28 (m, 8H, $CH_3CH_2CH_2$), 0.85 (t, 6H, CH_3). IR ν_{SO}: 1026. M.p: 125-129.

2.2.6. 1,3-Bis(phenylsulfinyl)propane (BPhSP)

1,3-Bis(phenylthio)propane (BPhTP, 10 g, 38 mmol) was added to 200 mL of glacial acetic acid, and the solution was cooled to 0 ºC, when 9 mL of 30 % H_2O_2 (76 mmol) was then added, and the resulting solution stirred for 24 h at r.t. prior to extraction with $CHCl_3$ (3 x 50 mL portions). The $CHCl_3$ was then neutralized with a saturated $NaHCO_3$ solution, and then the $CHCl_3$ layer was washed with H_2O and dried over $MgSO_4$. The $MgSO_4$ was removed and the $CHCl_3$ was removed by rotary evaporation to leave a white crude product; this was recrystallized with a CH_2Cl_2 (7 mL) and Et_2O (50 mL) mixture. Yield 2.1 g (19 %). Anal. Calc. (found) for $C_{15}H_{16}O_2S_2$: C, 61.61 (61.4); H, 5.51 (5.4) %. ^{1}H-NMR: δ7.50 (m, 10H, C_6H_5), 2.90 (m, 2H, $CH_2CH_2CH_2$), 2.15 (m, 4H, C$H_2$$CH_2CH_2$). IR ν_{SO}: 1021, 1040, 1084. M.p: 137-140.

2.2.7. 1,2-Bis(butylsulfinyl)ethane (BBSE)

BBSE was prepared as in Section 2.2.1, but using 5,8-dithiadodecane (BBTE, 10 mL, 48 mmol) in DMSO (8 mL, 97 mmol) and conc. HCl (200 μL). Yield 2.3 g (20 %). Anal. Calc. (found) for

$C_{10}H_{22}O_2S_2$: C, 50.37 (50.3); H, 9.30 (9,4) %. ^{1}H-NMR: δ 3.20, 3.00 (m, 2H each, S(O)CH_2CH_2S(O)), 2.75 (m, 4H, CH_2S(O)), 1.72 (m, 4H, $CH_3CH_2CH_2$), 1.45 (m, 4H, CH_3CH_2), 0.95 (t, 6H, CH_3). IR ν_{SO}: 1014. M.p: 172-173.

2.2.8. 1,2-Bis(pentylsulfinyl)ethane (BPeSE)

BPeSE was prepared as in Section 0, but using 6,9-dithiatetradecane (BPeTE, 10 mL, 40 mmol) in DMSO (7 mL, 80 mmol) and conc. HCl (200 µL). Yield 3.9 g (34 %). Anal. Calc. (found) for $C_{12}H_{26}O_2S_2$: C, 54.09 (54.1); H, 9.83 (10.1) %. ^{1}H-NMR: δ3.20, 3.10 (m, 2H each, S(O)CH_2CH_2S(O)), 2.80 (m, 4H, CH_2S(O)), 1.80 (m, 4H, $CH_3CH_2CH_2CH_2$), 1.40 (m, 8H, $CH_3CH_2CH_2$), 0.93 (t, 6H, CH_3). IR ν_{SO}: 1014, 1073, 1100. M.p: 134-135.

2.2.9. 1,2-Bis(hexylsulfinyl)ethane (BHSE)

BHSE was prepared as in Section 0, but using 7,10-dithiahexadecane (BHTE, 10 mL, 38 mmol) in DMSO (6 mL, 76 mmol) and conc. HCl (200 µL). Yield 6.2 g (55 %). Anal. Calc. (found) for $C_{14}H_{30}O_2S_2$: C, 57.09 (57.0); H, 10.27 (10.2) %. ^{1}H-NMR: δ 3.20, 3.10 (m, 2H each, S(O)CH_2CH_2S(O)), 2.80 (m, 4H, CH_2S(O)), 1.80 (m, 8H, $CH_3CH_2CH_2CH_2CH_2$), 1.40 (m, 8H, $CH_3CH_2CH_2$), 0.93 (t, 6H, CH_3). IR ν_{SO}: 1016, 1114. M.p: 176.5-177.5.

2.2.10. 1,2-Bis(cyclohexylsulfinyl)ethane (BCySE)

BCySE was prepared as in Section 0, but using 1,2-bis(cyclohexylthio)ethane (BCyTE, 10 mL, 40 mmol) in DMSO (6 mL, 77 mmol) and conc. HCl (200 µL). Yield 9.1 g (80 %). Anal. Calc. (found) for $C_{14}H_{26}O_2S_2$: C, 57.89 (58.1); H, 9.02 (9.1) %. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ3.60 (m, 4H, CH_2CH_2), 2.56, 2.15 (m, 2H each, H_2), 1.69 (m, 2H, H_1), 1.35 (m, 12H, $H_{3,4}$); H atoms numbered as for BCyTE [1]. IR ν_{SO}: 1018. M. p: 172-174.

2.3. Synthesis of mononuclear Ru(II) disulfoxide complexes

*2.3.1 Trans-$RuCl_2(BMSE)_2$ (**1**)*

Complex **1** was made in 80% yield by addition of BMSE to the Ru-blue solution, as reported [3].

*2.3.2. Cis-$RuCl_2(BESE)_2$ (**2**)*

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A solution of BESE (210 mg, 1.2 mmol) in MeOH (5 mL) was added to a solution of $K_3[RuCl_6]$ (250 mg, 0.6 mmol) in H_2O (15 mL), and the mixture then heated to 50 ºC for 5 h, during which the light brown solution became yellow and a yellow precipitate formed. Yield 112 mg (36 %). Anal. Calc. (found) for $C_{12}H_{28}Cl_2O_4RuS_4$: C, 26.86 (26.7); H, 5.26 (5.2) %. ^{1}H-NMR (D_2O, 200 MHz) δ 3.95-2.95 (m, 16H, C*H*$_2$S(O)C*H*$_2$), 1.45, 1.30 (t, 6H each, C*H*$_3$). IR ν_{SO}: 1092, 1122. The spectroscopic data agree well with those previously reported [3].

*2.3.3. Trans-$RuCl_2(BESE)_2 \cdot H_2O$ (**3**)*

To a solution of $[RuCl(BESE)(H_2O)]_2(\mu\text{-}Cl)_2$ (25 mg, 0.035 mmol (see Section 0) in H_2O (10 mL) was added BESE (12.2 mg, 0.07 mmol), and the resulting yellow solution was refluxed for 4 h before being reduced in volume; the product formed as a crystalline powder. X-ray quality crystals were formed by slow evaporation of an aq. solution of the complex. Yield 12 mg (33 %). Anal. Calc. (found) for $C_{12}H_{28}Cl_2O_4RuS_4 \cdot H_2O$: C, 25.98 (26.1); H, 5.4 (5.2) %. ^{1}H-NMR (D_2O, 200 MHz): δ 3.70 (m, 16H, C*H*$_2$S(O)C*H*$_2$), 1.45 (m, 12H, C*H*$_3$). IR ν_{SO}: 1093, 1119. UV-Vis (H_2O) 374 (2.78), 310 (3.19).

*2.3.4. Trans-$RuCl_2(BPSE)_2 \cdot H_2O$ (**4**)*

To a solution of *cis*-$RuCl_2(DMSO)_4$ (172 mg, 0.36 mmol) in MeOH (10 mL) was added a solution of BPSE (150 mg, 0.70 mmol) in MeOH (5 mL). The resulting yellow solution was refluxed for 3 h when a yellow precipitate formed. Yield 99 mg (47 %). Anal. Calc. (found) for $C_{16}H_{36}Cl_2O_4RuS_4 \cdot H_2O$: C, 31.47 (31.6); H, 6.27 (5.9) %. ^{1}H-NMR: δ 3.75, 3.35 (m, 8H each, C*H*$_2$S(O)C*H*$_2$), 2.30, 2.85 (m, 4H each, CH$_3$C*H*$_2$), 1.10 (t, 12H, C*H*$_3$). IR ν_{SO}: 1094. The spectroscopic data agree well with those reported [3].

Other methods using $RuCl_3 \cdot 3H_2O$ and $K_3[RuCl_6]$ as precursors for the attempted synthesis of *cis*-$RuCl_2(BPSE)_2$ also led to isolation of *trans*-$RuCl_2(BPSE)_2$.

*2.3.5. Cis-$RuCl_2(BBSE)_2$ (**5**)*

Conc. HCl (100µL) was added to a solution of $RuCl_3 \cdot 3H_2O$ (100 mg, 0.4 mmol) in EtOH (30 mL), and the mixture was refluxed for 5 h; BBSE (182 mg, 0.8 mmol) was then added, and the mixture was refluxed for a further 6 h. The resulting yellow solution was then reduced in volume until a fine yellow

precipitate formed, and this was collected. Yield 52 mg (21 %). Anal. Calc. (found) for $C_{20}H_{44}Cl_2O_4RuS_4$: C, 37.03 (37.0); H, 6.83 (6.8) %. X-ray quality crystals of an EtOH solvate were formed by slow evaporation of an EtOH/CH_2Cl_2 solution of the complex. ^{1}H-NMR: δ 3.60 (m, 16H, C*H*$_2$S(O)C*H*$_2$), 1.55 (m, 16H, $CH_3CH_2CH_2$), 0.98 (m, 12H, C*H*$_3$). IR ν_{SO}: 1081, 1126. UV-Vis (CH_2Cl_2) 236 (4.38).

