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Stereoselective Oxidation of Sulfides in the Presence of Chiral Peroxovanadium Complexes

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Abstract—Oxo- and diperoxovanadium complexes with chiral ligands—*L*-proline and Schiff bases—have been synthesized. In the presence of these complexes, prochiral alkyl aryl sulfides have been stereoselectively oxidized to optically active sulfoxides with the enantiomeric excess up to 85%.

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Optically active sulfoxides are an important class of compounds widely used in asymmetric synthesis. The most popular method of synthesis of optically active sulfoxides is enantioselective oxidation of readily available prochiral sulfides [1].

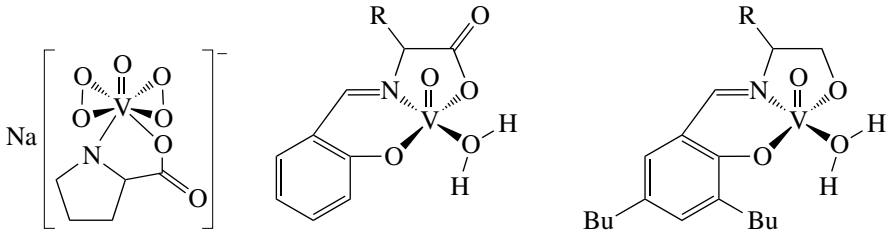
Transition metal (including vanadium) peroxo complexes with sterically hindered tridentate ligands, optically active Schiff bases, are promising oxidants for stereoselective transformation of sulfides into sulfoxides [2, 3]. Such oxidative systems oxidize prochiral sulfides to chiral sulfoxides with high stereoselectivity, the oxidation efficiency depending on the structure of the ligand and initial Schiff base [1, 4].

In the present work, the following chiral complexes were used for stereoselective oxidation of sulfides: diperxovanadium complex with *L*-proline **1** and oxovanadium complexes with optically active Schiff bases **2**–**5** (Scheme 1).

The ligands for complexes **2** and **3** were obtained in situ and were not isolated separately [5]. The ligands for complexes **4** and **5** were preliminarily synthesized.

Peroxovanadium complex **1** was synthesized as described in [6]. Upon the reaction, yellow-orange crystals were precipitated from the solution. These crystals are stable in the solid state at low temperature (below 0°C) for several hours; soluble in methylene chloride, acetone, ethyl acetate, and other solvents of medium polarity; and poorly soluble in water. According to elemental analysis, complex **1** contains five water molecules; i.e., it is a pentahydrate.

In the IR spectrum of complex **1**, the strongest bands correspond to crystal water vibrations (3450–3200 cm^{-1}) and to the stretching vibrations of the oxodiperoxovanadium moiety (968 cm^{-1} (V=O), 879 and 858 cm^{-1} (O–O)). It is worth noting that these band maxima coincide with the literature data [7] within 4 cm^{-1}. The ligand vibrations in **1** give rise, first of all, to the band at 1766 cm^{-1} (its position is virtually the same as in the spectrum of crystalline proline) and to a number of weak bands in the range 950–1200 cm^{-1}. The positions and intensities of most bands in the IR spectrum of **1**, especially in the range 1700–1300 cm^{-1}, are virtually the same as in the spectra of the ligand. The spectrum of **1** shows the pattern typical of seven-coordinate diperoxo complexes: a broad band at 575 cm^{-1} and a medium band at 625 cm^{-1} correspond-



1 **2** R = CH_3, **3** R = CH_2Ph **4** R = *i*-Pr, **5** R = CH_2Ph

Scheme 1.

Table 1. ^{51}V NMR chemical shifts of complexes **2–5**

Complex	**2**	**3**	**4**	**5**
δ (ppm)*	–554.446 (I) –569.124 (II)	–553.621 (I) –572.253 (II)	–536.915 (I) –554.789 (II)	–547.023 (I) –560.107 (II)

* From $VOCl_3$.

ing, respectively, to the symmetric and asymmetric vibrations of the $V–O_{peroxo}$ moiety.