*2.3.6. Cis-$RuCl_2(BPeSE)_2$ (**6**)*

The procedure was as in Section 2.3.5, but using BPeSE (204 mg, 0.8 mmol). The yellow product was purified by column chromatography using neutral alumina with 5 % EtOH/CH_2Cl_2. Crystals, obtained by slow evaporation of an EtOH/CH_2Cl_2 solution of the complex, were subjected to X-ray analysis, but excessive thermal motion due to the long pentyl groups prevented an accurate structure determination; however, cis-geometry was established. Yield 24 mg (9 %). Anal. Calc. (found) for $C_{24}H_{52}Cl_2O_4RuS_4$: C, 40.89 (41.0); H, 7.43(7.6) %. ^{1}H-NMR: δ 3.70 (m, 16H, C*H*$_2$S(O)C*H*$_2$), 2.30, 1.85 (m, 4H each, C*H*$_2$C*H*$_2$S(O)), 1.45 (m, 16H, $CH_3CH_2CH_2$), 0.90 (m, 12H, C*H*$_3$). IR ν_{SO}: 1081, 1128. UV-Vis (CH_2Cl_2) 240 (4.17).

*2.3.7. Cis-$RuCl_2(BCySE)_2$ (**7**)*

The procedure used was as in Section 2.3.5. but using BCySE (222 mg, 0.8 mmol) The collected, orange-yellow precipitate was collected. Yield 86 mg (30 %). Anal. Calc. (found) for $C_{28}H_{52}Cl_2O_4RuS_4$: C, 44.67 (44.3); H, 6.96 (7.0) %. Crystals suitable for X-ray analysis were formed by slow evaporation of the reaction solution. The ^{1}H-NMR spectrum of the title complex is a complicated pattern of overlapping multiplets in the δ 1.0-4.4 region. Attempts to assign the spectrum using ^{13}C, HETCOR, ATP and ^{1}H decoupling experiments were unsuccessful. IR ν_{SO}: 1046, 1100. UV-Vis (CH_2Cl_2) 428 (2.81), 338 (3.01).

2.3.8. Cis-$RuCl_2(BESP)_2$ (**8**)

The procedure used was described in Section 2.3.5**,** but using BESP (150 mg, 0.8 mmol); the resulting yellow solution was evaporated to near dryness, and the complex was purified by column chromatography as described in Section 2.3.6. Yield 77 mg (36 %). Anal. Calc. (found) for $C_{14}H_{32}Cl_2O_4RuS_4$: C, 29.78 (29.6); H, 5.71 (5.8) %. Crystals (containing one EtOH and one H_2O solvate

molecules) suitable for X-ray analysis were formed by vapour diffusion of EtOH into a CH_2Cl_2 solution of the complex. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.45 (m, 16H, C*H*$_2$S(O)C*H*$_2$), 2.75, 2.10 (m, 2H each, $CH_2CH_2CH_2$), 1.45 (m, 12H, C*H*$_3$). IR ν_{SO}: 1042, 1088. UV-Vis (CH_2Cl_2) 348 (2.62), 262 (4.04), 246 (4.01).

2.4. Synthesis of dinuclear Ru(II) disulfoxide complexes

*2.4.1. [RuCl(BESE)(H$_2$O)]$_2$(μ-Cl)$_2$ (**9**)*

The procedure used was as given in Section 2.3.5, but using BESE (70 mg, 0.4 mmol). The yellow precipitate was collected. Yield 87 mg (60 %). Anal. Calc. (found) for $C_6H_{16}Cl_2O_3RuS_2$: C, 19.35 (19.6); H, 4.33 (4.38); S, 17.22 (17.4) %. ^{1}H-NMR (D_2O, 200 MHz): δ 3.60 (m, 16H, $CH_2S(O)CH_2$), 1.50 (m, 12H, CH_3). UV-Vis (H_2O) 424 (2.63), 326 (3.16), 278 (3.42), 238 (3.47). IR ν_{SO}: 1042, 1071, 1118. Crystals for X-ray analysis were formed by slow evaporation of an aq. solution of the complex, and were found to contain one H_2O solvate per molecule. TGA (crystals): Calc. for loss of $3H_2O$, 7.1 %, and plus loss of 2BESE, 51.5 %; found: 6.8 % (from ~20 to ~220°C) and 46.0 % (from ~220 to ~370°C). Λ_M 358 (in H_2O, increasing to this steady value after 20 min).

*2.4.2. [RuCl(BPSE)(H$_2$O)]$_2$(μ-Cl)$_2$ (**10**)*

The procedure used was as given in Section 2.3.5 but using BPSE (84 mg, 0.4 mmol) to give the collected, yellow precipitate. Yield 70 mg (46 %). Anal. Calc. (found): for $C_8H_{20}Cl_2O_3RuS_2$: C, 24.00 (23.6); H, 5.03 (4.8) %. ^{1}H-NMR (D_2O, 400 MHz) δ 3.70 (m, 16H, $CH_2S(O)CH_2$), 2.00 (m, 8H, CH_2CH_3), 1.05 (m, 12H, CH_3). IR ν_{SO}: 1048, 1083, 1119. UV-Vis (H_2O): 268 (4.60). Λ_M 282 (in H_2O, increasing to this steady value after 30 min).

*2.4.3. [RuCl(BBSE)(H$_2$O)]$_2$(μ-Cl)$_2$ (**11**)*

The procedure used was that of Section 2.3.5, but using BBSE (95 mg, 0.4 mmol). The yield of the yellow precipitate was 100 mg (61 %). Anal. Calc. (found) for $C_{10}H_{24}Cl_2O_3RuS_2$: C, 28.04 (28.5); H, 5.43 (5.4) %. ^{1}H-NMR (D_2O, 400 MHz) δ 3.65 (m, 16H, C*H*$_2$S(O)C*H*$_2$), 2.00 (m, 8H, C*H*$_2$C*H*$_2$CH$_3$), 1.49 (m, 8H, C*H*$_2$C*H*$_3$), 0.95 (m, 12H, C*H*$_3$). IR ν_{SO}: 1046, 1098, 1116. UV-Vis (H_2O): 424 (2.92), 268 (4.39). Λ_M 497 (in H_2O, increasing to this steady value after 30 min).

2.5. Synthesis of a dinuclear Ru(II)/Ru(III) disulfoxide complex

*2.5.1.[RuCl(BPSP)]$_2$(μ-Cl)$_3$ (**12**)*

The procedure used was again that of Section 2.3.5, but with use of BPSP (172 mg, 0.8 mmol). A final orange solution was evaporated to near dryness, when CH_2Cl_2 (5 mL) was added, and X-ray quality crystals formed during slow evaporation of the solution. EA was done on a crushed crystal that was dried *in vacuo* at 70 ºC overnight. Yield 24 mg (15 %). Anal. Calc. (found) for $C_{18}H_{40}Cl_5O_4Ru_2S_4$: C, 26.11 (26.1); H, 4.87 (5.1) %. ^{1}H-NMR: δ 2.18 (broad peak), 1.10 (broad peak). ^{1}H-NMR (D_2O, 200 MHz) δ 3.95 (m, 4H, S(O)C*H*$_2$CH$_2$C*H*$_2$S(O)), 3.40 (m, 4H, C*H*$_2$S(O)), 2.62 (m, 2H, CH$_2$C*H*$_2$CH$_2$), 1.90 (m, 4H, CH$_2$C*H*$_2$CH$_3$), 1.10 (m, 6H, C*H*$_3$). IR ν_{SO}: 1053, 1084. UV-Vis (immediately upon dissolution in CH_3CN): 424 (2.52), 324 (2.94), 286 (3.32). UV-Vis (after 20 min in H_2O) 450 (3.78), 318 (4.42), 282 (4.78). No conductivity was observed in CH_3CN. Λ_M 2 ($CHCl_3$, time independent). Λ_M 234 (H_2O, increasing to a steady value at 20 min). The colour of the solutions used for UV-Vis and conductivity did not change over the period of the experiments. The crystal structure revealed the presence of 2 H_2O and 2.5 CH_2Cl_2 per molecule. TGA (crystals formulated as·2 H_2O or·2 H_2O·2.5 CH_2Cl_2, the two crystal formulae being used since the CH_2Cl_2 solvates are readily lost at ambient conditions). Calc. for loss of 2H_2O, 4.2 or 3.3 %, and for loss of 2BPSP, 54.2 %; found: 6.1 % (from ~20 to ~200 °C) and 51.9 % (from ~200 to ~300 °C). μ_{eff} = 1.7 ± 0.1 B. M.

2.6. Synthesis of a dinuclear Ru(III) disulfoxide complex

*2.6.1. [RuCl$_3$(BPhSE)]$_2$(μ–BPhSE)·x H_2O : x = 1 **(13a)**, 2 **(13b)***

(a) A solution of $RuCl_3·3H_2O$ (100 mg, 0.38 mmol) in MeOH (30 mL) and conc. HCl (100 µL) was refluxed under 1 atm N_2 for ~2 h when the colour became light orange. BPhSE (222 mg, 0.80 mmol) was then added and the solution refluxed under N_2 for another 5 h, this forming a yellow precipitate.

(b) BPhSE was also refluxed with $RuCl_3·3H_2O$ in EtOH according to the procedure reported in Section 2.3.5.

(c) BPhSE was similarly reacted with the other Ru precursors $K_3[RuCl_6]$, the Ru 'Blue' [8] solution, and the Ru 'Red' solution [9].

All the above procedures generated yellow precipitates that were filtered off, washed twice with EtOH, and dried overnight *in vacuo* at 70 ºC. ^{1}H NMR (CD_2Cl_2, 300 MHz) (paramagnetic): δ 3.9 (bs,

CH_2), 7.4 (bm, Ph groups). Anal. Calc. for $C_{42}H_{42}Cl_6O_6S_6Ru_2 \cdot H_2O$: C, 39.78; H, 3.50. Anal. Found (for syntheses using $RuCl_3 \cdot 3H_2O$ and $K_3[RuCl_6]$) C, 39.74 - 39.81; H, 3.64 - 3.81%. Anal. Calc. for $C_{42}H_{42}Cl_6O_6S_6Ru_2 \cdot 2H_2O$: C, 39.22; H, 3.61. Anal. Found (for syntheses using Ru 'Blue' and 'Red' solutions) C, 39.09 - 39.22; H, 3.49 - 3.56 %. IR ν_{so}: 1070, 1082, 1105, 1116. Mass spectrum [LSIMS, m/z, matrix: thioglycerol]: 1142 [M^+ - 3Cl], 972 [M^+ - BPhSE]. Λ_M (CH_2Cl_2): 0.6.

2.7. X-ray crystallography

The data for the six structures were collected on a Rigaku AFC7/ADSC CCD diffractometer with graphite monochromated Mo-Kα radiation. All crystals were mounted on glass fibers with oil, and data were collected at -93 °C. Data for complex **3** were collected to a maximum 2θ of 64.3°, whereas data for **5**, **8**, and **12** were all collected to a maximum of 60.1°; for **7** and **9**, the maximum was 59.9 and 61.1°, respectively. The structures were solved using Intrinsic Phasing [10] and refined using Shelxl-2018 [11]. Complex **12** crystallizes with two crystallographically independent molecules, with five CH_2Cl_2 and four H_2O molecules in the asymmetric unit of which two CH_2Cl_2 and one H_2O molecule are disordered and thus modeled in two orientations; **8** crystallizes with one EtOH and one H_2O molecule in the asymmetric unit; the EtOH is disordered and was modeled in two orientations; **5** has one disordered butyl group that was modeled in two orientations, in addition to one disordered EtOH solvent; **7** crystallizes with two disordered cyclohexyl groups, each modeled in two orientations. Additionally, there was residual electron density from solvent molecules that could not be modeled, and as a result the PLATON/SQUEEZE program was used to generate a solvent-free data set. Complex **9** crystallizes with two half-molecules and one H_2O molecule in the asymmetric unit. All none H-atoms were refined anisotropically, and the H-atom positions were calculated geometrically and refined using a riding model.

3. Results and discussion

3.1. The disulfoxides

Ten new disulfoxides (Table 1) were synthesized by oxidation of the corresponding dithioethers using literature methods. The dialkylsulfoxides were synthesized by an acid catalyzed, DMSO oxidation [13], whereas the diarylsulfoxides were synthesized by H_2O_2 oxidation [14]. The disulfoxides are characterized by EA, IR and ^{1}H NMR spectroscopies, and melting points (Section 2.2, and Table 2).

Other methods for oxidizing sulfides to sulfoxides are known [15].

The new disulfoxides were synthesized as mixtures of diastereomers (the *RR*/*SS* pair, and the *meso* *RS/SR*) but, as reported, use of several recrystallizations can yield one diastereomer [5,16], and separation of the BPhSE enantiomers has been achieved by column chromatography on lactose [17]. A report has stated that the sole product obtained from the DMSO oxidation is the higher melting isomer, which has been identified as the racemic mixture of the *RR* and *SS* forms [18]. However, X-ray analyses

Table 2. Melting points and ν_{SO} (cm^{-1}) for disulfoxides.

Compound	M. p. (ºC)	Ref.[a]	ν_{SO} (cm^{-1}) [ref]
BMSE(*RS*)	158-162[b] and 165-166[c]; 163-164;[c] 169-170;[c] 174-175[d]	36;14;13;16	1018 [3,13][e]
BMSE(*rac*)	117-119[b] and 118-120[f]; 128-130;[c] 132-133[d]	36;14;16	1018 [3,13][e]
BESE	142-145;[g] 149-149.5;[c] 148-149; 150[h]	18;13;tw;14	1019 [13]; 1015 (3,tw)
BPSE	161-162.5;[i] 162-164	13; tw	1012 (13); 1010 (tw)
BBSE	172-173	tw	1014
BPeSE	134-135	tw	1014,1073,1100
BCySE	172-174	tw	1018
BHSE	176.5-177.5	tw	1016,1114
BPhSE(*RS*)	166-167[j,k]	19; 5	1033 [5]
BPhSE(*SS*)	120-122;[j]122-123[k]	19; 5	1037 [5]
BPhSE	165-170	tw	1035,1089
BMSP	117-118[l]	13	1050 [3]
BESP	127-130	tw	1016,1047
BPSP	140-143	tw	1021,1075
BBSP	146-148	tw	1021
BPeSP	125-129	tw	1026
BPhSP	137-140	tw	1021,1040,1084

[a]tw, this work. The superscripts [b-d] and [g-l] indicate the recrystallization solvents that were used in each case. [b]EtOH/ethyl acetate. [c]EtOH. [d]Acetone/ethyl acetate. [e]The value 1018 cm^{-1} is quoted for a crude product (M. p. 125-164 ° C). [f]Recrystallized from the mother liquor using ethyl acetate and toluene. [g]Benzene. [h]Ethyl acetate. [i]Benzene/hexane 3:2. [j]Chloroform and petroleum ether. [k]$CHCl_3$/light petroleum and ethanol. [l]THF.

of $RS(O)(CH_2)_2S(O)R$ [R = Me (BMSE) [16] and ^{n}Pr (BPSE) and phenyl (BPhSE) [5] suggest that generally the higher melting isomer is that of the *meso* form (*vs.* the *rac* form) (Table 2) [19].

Our attempts to crystallize the disulfoxides were unsuccessful; attempts included variation of solvent combinations, temperatures, and sublimation methods. For example, some "crystals" of BPSP were found not to be single crystals of X-ray quality, as found by others [20]. Svinning *et al*. [16] have noted that crystals of the lower melting isomer (*rac*-BMSE) were "clusters of interpenetrating needles that were easily shattered or deformed".

An attempt to synthesize 1,2-bis(ethylsulfinyl)methane (BESM) following the procedure given in Section 2.2.1, but using BETM (9 mL, 79 mmol), DMSO (10.44 mL, 158 mmol) and conc. HCl(200 uL), was unsuccessful. An isolated, white powder product was purified by sublimation under vacuum at 80 ^{o}C, but was insoluble in most common solvents and only slightly soluble in DMSO. Elemental analyses, NMR and mass spectrometry data were inconclusive.

3.2. The disulfoxide complexes

3.2.1. General comments

Our group initially used *cis*-$RuCl_2(DMSO)_4$ and *cis*-$RuCl_2(TMSO)_4$ as precursors for synthesis of biologically active $RuCl_2(sulfoxide)_2(nitroimidazole)_2$ complexes [21], and, in order to reduce the number of possible isomers in such complexes, disulfoxides were subsequently used. This first led us to report in 1997 syntheses of the fully characterized complexes (i.e. with X-ray structures) *cis*-$RuCl_2(BMSP)_2$, *trans*-$RuCl_2(BMSE)_2$ (complex **1**), *cis*-$RuCl_2(BESE)_2$ (**2**), and *trans*-$RuCl_2(BPSE)_2$; the Ru-blue solution formed by H_2-reduction of $RuCl_3 \cdot 3H_2O$ in MeOH was used as the Ru-precursor [3]. In this current paper, five cis and two trans complexes of the type $RuCl_2(disulfoxide)_2$ (**2** to **8)** are isolated using other Ru precursors. Of interest, the earlier synthesis of **2** gave a 55% yield [3], about 20% higher than using $K_3[RuCl_6]$ as precursor (Section 2.3.2); **2** has also been synthesized using as precursors $RuCl_3 \cdot 3H_2O$, the Ru-red solution, and *trans*- or *cis*-$RuCl_2(DMSO)_4$, yields being about 70, 50, and 35 %, respectively [22]. Coincidentally, the same yield of 47% was found for *trans*-$RuCl_2(BPSE)_2$ (**4**), using either the Ru-blue solution or c*is*-$RuCl_2(DMSO)_4$.

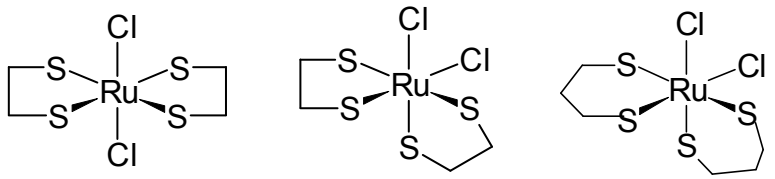
Obvious is that reaction products depend on the ratio of disulfoxide: Ru; e.g., a 2:1 ratio with BBSE forms a mononuclear bis(disulfoxide) complex (**5**), whereas with a 1:1 ratio the product is **11**, a dinuclear, bridged chloro species. Unique is the 2:1 ratio with BPhSE that forms the bridged disulfoxide

complex **13**; this could result from a steric factor, although the related BCySE at the 2:1 ratio gives **7**, the mononuclear bis(disulfoxide) complex.