The ^{51}V NMR spectrum of complex **1** in the organic phase (CH_2Cl_2) is represented by a singlet at –642.345 ppm typical of oxodiperoxovanadium complexes. The vanadium signal of complex **1** is shifted downfield from the signals of peroxovanadium complexes with pyridine ligands [8], which confirms our previous conclusion concerning the existence of a correlation between the chemical shift and the electron-donating properties of ligands.

Oxovanadium complexes **2** and **3** were synthesized as described in [5] by the reaction of vanadyl sulfate $VOSO_4$ with salicylaldehyde and α-amino acids *L*-alanine (**2**) and *L*-phenylalanine (**3**). The ligand in complexes **2** and **3** is a dibasic tridentate Schiff base.

Vanadium complexes **4** and **5** were synthesized by the reaction of vanadyl acetylacetonate $VO(acac)_2$ with optically active ligands **10** and **11** as described in [9, 10]. In each case, the reaction yielded dark green viscous precipitates insoluble in water, acetone, and benzene and soluble in methanol, chloroform, and methylene chloride.

In the IR spectra of complexes **2–5**, the strongest bands correspond to the crystal water vibrations (3450–3200 cm^{-1}), as well as to the V=O stretching vibrations (980, 975, 970, and 975 cm^{-1}, respectively). The band at 1625 cm^{-1} is due to the CH=N stretching vibrations of the ligand.

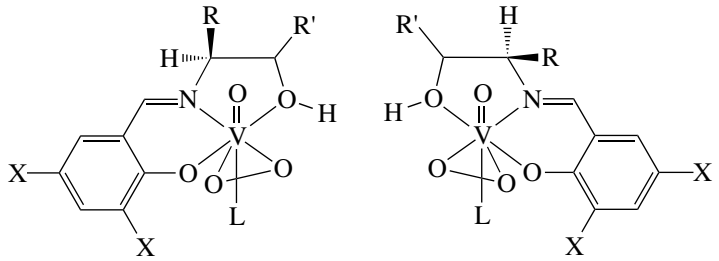
Previously [11], we studied the structure of complex **2**—[2-(*N*-salicylidene)aminopropionato]oxovanadium monohydrate $C_{10}H_9N_1O_5V_1$—by X-ray crystallography.

The ^{51}V NMR spectra of complexes **2–5** show two signals in the range from –530 to –575 ppm corresponding to oxovanadium complexes. The chemical shifts of vanadium atoms in oxo complexes **2–5**, as in oxo diperoxo complexes, are determined by the electron-donating properties of the ligands in the coordination sphere: the stronger the electron-donating properties of the ligand, the larger the electron shielding and, correspondingly, the larger the downfield shift of the signals (Table 1).

The presence of two signals in the spectra of complexes **2–5** can be evidence of the existence of two diastereomeric *endo* and *exo* forms of each of these complexes (Scheme 2).

The catalytic activity of the resulting chiral complexes in the asymmetric oxidation of prochiral sulfides was studied for ethyl phenyl sulfide (**11**) and phenyl benzyl sulfide (**12**). The results of oxidation experiments are presented in Table 2 (Scheme 3).

The oxidation of ethyl phenyl sulfide and phenyl benzyl sulfide by hydrogen peroxide under asymmetric catalysis conditions in the presence of vanadium complexes yields ethyl phenyl sulfoxide and phenyl benzyl sulfoxide as major products. Formation of sulfone mixtures was observed in none of the cases. The chemical yields of the sulfoxides are rather high (Table 2). The optical rotation, absolute configuration, and enantiomeric excess of sulfoxides were calculated from the absolute angles of rotation of known enantiopure sulfoxides. For some sulfoxides, the enantiomeric excess data were confirmed by high-performance liquid chro-



endo-I *exo*-II

2: X = H, R' = O, R = CH_3; **3**: X = H, R' = O, R = CH_2Ph;
4: X = *t*-Bu, R' = H, R = $CH(CH_3)_2$; **5**: X = *t*-Bu, R' = H, R = CH_2Ph

Scheme 2.