All the $RuCl_2$(disulfoxide)$_2$ complexes contain only S-bonded disulfoxides as seen by IR data (Table S1). The disulfoxide ligands in the four earlier published structures have opposite chiralities at the two chiral S-atoms [3], whereas the trans complexes are centrosymmetric, with mutually trans S-atoms having opposite configurations, and are non-chiral. The two cis-complexes have C_2 symmetry with the pair of mutually trans S-atoms having the same chirality. The cis-complexes are chiral, but in both cases the crystal structures showed that the samples contain an equal number of the two enantiomers [3]. There is special interest in these complexes, because the *trans* Ru-disulfoxide species accumulate in cells and bind to DNA to a greater extent than the *cis*-species, leading to greater *in vitro* biological activity [3].

Both *cis*- and *trans*-$RuCl_2(DMSO)_4$ were tried as precursors in sulfoxide-exchange reactions; however, reaction of *trans*-$RuCl_2(DMSO)_4$ (or $RuCl_3{\cdot}3H_2O$) with BESE gave *cis*-$RuCl_2(BESE)_2$ (**2**) (Section 2.3.2), and reaction of *cis*-$RuCl_2(DMSO)_4$ with BPSE gave *trans*-$RuCl_2(BPSE)_2$ (**4**) (Section 2.3.4). Attempts to use photolysis to affect the isomerization of *cis*-$RuCl_2(BESE)_2$ to *trans*-$RuCl_2(BESE)_2$, as reported by Alessio *et al.* for the isomerization of *cis*-$RuCl_2(DMSO)_4$ to *trans*-$RuCl_2(DMSO)_4$ [23], were unsuccessful. Of interest, the fully characterized, water-soluble complex $[RuCl(BESE)(H_2O)]_2(\mu\text{-}Cl)_2$ (**9**) (Section 2.4.1) with two equivalents of BESE did generate *trans*-$RuCl_2(BESE)_2$ (**3**). In attempts to synthesize mixed disulfoxide complexes, **9** was also reacted with BESP; however, *cis*-$RuCl_2(BESE)_2$ was obtained by recrystallization of the reaction product from aqueous solution. An electrospray mass spectrum of **9** in aqueous solution showed peaks at 709 [M^+- Cl], 690 [M^+- Cl - H_2O], and 672 [M^+- 2Cl], showing that the dimer does not dissociate to monomer.

The Calligaris group carried out a molecular mechanics investigation of three of our complexes, and concluded that complexes **1**, **2** and **4** correspond to the lowest strain diastereomers [24]. Figure 1 shows basic S-bonded structures of the cis- and trans-complexes. Further, the minimum energy structure for a *cis*-isomer, e.g**. 2**, is the diastereomer containing *meso*-BESE ligands, and this requires *trans* S-atoms with the same *R* or *S* chirality. The lowest energy for **1** and **4** is with mutually *trans* S-atoms of opposite chirality. Analogous diastereomers have been observed in the crystal structures of both *trans*-$RuCl_2(BMSE)_2$ and *trans*-$RuCl_2(BPSE)_2$ [3,24].



1, **4** **2** **8**

Figure 1. Basic structures, not showing the alkyl groups or the O-atoms attached to the S-atoms: e.g. *trans*-$RuCl_2(BMSE)_2$ (**1**), *cis*-$RuCl_2(BESE)_2$ (**2**), *trans*-$RuCl_2(BPSE)_2$ (**4**), and *cis*-$RuCl_2(BESP)_2$ (**8**); S^S = chelating disulfoxide.

The S-bonded disulfoxides are confirmed by crystallography data for all the complexes **3**-**8**, except **6**. In contrast to the water-soluble, bridged chloro-complexes **9**-**12** (Sections 2.4, 2.5), no conductivity was observed for complexes **3**-**8** in chlorinated solvents. As well as three Ru_2^{II} chelating disulfoxide complexes (**9**-**11**), with $[RuCl(BESE)(H_2O)]_2(\mu\text{-}Cl)_2$ (**9**) being structurally characterized, a Ru^{II}/Ru^{III}, mixed-valence complex $[RuCl(BPSP)]_2(\mu\text{-}Cl)_3$ (**12**) was isolated (Section 2.5.1). Again, all these complexes contain only S-bonded sulfoxides.

Reactions of BPhSE, BHSE, B^{i}PSP, BBSP, BPeSP, BPhSP and BMSB with $RuCl_3{\cdot}3H_2O$, using the Section 2.3.5 procedure, gave yellow, uncharacterized products that in column chromatography showed several bands or, in the case of BMSB, the isolated product was insoluble in common solvents. Elemental analyses for products obtained from the major chromatography bands, and the BMSB product, were variable from repeat reactions.

Of note, an attempt to oxidize 1,3-bis(phenylthio)propane (BPhTE) to BPhSP using air/DMSO oxidation led to an oily product, which by TLC, ^{1}H NMR spectroscopy and ν_{SO} data, appeared to be the disulfoxide. However, reaction of this oil with $RuCl_3{\cdot}3H_2O$, using the procedure described in Section 2.3.5, led to the isolation of red crystals that were submitted for X-ray analysis. The structural diagram (Figure S1) revealed *cis*-$RuCl_2$(BPhSP)(1-phenylthio-3-(phenylsulfinyl)propane), i.e. one coordinated disulfoxide and one 'half-oxidized' dithioether! Large thermal motion prevented an accurate determination of the structure; however, *cis* geometry was established. The oxidation of dithioethers using just one-half of the required oxidant could more generally lead to a novel series of such thioether/sulfoxi Ru complexes.

Of interest, the *in situ* reduction of both the $RuCl_3 \cdot 3H_2O$ and the Ru(III) precursor $[RuCl_6]^{3-}$ to Ru(II) products is possibly due to the disulfoxide acting as a reductant that is oxidized to the corresponding sulfone; this might account for the relatively low yields in syntheses using either the 2:1 or 1:1 disulfoxide:Ru ratios. Higher yields might result by using increased sulfoxide concentration. The redox process is mentioned in Section 3.2.3 and has been discussed previously [1].

*3.2.2. $RuCl_2$(disulfoxide)$_2$ complexes **3** to **8***

The ^{1}H NMR spectrum (in D_2O) of free BESE consists of multiplets at δ 3.30 (CH_2CH_2), 2.92 (CH_3CH_2), and a triplet at 1.23 (CH_3), which in *trans*-$RuCl_2$(BESE)$_2$ (**3**) are shifted downfield to a coalesced peak at δ 3.70 (for the CH_2 protons) and a multiplet at δ 1.45 (CH_3); the spectrum does not change over 3 weeks, and is consistent with the *trans* crystal structure. Complex **3** crystallizes in a centrosymmetric space group (Figure 2), with slightly distorted octahedral geometry at the Ru with *trans* angles of 180.0 º and *cis* angles that range from 85.43(4)-90.87(3) º (Table 3); the structural data are similar to those of *trans*-$RuCl_2$(BMSE)$_2$ (**1**) and *trans*-$RuCl_2$(BPSE)$_2$ (**4**) [3]. Indeed, the key bond lengths and angles are very similar in all the Ru^{II}-disulfoxide complexes : e.g., the S-O bond lengths for complexes **2**-**5**, **7** and **8**, and even for the dinuclear $[RuCl(BESE)(H_2O)]_2(\mu\text{-}Cl)_2$ (**9**), average about 1.48 Å with little change (± 0.04 Å) (see Tables 3, S2). Table 4 shows the relative configurations of the S-atoms seen in the $RuCl_2$(disulfoxide)$_2$ structures.

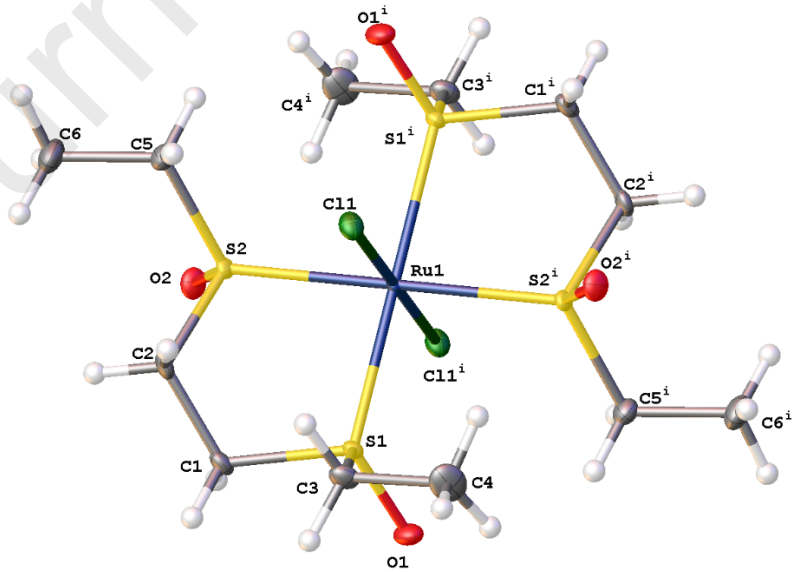


Figure 2. An ORTEP drawing of *trans*-$RuCl_2(BESE)_2$ (**3**) with 50 % probability thermal ellipsoids shown.