Table 2. Asymmetric oxidation of prochiral sulfides **11** and **12**

Sulfide	Catalyst	Sulfoxide yield, %	ee*, %	$[\alpha]_D^{25}$, deg	Concentration, mol/L, $CHCl_3$
Ethyl phenyl sulfide **11**	1	96	27**	–98.4	0.13
	2	98	75	–273.2	0.13
	3	97	78	–280.3	0.10
	4	95	65	–235.9	0.13
	5	95	59**	–214.8	0.13
Phenyl benzyl sulfide **12**	1	98	29**	–30.2	0.50
	2	97	85**	–88.5	0.50
	3	98	83**	–86.4	0.50
	4	92	70**	–72.9	0.50
	5	98	67**	–69.8	0.50

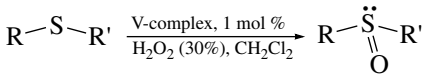
Notes: * The enantiomeric excess (ee) was calculated using the on optical rotation of enantiopure sulfoxides **13** and **14** [12–15].
** Confirmed by HPLC.

matography (HPLC) on a chiral sorbent, silica gel with grafted (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine. Previously, this sorbent was found to be efficient for chromatographic separation of racemic sulfoxides [16].

The oxidation of sulfides by vanadium complexes **1**–**5** with ligands in the (*S*) configuration yields, in each case, corresponding (*S*)-sulfoxides. The highest enantioselectivity of sulfoxides was observed when complexes **2** and **3** were used, and the lowest enantioselectivity was observed for complex **1** with proline as the ligand. This is due to the fact that this complex is an oxo diperoxo complex, in which, as in other such complexes, the nucleophilic attack of the sulfide occurs at a peroxide oxygen. In this case, proline does not protect the peroxide oxygen atoms so that they can be attacked on several sides. This factor is responsible for the low enantioselectivity of the resulting sulfoxides (Scheme 4).

In the case of monoperoxo complexes with tridentate ligands, the number of vacant sites for insertion of the substrate into the complex is sharply limited as compared with the diperoxo complex. The enantioselectivity of the process thereby increases, and, due to increasing steric hindrances, the yield of sulfoxide is higher when the ligand has a *tert*-butyl group (Scheme 5).

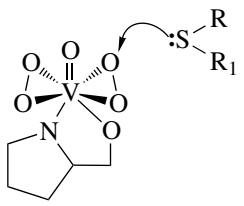
Thus, peroxovanadium and oxovanadium complexes exhibit specific properties that make it possible to use them for regio- and stereoselective oxidation of organic sulfides in aqueous and organic media.



11, **12** (*S*)-**13**, (*S*)-**14**

11, **13**: R = Ph, R' = Et; **12**, **14**: R = Ph, R' = CH_2Ph

Scheme 3.



Scheme 4.

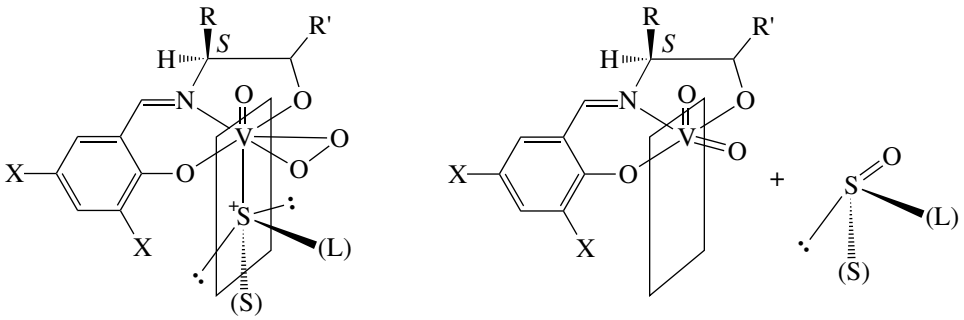
EXPERIMENTAL

Electron impact mass spectra (70 eV) were recorded on a Finnigan MAT 112S mass spectrometer. Gas chromatography/mass spectrometry analysis was performed on a Hewlett-Packard 5972MSD instrument in the chromatographic mode, with the temperature being programmed in the range 110–290°C at a rate of 10 K/min (helium as the carrier gas; ionization energy, 70 eV).