An attempted, new synthesis of *trans*-$RuCl_2(BPSE)_2$ from *cis*-$RuCl_2(DMSO)_4$ was essentially successful, but the product, complex **4**, contained an H_2O solvate. The NMR data in CD_2Cl_2 agreed with the published data for the non-solvated complex [3].

Table 3. Selected Bond Lengths (Å) and Bond Angles (º) for $[RuCl(BESE)(H_2O)]_2(\mu\text{-}Cl)_2\cdot H_2O$, *trans*-$RuCl_2(BESE)_2$ and *cis*-$RuCl_2(BESE)_2$.

Bond or Angle	$[RuCl(BESE)(H_2O)]_2(\mu\text{-}Cl)_2\cdot H_2O$	*Trans*-$RuCl_2(BESE)_2$	*Cis*-$RuCl_2(BESE)_2$[a]
Ru-Cl[b]	2.4087(10);[c] 2.4636(10)[d]		
Ru-Cl[e]	2.3994(11)[c]	2.4022(8)	2.4217(8)-2.4486(8)[d]
Ru-S	2.1985(9);[c] 2.1961(13)[f]	2.3209(9), 2.3288(9)	2.2712(8)-2.2738(8);[c] 2.2973(8)-2.3076(8)[d]
Ru-O	2.138(2)[d]		
S-O	1.477(2), 1.489(2)	1.478(12)-1.479(2)	1.470(2)-1.479(2)
C-S	1.805(4)-1.795(3)	1.794(3)-1.809(3)	1.796(3)-1.814(3)
cis angles	82.14(4)-95.01(4)	85.43(4)-90.87(3)	87.19(3)-92.08(3)
trans angles	171.75(3)-177.88(7)	180.0	176.92(3)-178.54(3)
Ru-Cl-Ru	96.89(4), 97.86(4)		
C-S-C	99.33(17)-103.1(17)	99.18(15)-101.33(15)	100.0(1)-102.8(1)
O-S-C	104.49(18)-107.45(14)	106.62(14)-108.15(15)	106.3(1)-109.3(1)
Ru-S-O	118.39(10)-120.53(13)	119.42(9)-119.42(10)	116.28(8)-120.43(8)
S-C-C[g]	106.3(2)-109.5(2)	106.72(19)-110.7(2)	106.5(2)-111.0(2)
S-C-C[h]	111.6(2)-113.7(3)	111.1(2)-112.4(2)	111.3(2)-112.0(2)
Ru-S-C[g]	105.32(12)-107.14(13)	103.47(11)-104.83(11)	103.0(1)-104.8(1)
Ru-S-C[h]	115.22 (13)	115.70(11)-116.75(11)	113.4(1)-117.3(1)

[a] Data taken from ref. 3. [b] Bridging. [c] *Trans* to Cl. [d] Of coordinated H_2O, trans to S. [e]Terminal. [f] Trans to O. [g] Backbone. [h] End substituents.

Table 4. The Relative Configurations of the S-atoms in Chelating Disulfoxide Complexes of Ru; S(4) and S(3) are taken as *trans* to S(2) and S(1), respectively.

Complex	S(1)	S(2)	S(3)	S(4)

trans-$RuCl_2(BMSE)_2$[a]	R	S	S	R
cis-$RuCl_2(BESE)_2$[a,b]	R[c]	S[d]	R[c]	S[d]
trans-$RuCl_2(BESE)_2$[b]	S	R	R	S
trans-$RuCl_2(BPSE)_2$[a,b]	S	R	R	S
cis-$RuCl_2(BBSE)_2 \cdot EtOH$[b]	R[c]	R[d]	S[c]	R[d]
cis-$RuCl_2(BCySE)_2$[b]	R[c]	S[d]	R[c]	S[d]
cis-$RuCl_2(BMSP)_2$[a,b]	R[c]	S[d]	R[c]	S[d]
cis-$RuCl_2(BESP)_2 \cdot EtOH \cdot H_2O$[b]	S[c]	R[d]	S[c]	R[d]
$[RuCl(BESE)(H_2O)]_2(\mu\text{-}Cl)_2 \cdot H_2O$[b]	S[c]	R[e]		
$[RuCl(BPSP)]_2(\mu\text{-}Cl)_3 \cdot 2H_2O \cdot 2.5CH_2Cl_2$[b]	S[c]	R[c]	R[c]	S[c]

[a] Data taken from ref. 3 [b] Unit cell contains both isomers. [c] *Trans* to Cl. [d] *Trans* to S. [e] *Trans* to O.

Cis-$RuCl_2(BBSE)_2$ (**5**, Figure 3) was synthesized in 21% yield from $RuCl_3 \cdot 3H_2O$. The ^1H NMR shifts are downfield of those of free BBSE that was not detected in the spectrum. The crystal structure revealed an EtOH solvate; selected bond lengths and bond angles (Table 5) are comparable to those of *cis*-$RuCl_2(BCySE)_2$ (Table 5), *cis*-$RuCl_2(BESE)_2$ (Table 3), and *cis*-$RuCl_2(BESP)_2$ and *cis*-$RuCl_2(BMSP)_2$ (Table S2, and ref. 3). Of note, opposite chiralities of the S(3) and S(4) atoms are found on one BBSE, and the same chiralities of S(1) and S(2) atoms on the other BBSE; this is the only complex with S(1) and S(2) having the same chirality (Table 4). The synthesis of **5** seemed plausible by use of a mixture of *meso*- and *rac-BBSE*, but the sharp melting point (**Error! Reference source not found.**) implies only one diastereomer of the ligand was present. The solvated complex is chiral with approximately C_2 symmetry, but the crystal structure is centrosymmetric and contains an equal number of the two enantiomers. Figure 3 shows the Δ isomer in which both *trans* S-atoms have *R* configuration. The unit cell shows the EtOH is H-bonded to both an O-atom and a Cl-atom; the H--O and the H--Cl distances are 2.12 and 2.71 Å, respectively, which are 0.58 and 0.19 Å shorter than the sum of the van der Waals radii of an O- and H-atom, and a Cl- and an H-atom, respectively [25], implying relatively strong interactions.

Cis-$RuCl_2(BPeSE)_2$ (**6**) required purification by column chromatography, and was obtained in only 9 % yield. The ^1H NMR shifts of BPeSE are again seen downfield upon coordination. The CH_3 signals were seen as a multiplet (presumably 2 overlapping triplets), compared, for example, to two triplet signals observed for *cis*-$RuCl_2(BESE)_2$ (see below). The X-ray analysis prevented an accurate structure due to excessive thermal motion the pentyl side-chains, but the *cis* geometry was established.

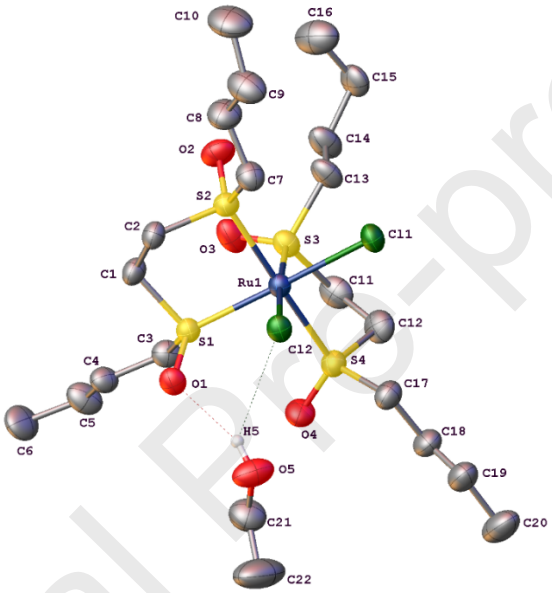


Figure 3. An ORTEP drawing of *cis*-$RuCl_2(BBSE)_2$·EtOH (**5**) with 50 % probability thermal ellipsoids shown; H-atoms (except for that of EtOH) are omitted for clarity.

The ^{1}H NMR spectrum of *cis*-$RuCl_2(BCySE)_2$ (**7)** is complicated because of the inequivalence of the cyclohexyl rings oriented in the cis geometry. The complex is chiral, has approximate C_2 symmetry with the pair of mutually *trans* S-atoms having the same S-chirality, and crystallizes in a centrosymmetric space group that contains equal numbers of the two enantiomers; Figure 6 depicts the Λ isomer in which the *trans* S-atoms both have *S* configuration. The molecule has a slightly distorted octahedral geometry at the Ru with *trans* angles ranging from 176.38(5) to 178.01(5) º and *cis* angles from 86.27(5) to 96.50(5) º (Table 5). Bond lengths and angles are comparable to those of *cis*-$RuCl_2(BBSE)_2$·EtOH (Table 5and *cis*-$RuCl_2(BESE)_2$ (Table 3). Each disulfoxide has opposite chiralities at the two chiral S-atoms (Table 4).

As with complex **6,** column purification was needed to give a 36% yield of *cis*-$RuCl_2(BESP)_2$ (**8**) Again, downfield ^1H NMR shifts of BESP are generally seen on its coordination, although the δ 2.45 multiplet of the free ligand becomes two multiplets at δ 2.75 and 2.10. The key bond lengths and angles (Table 6) are close to those of *cis*-$RuCl_2(BMSP)_2$ [3] and the other *cis*-$RuCl_2(disulfoxide)_2$ complexes. The complex crystallizes in a centrosymmetric space group and contains equal numbers of the two isomers; Figure 4 depicts the Δ isomer in which the *trans* S-atoms both have the *R*-configuration; the unit cell contains a water molecule H-bonded to an O-atom of a disulfoxide and to the EtOH solvate (Figure 5). The average H--O distance is 1.89 Å, which is 0.81 Å shorter than the sum of the van der Waals radii of an H- and an O-atom (2.70 Å), implying strong H-bond interactions between the water molecule, and the complex and the EtOH [25].