The ^{51}V NMR spectra (52.6 MHz) were recorded on a Tesla Bruker AC-200 radiospectrometer (single-pulse excitation; excitation pulse width, 4 μs; repetition time, 1 s; number of scans, 460). $VOCl_3$ ($\delta = 0$ ppm) was used as the external reference, and $CHCl_3$ was the solvent.

The IR spectra were recorded as thin films and CH_2Cl_2 and $CHCl_3$ solutions on a Specord M80 spectrophotometer in the range 400–4000 cm^{-1} with the resolution 2.5–4.0 cm^{-1}.

HPLC analysis was carried out on a liquid chromatopraph consisting of a Beckman Model 114M high-pressure pump, a Rheodyne Model 712S injector with a loop, and a Carlo Erba Micro UV-Vis 20 detector. Separation was carried out on a Pirkle DNBPG chro-



X = H or *t*-Bu; R = Alk; R' = H or O;
(S) is a small substituent, and (L) is a large substituent

Scheme 5.

matographic column, 250 × 4.6 mm, packed with SiO_2 (5 μm) with covalently grafted (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine. The mobile phase was a CH_2Cl_2–hexane mixture (1 : 1). Chromatographic peaks were detected at 254 nm.

The course of the reaction and the purity of the products were monitored by TLC on Silufol UV-254 plates. Depending on the qualitative composition of the reaction mixture, eluent mixtures of different polarity were used. Specific rotations were measured on a Rudolf Research polarimeter (σ = 0.0001°). Elemental analysis was carried out on a Carlo Erba microanalyzer.

Synthesis of Vanadium Complexes

Peroxovanadium complex 1, containing *L*-proline as the ligand, was obtained as described in [6]. Ten millimoles of $NaVO_3 \cdot 2H_2O$ was dissolved in 20 mL of water, the solution was cooled to 5°C, and 0.1 mol of 50% H_2O_2 was added.The resulting solution was stirred for 2 min. Then, 15 mmol of *L*-proline dissolved in a small amount of water was added. The solution was stirred for 15 min and simultaneously cooled to 0°C. At this temperature, the solution was left for crystallization. The resulting yellow-orange crystals were separated from the supernatant by decantation.

For $C_5H_{17}NNaO_{12}V$ anal. calcd. (%): C, 16.82; H, 4.80; N, 3.92.

Found (%): C, 16.86; H, 4.65; N, 3.90,

IR (ν, cm^{-1}): 1766, 968, 879, 858, 625, 575. ^{51}V NMR (δ, ppm): –642.345.

Oxovanadium complexes **2** and **3** were synthesized as described in [5]. The ligands were the Schiff bases obtained in situ by the reaction of salicylaldehyde with α-amino acid (*L*-alanine, *L*-phenylalanine). The yield of **2** and **3** was ~80% (with respect to $VOSO_4 \cdot 2H_2O$, mp 250°C (from MeOH).

Complex 2. IR (ν, cm^{-1}): 3500, 1625, 980. ^{51}V NMR (δ, ppm): –554.446, –569.124.

Complex 3. IR (ν, cm^{-1}): 3500, 1625, 975, 972. ^{51}V NMR (δ, ppm): –553.621, –572.253.

Complexes 4 and 5 with Schiff bases 9 and 10 as the ligands. Ligands **9** and **10** were synthesized by the reaction of 3,5-di-*tert*-butylsalicylaldehyde with (*S*)-2-amino alcohols obtained from the corresponding α-amino acids.

3,5-Di-tert-butylsalicylaldehyde (6) was obtained as described in [17]. Aldehyde **6** was purified from impurities and 5-*tert*-butylsalicylaldehyde traces by column chromatography on SiO_2. A CH_2Cl_2–hexane mixture (1 : 1) was used as the eluent. Yield, 62%; mp 53–56°C (from MeOH) (lit.: mp 53–56°C [17]). MS, *m*/*z* (I_{rel}, %): 234(22), 219(100), 163(10), 135(8), 57(30), 41(14).