Table 5. Selected Bond Lengths (Å) and Bond Angles (º) of *cis*-$RuCl_2(BBSE)_2$·EtOH and *cis*-$RuCl_2(BCySE)_2$.

Bond or Angle	*cis*-$RuCl_2(BBSE)_2$·EtOH	*cis*-$RuCl_2(BCySE)_2$
Ru-Cl	2.4101(11), 2.4294(9)[a]	2.4217(9), 2.4398(9)[a]
Ru-S	2.3059(11), 2.3059(11);[a] 2.2658(10), 2.2918(10)[b]	2.3428(9), 2.3500(9);[a] 2.3008(9), 2.3008(19)[b]
S-O	1.479(3), 1.482(3);[a] 1.468(3), 1.481(3)[b]	1.451(3), 1.462(3);[a] 1.483(2), 1.489(3)[b]
C-S	1.795(4)-1.833(5)	1.797(3)-1.856(5)
cis angles	85.59(4)-96.21(4)	86.13(3)-96.78(3)
trans angles	172.98(3)-177.39(3)	176.34(13)-178.05(3)
Ru-S-O	116.97(11)-118.96(13)	117.6(11)-119.69(13)
O-S-C	105.41(18)-109.1(2)	106.73(15)-108.5()
C-S-C	101.6(2)-102.9(2)	98.93(17)-104.83(17)
S-C-C[c]	107.2(3)-112.6(3)	107.2(3)-110.2(2)
S-C-C[d]	111.3(3)-113.9(3)	106.0(2)-113.8(5)
Ru-S-C[c]	102.77(17)-104.59(15)	101.75(12)-104.44(12)
Ru-S-C[d]	114.16(14)-119.88(14)	115.64(2)-118.37(11)

[a] *Trans* to S. [b] *Trans* to Cl. [c] Bonds involving backbone carbons. [d] The C-atom of an alkyl substituent.

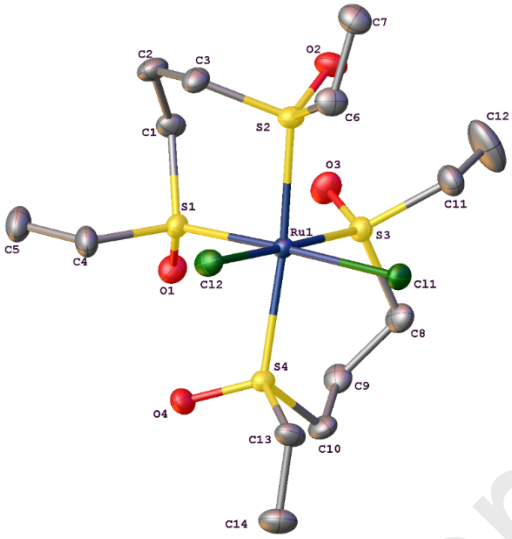


Figure 4. An ORTEP drawing of *cis*-$RuCl_2(BESP)_2 \cdot EtOH \cdot H_2O$ with 50 % probability thermal ellipsoids shown; H-atoms are omitted for clarity.

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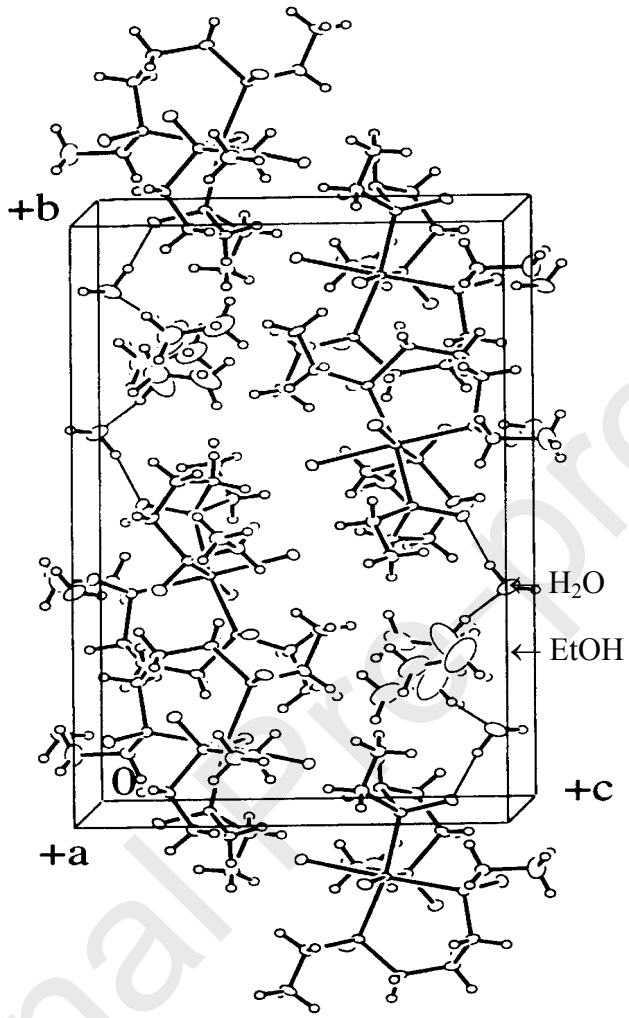

Figure 5. The unit cell of *cis*-$RuCl_2(BESP)_2 \cdot EtOH \cdot H_2O$ (**8**) showing the EtOH and H_2O solvate molecules.

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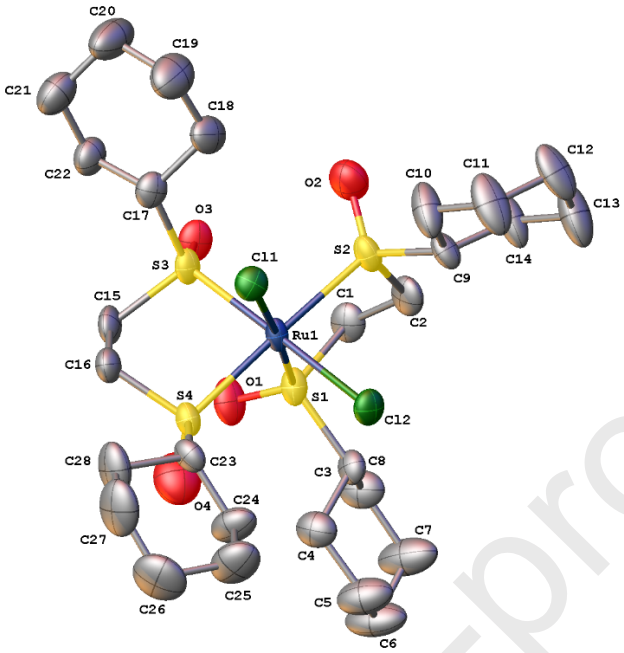

Figure 6. An ORTEP drawing of *cis*-$RuCl_2(BCySE)_2$ (**7**) with 50 % probability thermal ellipsoids shown; H-atoms are omitted for clarity.

Table 6. Selected Bond Lengths (Å) and Bond Angles (º) of *cis*-$RuCl_2(BESP)_2 \cdot EtOH \cdot H_2O$ and *cis*-$RuCl_2(BMSP)_2$.

Bond or Angle	*cis*-$RuCl_2(BESP)_2 \cdot EtOH \cdot H_2O$	*cis*-$RuCl_2(BMSP)_2$[a]
Ru-Cl	2.4211(10), 2.4299(11)[b]	2.4354(7), 2.4395(7)[b]
Ru-S	2.3307(11), 2.3549(10);[b] 2.2751(10), 2.2892(11)[c]	2.3518(7), 2.3569(7);[b] 2.2682(6), 2.2710(6)[c]
S-O	1.487(3), 1.491(3);[b] 1.477(2), 1.491(3)[c]	1.473(2), 1.480(2);[b] 1.476(2), 1.480(2)[c]
C-S	1.791(4)-1.820(3)	1.773(3)-1.801(3)
cis angles	84.93(4)-97.66(4)	83.42(2)-97.55(2)
trans angles	171.62(4)-175.51(3)	174.21(2)-178.42(2)
Ru-S-O	113.63(12)-118.45(12)	113.91(8)-116.51(9
C-S-O	105.86(17)-107.69(18)	104.9(1)-107.1(1)
C-S-C	98.58(19)-102.1(2)	98.9(2)-100.6(1)
S-C-C[d]	112.3(3)-116.4(3)	114.4(2)-115.6(2)
S-C-C[e]	111.8(3)-113.0(3)	
C-C-C	112.0(3)-117.8(3)	113.1(3), 113.4(2)
Ru-S-C[d]	110.03(12)-115.69(14)	115.3(1)-115.80(9)
Ru-S-C[e]	112.08(13)-115.49(14)	111.2(1)-113.6(1)

[a] Data taken from ref. 3 [b] *Trans* to S. [c] *Trans* to Cl. [d] Bonds involving backbone carbons. [e] The C-atom of an alkyl substituent.

3.2.3. Dinuclear Ru^{II}_2-chelating disulfoxide complexes

The syntheses of *cis*-$RuCl_2(BESE)_2$ involved reaction of two equivalents of BESE with one of a Ru precursor (Section 2.3.2). However, on use of just one equivalent of the disulfoxide with $RuCl_3 \cdot 3H_2O$, the water-soluble, structurally characterized, dinuclear Ru_2^{II} complex $[RuCl(BESE)(H_2O)]_2(\mu\text{-}Cl)_2$ (**9**) (Section 2.4.1) was obtained, and the BPSE and BBSE analogues (**10** and **11**), also water-soluble, were made similarly (Sections 2.4.2, 2.4.3). As noted (Section 3.2.1), and of importance, reaction of **9** with two equivalents of BESE then led to isolation of *trans*-$RuCl_2(BESE)_2$ (**3**) (Section 2.3.3). The disulfoxides in **9-11** are all S-bonded, this being consistent with ^{1}H NMR spectra (in D_2O) that show appropriate downfield shifts from the resonances of the free ligand [27]. A mixed-valence Ru^{II}/Ru^{III} complex $[RuCl(BPSP)]_2(\mu\text{-}Cl)_3$ (**12**) (Section 2.5), and a Ru_2^{III} complex $[RuCl_3(BPhSE)]_2(\mu\text{-}BPhSE)$ (**13**) (Section 2.6) were also isolated, and these complexes also contained only S-bonded sulfoxides.

The "equilibrium" conductivities for **9-11** in water (~ 10^{-4} M, Λ_M 358, 282 and 497, respectively), correspond to those of a 2:1-3:1, 2:1 and 3:1 electrolyte, respectively, when compared to those of salts [26]. Addition of aq. NaOH to **9** showed that two protons/molecule are titrated (Table S3). Further, the measured equivalent conductance of 10^{-3} M HCl, ~ 430 (*cf.* literature value of ~ 420 at 25 °C [28] was reduced to ~ 350 on addition of 10^{-3} M aq. solution of *cis*-$RuCl_2(BESE)_2$ whose molar conductance is ~ 33.9 [3]). The conductivity data are consistent with loss of 2 equiv. of both H^+ and Cl^- per molecule of **9**, and thus the the^{1}H NMR data (in D_2O) presumably refer to such a species. Addition of 2 equivalents of $AgNO_3$ to a solution of **9** formed an immediate precipitate of AgCl, but the ^{1}H NMR spectrum of the filtrate was the same as that of the spectrum of **9**; addition of a further equivalent of $AgNO_3$ to the filtrate gave no precipitate, and the ^{1}H NMR was unchanged. Of note, the C-analyses of **10** and **11** differ from the calculated values by ~0.4, somewhat outside acceptable values; reactivity with moisture is the most likely reason for this.

The structure of **9** is shown in Figure 7, and selected bond lengths and angles are given in Table 3, with those of *cis*- and *trans*-$RuCl_2(BESE)_2$. The asymmetric unit consists of two independent half-molecules and a water molecule (Figure 8), the H(33)--O(4) and H(34)--Cl(2) distances, 1.81 and 2.28 Å, respectively, indicating strong H-bond interactions. The *cis* and *trans*-angles at the Ru are from 82.14 to 95.01° and 171.75 to 177.88°, respectively. The Ru-Cl-Ru bridging angles are 96.89 and 97.86°,

the Ru-atoms being further apart than the 70.53° of an ideal cofacial bioctahedron [29]; no Ru-Ru interaction was detected out to 3.90 Å. The usual range for a Ru-Ru bond with bridging ligands is typically ~ 2.28 to 3.04 Å [30].

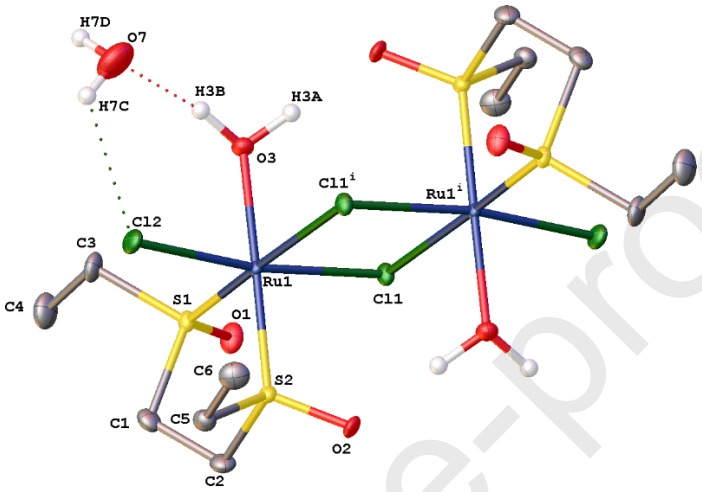

Figure 7. An ORTEP drawing of $[RuCl(BESE)(H_2O)]_2(\mu\text{-}Cl)_2$ (**9**) showing the H_2O solvate.

The BPSE and BBSE complexes presumably have the corresponding dinuclear, dichloro-bridged structures. All three, water-soluble, complexes (**9-11**) were tested *in vitro* for cytotoxicity, accumulation and DNA-binding properties in Chinese hamster ovary cells; findings with these and other Ru-disulfoxide species [4] will be reported elsewhere.

From the general synthetic procedure for the $RuCl_2(disulfoxide)_2$ complexes (Section 2.3.5.), but using BPSP, a 15 % yield of the unexpected dinuclear, water-soluble, mixed-valence complex $[RuCl(BPSP)]_2(\mu\text{-}Cl)_3$ (**12**) was obtained. The structure of a crystal, obtained from a saturated solution of CH_2Cl_2 (Figure 8) confirms the S-bonded disulfoxides, also evident from the ν_{SO} data (Table S1), and also reveals $2H_2O$ and $2CH_2Cl_2$ solvates per molecule. The complex crystallizes in an acentric space group containing a glide plane and thus the crystal structure contains enantiomeric pairs. Figure 8 depicts one of the enantiomers, whereas Figure 9 shows the four H-bonded H_2O molecules that 'connect' the two asymmetric units. The chiralities at the S-atoms on each of the BPSP ligands are *R* and *S*, respectively (Table 4). Selected bond lengths and angles for the two asymmetric units are given in Tables 7 and 8, respectively; the two Ru-atoms are indistinguishable, consistent with a delocalized

Ru^{II}/Ru^{III} system. The bond lengths are in fact comparable to those found in $[RuCl(BESE)(H_2O)]_2(\mu\text{-}Cl)_2$ showing the H_2O solvate., for e.g., Ru-Cl is 2.466-2.482 Å (bridging, *trans* to S) and Ru-S is 2.198-2.225 Å (Table 7). In more detail, the geometry about each Ru is irregular octahedral with *cis* angles of 79.36-97.51º and *trans* angles of 168.64-174.64º (Table 8). The μ-Cl trans to terminal chlorides has a shorter Ru-Cl distance 2.386-2.408 Å) than the μ-Cl ligands trans to sulfur (2.466-2.482. (Table 7). This implies a weaker *trans* influence of the chloro ligands that produces a wider Ru-Cl(1)-Ru angle (84.62 and 85.02º) compared to the other two Ru-Cl-Ru (81.24-82.60º). The range of the bridging angles and the Ru-Ru distance (3.230 and 3.232 Å) is outside those observed for a Ru-Ru bonded system [29].

The distances between the water H-atom and the disulfoxide O-atoms distances are 1.61-1.76 Å; these

are much shorter than the sum of the van der Waals radii of the atoms (2.70 Å) [25], showing strong H-bonds interaction between the two asymmetric units. The same approach for degree of H-bonding of the CH_2Cl_2 to the O-atoms reveals very weak interactions (2.77-2.93 compared to 2.90 Å) [25]. Of interest, a

reported structure has shown parallel layers of $[Cu(BPSP)_2(ClO_4)]_n^{n+}$ cations that are intercalated by $n[ClO_4]^-$ anions with the O-atom of the BPSP acting as a bridging link between the Cu atoms [31].

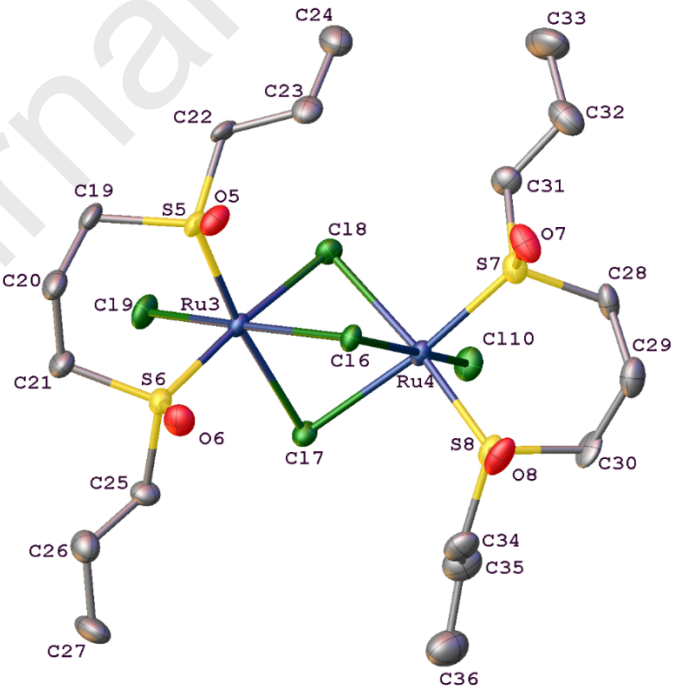

Figure 8. An ORTEP drawing of one unit of $[RuCl(BPSP)]_2(\mu\text{-}Cl)_3$ (**12**) with 50 % probability thermal ellipsoids shown; H-atoms are omitted for clarity.