(*S*)-(+)-2-Amino-3-methyl-1-butanol (*L*-valinol) (7) and (2*S*)-2-amino-3-phenylpropanol (*L*-phenylalaninol) (8) were obtained by reducing *L*-valine and *L*-phenylalanine by $LiAlH_4$. Alcohol **7**: yield, 80%; mp 55–56°C. Alcohol **8**: yield, 80%; mp 89–90°C (from PrOH) (lit.: mp 91–92°C [18]).

(*S*)-2-(*N*-3,5-Di-tert-butylsalicylidene)amino-3-methyl-1-butanol (9) and (*S*)-2-(*N*-3,5-di-tert-butylsalicylidene)amino-3-phenyl-1-propanol (10) were synthesized as described in [10]. The yield of **9** and **10** was ~80%, and their ^1H and ^{13}C NMR spectra were identical to those reported in [9, 10].

Complexes 4 and 5 with 9 and 10 as the ligands. To a solution of 0.05 mmol of $[VO(acac)_2]$ in 10 mL of CH_2Cl_2, 0.075 mmol of the corresponding ligands was added. The resulting solution was kept for 3 h at 0°C. The resulting dark green viscous precipitate was filtered off, washed with distilled water, 50% EtOH, and ether, and dried in a vacuum desiccator at 40°C. Complex **4**: yield, 81%. IR (ν, cm^{-1}): 3450–3200, 1625, 970. ^{51}V NMR (δ, ppm): –536.915, –554.789. Complex **5**: yield, 78%. IR (ν, cm^{-1}): 3450–3200, 1625, 975. ^{51}V NMR (δ, ppm): –547.023, –560.107.

Asymmetric Oxidation of Prochiral Sulfides

The oxidant was a 30% aqueous H_2O_2. The concentration of H_2O_2 was monitored by titration with potassium permanganate [19]. Prior to the experiments, the initial phenyl benzyl sulfide was additionally purified by vacuum distillation. Ethyl phenyl sulfide was synthesized according to [20]. Oxidation of the sulfides was carried out by the following schemes.

A. Oxidation by oxodiperoxovanadium complex 1. A reaction mixture containing 10 mmol of the sulfide dissolved in 10 mL of CH_2Cl_2, 31 mmol of 30% H_2O_2, 0.03 mmol of $NaVO_3 \cdot 2H_2O$, 0.02 mmol of $Bu_4N^+Br^-$ in 20 mL of CH_2Cl_2, and 0.06 mmol of the ligand (*L*-proline) dissolved in a small amount of water was stirred for 4 h at 30°C in a thermostated reactor in an argon atmosphere. The aqueous layer was extracted with ether (2×20 mL), and the combined organic layers were washed with water and dried by $MgSO_4$. The solvent was removed, and the organic phase (to remove excess water) was applied to a filter column with SiO_2 and eluted with an acetone–hexane mixture (4 : 1).

B. Oxidation by peroxovanadium complexes (2, 3/H_2O_2) [9]. To 10 mmol of the sulfide dissolved in 10 mL of CH_2Cl_2, 0.03 mmol of complex **2** or **3** dissolved in a small amount of CH_2Cl_2 was added. To this solution, 31 mmol of 30% H_2O_2 was carefully added under stirring (12 h, 30°C). Further treatment was as described above (A).

C. Oxidation by peroxovanadium complexes (4, 5/H_2O_2). To 4.2 mmol of the corresponding sulfide, a solution of 0.042 mmol of $VO(acac)_2$ and 0.06 mmol of the Schiff base with 2-aminoalcohol **9** or **10** in 10 mL of CH_2Cl_2 was added. The resulting solution was thermostated at 1°C, and 4.7 mmol of 30% H_2O_2 was carefully added. The reaction mixture was heated to 30°C over 1 h and stirred at this temperature for another 12 h. Further treatment was as described above (A). The structure of the resulting sulfoxides (ethyl phenyl sulfoxide and phenyl benzyl sulfoxide) was confirmed by comparison the IR, ^1H NMR, and mass spectral data with the literature data [8, 12, 15]. The yields, absolute configurations, and enantiomeric excesses determined for these sulfoxides are presented in Table 2.

ACKNOWLEDGMENTS

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