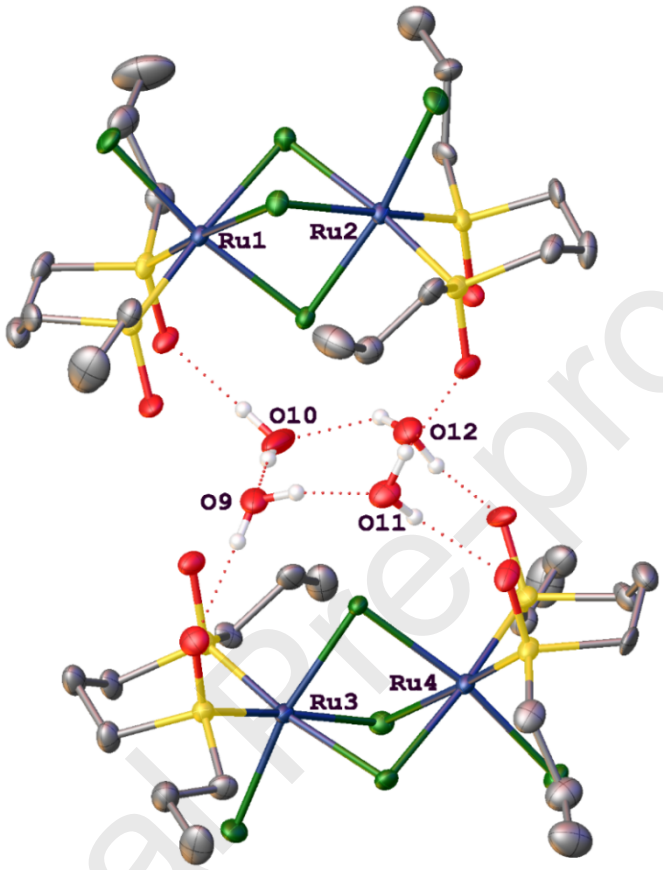

Figure 9. A diagram of $[RuCl(BPSP)]_2(\mu\text{-}Cl)_3$ (**12**) showing short H-bonds connecting two asymmetric units via 4 H_2O molecules (the CH_2Cl_2 atoms are not shown).

The broad ^1H NMR shifts, seen for **12** in D_2O, with the exception of the Me multiplet at 0.90, are again downfield of the free ligand shifts. The ^1H spectrum in $CDCl_3$ consists of two broad peaks at δ 2.18 and 1.10 are consistent with delocalized Ru^{II}/Ru^{III} centres. The solution μ_{eff} value in $CDCl_3$,1.7 ± 0.1 B.M. is consistent with one unpaired electron per dimer molecule. The crystallographic and ^1H NMR data suggest that complex **12** is best formulated as a valence-delocalized class III system [32].

The complex exhibited no conductivity in $CHCl_3$, but Λ_M in H_2O (per mole of dimer) increased to a steady value of 234 at 20 min, the value of a 2:1 electrolyte (see Section 3.2.3); the chemical behaviour in aqueous solution has been studied further [4], and details will be published together those of the other water-soluble complexes **9-11** [33].

The low synthetic yield of **12** likely results from redox chemistry, this being indicated by a distinctive dithioether odour detected during the workup of the synthesis. This could be formed by oxidation of Ru^{II} (formed by EtOH reduction of $RuCl_3 \cdot 3H_2O$) that could then be re-oxidized to Ru^{III} by the disulfoxide that would be reduced to the dithioether [1].

Table 7. Selected Bond Lengths for the Two Asymmetric Units of $[RuCl(BPSP)]_2(\mu\text{-}Cl)_3$

Bond	Length (Å)
Ru-Cl[a]	2.386(2)-2.408(2);[b] 2.466(2)-2.482(2)[c]
Ru-Cl[d]	2.381(2)-2.391(15)
Ru-S	2.198(2)-2.225(3)
S-O	1.475(7)-1.497(7)
C-S	1.790(10)-1.811(10)

[a] Bridging. [b] *Trans* to Cl. [c] *Trans* to S. [d] Terminal.

Table 8. Selected Bond Angles for the Two Asymmetric Units of $[RuCl(BPSP)]_2(\mu\text{-}Cl)_3$.

Bond angle	Angle (º)	Angle	Angle (º)
cis angles	79.36(8)-97.51(8)	Ru-S-O	117.4(3)-119.8(3)
trans angles	168.64(9)-174.64(9)	S-C-C[a]	109.5(7)-113.3(8)
Ru-Cl-Ru	81.24(7)-82.60(7)[c] 84.62(7) and 85.02(7)[d]	S-C-C[b]	110.9(7)-117.3(7)
C-S-C	99.7(5)-101.6(5)	Ru-S-C[a]	111.2(3)-112.3(4)
O-S-C	102.2(5)-106.8(5)	Ru-S-C[b]	111.0(3)-115.0(3)

[a] Backbone. [b] End substituents. [c] *Trans* to sulfur. [d] *Trans* to chloride.

3.2.4 A Dinuclear Ru^{III}_2 complex with a chelated and a bridging disulfoxide

The compound $[RuCl_3(BPhSE)]_2(\mu\text{–}BPhSE)$ was isolated with one or two H_2O solvate molecules, complexes **13a** and **13b**, respectively, depending on the Ru precursor: $RuCl_3 \cdot 3H_2O$ and $K_3[RuCl_6]$ formed **13a**, whereas the blue and red Ru solutions gave **13b**. The ^{1}H-NMR data show paramagnetic species, and repeat elemental analyses support the formulation with one or two water molecules. The IR stretches 1070, 1082, 1105, and 1116 cm^{-1} reveal S-bound sulfoxide when compared with the values for free BPhSE (1035, 1089 cm^{-1}), and no bands are seen in the region of O-bound sulfoxide. The mass spectrum shows peaks at 1142 [M^+-3 Cl], and 972 [M^+-BPhSE]. The complexes were non-conducting

in CH_2Cl_2 (0.6 $\Omega^{-1}cm^2mol^{-1}$) [26]; dissolving them in DMSO immediately formed *trans*-$RuCl_2(DMSO)_4$ as shown by ^{1}H-NMR data. There is no direct evidence for the bridging disulfoxide, but the formulation shown is the most obvious. Such complexes with bridging *S*-disulfoxide or *O*-disulfoxide complexes are known, e.g. with Pt [34] and Cu [31], respectively, and we have reported on $[RuCl_2(p\text{-cymene})]_2(\mu$-*S*-disulfoxide) species with BESE, BESP, and $[RuCl(p\text{-cymene})(BESE)]PF_6$ [35] but, to the best of our knowledge, **13a/b** are the first Ru(III) complexes with a bridging disulfoxide.

4. Conclusions

The oxidations of recently reported dithioethers $RS(CH_2)_nSR$, where n = 2 or 3 and R is an alkyl or aryl chain [1], to the corresponding disulfoxides $R\text{-}S(O)\text{-}CH_2)_n\text{-}(O)S\text{-}R$ were successful. Their reactions with various Ru precursors provided a surprisingly wide range of S-bonded sulfinyl complexes of the types *cis* and *trans*-$Ru^{II}Cl_2(disulfoxide)_2$, $[Ru^{II}Cl_2(disulfoxide)(H_2O)]_2(\mu\text{-}Cl)_2$, and $[Ru_2^{II/III}Cl(disulfoxide)]_2(\mu\text{-}Cl)_3$ that were well characterized, including X-ray data. A further Ru_2^{III} complex, probably $RuCl_3(BPhSE)]_2(\mu$-BPhSE) with the bridging disulfoxide 1,2 bis(phenylsulfinyl)ethane, was also synthesized. Some of the complexes, especially the water-soluble species, have potential for biological properties, such as cell accumulation and toxicity, and DNA binding [3]. The key synthetic work in our recent paper [1] and in this current paper is now complete, and biological findings on the new disulfoxide species are now being organized for publication.

Acknowledgements

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Appendix A. Supplementary data

Supplementary material contains Table S1-S3, and Fig. S1. Full experimental parameters and details of the structures are given in CIF format in the Supplementary Information; CCDC numbers 1946430-1946435 contain the supplementary crystallographic data for complexes **3**, **12, 8, 5 7** and **9**, respectively; these data can be obtained free of charge from The Cambridge Crystallographic Data Centre via

http://www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online at https://……..

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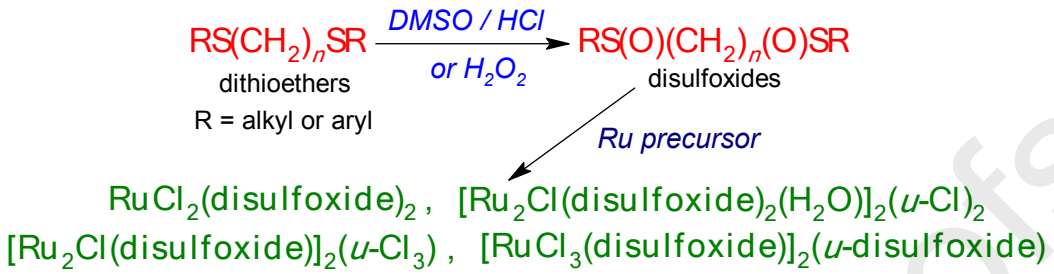

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