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Journal of Molecular Catalysis A: Chemical 157 (2000) 91–95

JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL

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Effect of portionwise addition of oxidant in asymmetric vanadium-catalyzed sulfide oxidation

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Received 25 July 1999; received in revised form 15 December 1999; accepted 24 December 1999

Abstract

Portionwise addition of hydrogen peroxide markedly augments enantioselectivity of sulfide to sulfoxide oxidation catalyzed by vanadium (IV)-Shiff base complexes, and this effect cannot be explained by temperature fluctuations. ^{51}V NMR spectra of reaction mixture detect two chiral peroxo complexes and one achiral diperoxo compound.

Keywords: V(IV)-complexes; Chiral Shiff bases; Sulfides; Sulfoxides; Asymmetric oxidation

1. Introduction

While synthesizing physiologically active sulfur-containing compounds [1], we faced a task of choosing an appropriate method for preparation of chiral sulfoxides. After the most effective systems were tried with model compounds [2,3], we chose the asymmetrical oxidation of sulfides by hydrogen peroxide in the presence of vanadium (IV) complexes with chiral Shiff bases [4–6]. An exceptionally simple experimental procedure, which is characteristic of the method under discussion, allows excellent results to be obtained in some cases [5]. Nevertheless, this reaction needed optimization in order to enhance the enantioselectivity for oxidation of polyfunctional sulfides, and we had to pay attention to the remark by Bolm and Bienewald [4] concerning the procedural details. They state that the single-step addition of all the necessary amount of hydrogen peroxide results in elevation of the temperature of the reaction medium and makes the process going towards formation of sulfones. The authors added hydrogen peroxide dropwise, at a non-specified rate though, to avoid this undesirable temperature effect. The following questions arise at this point.

Is short-time temperature jump only responsible for a decrease in the enantioselectivity of the oxidation of sulfides to sulfoxides?

Is it possible that the concentration of the

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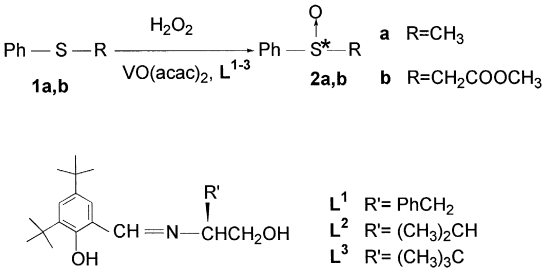
1381-1169/00/$ - see front matter
PII: S1381-1169(00)00037-6

oxidant and, hence, the rate of addition of it, influence the reaction enantioselectivity?

Notice that earlier works dealt with asymmetric oxidation of sulfides in the presence of vanadium complexes; the enantioselectivity was improved by modifying the structure of the chiral ligands [4,6]. As to the reaction under consideration, we tried for the first time to improve the enantioselectivity by varying the rate of the oxidant feeding. Below is the presumed pathway of oxidation of sulfides 1a,b into chiral sulfoxides **2a,b** catalyzed by vanadium (see Scheme 1).

2. Experimental

^{51}V NMR spectra were recorded at 105.24 MHz using a Bruker MSL-400 spectrometer with cylindrical 5 mm tubes. The operating conditions were the following: 50 000 Hz sweep width, 90° radio-frequency pulse, 13 μs duration; $VOCl_3$ was used as the external reference. The errors in measuring ^{51}V chemical shifts were ± 1 ppm for a line width below 500 Hz. ^1H and ^{13}C NMR spectra were obtained with a Bruker AC-200 spectrometer and recorded in $CDCl_3$ and IR spectra were recorded in KBr with a Specord M-80 instrument. Optical rotations were measured with a JASCO model DIP-360 polarimeter. Enantiomeric excesses (e.e.) were calculated using known optical rotation values of enantiomerically pure sulfoxides **2a,b** [3,7]. (*S*)-2-aminoalcohols were obtained from corresponding commercially avialable amino-acids as described in Ref. [8].



Scheme 1.

2.1. Synthesis of Shiff bases

Equivalent amounts of (*S*)-2-aminoalcohol and 3,5-di-*tert*-butylsalicylic aldehyde were dissolved in an appropriate volume of $CHCl_3$ and stand over anhydrous Na_2SO_4 until the complete disappearance of aminoalcohol was evidenced by TLC (approx. 1 day). Short column purification and drying in high vacuo gave the pure products as the yellow amorphous solids or syrups.

2.1.1. (S)-2-(N-3,5-di-tert-Butylsalicylidene)-amino-3-phenyl-1-propanol (L¹)

Yield 78%. NMR spectra, δ_H: 1.31 s [9H, $C(CH_3)_3$], 1.47 s [9H, $C(CH_3)_3$], 2.94 m (2H, CH_2Ph), 3.52 m (1H, N—CH), 3.75 m (2H, CH_2OH), 7.02 d (1H), 7.21 m (3H), 7.27 m (2H), 7.41 d (1H), 9.19 s (1H,CH═N); δ_C: 29.30 and 31.32 [6C, $C(CH_3)_3$], 34.96 (CH_2Ph), 39.00 and 45.75 [2C, $C(CH_3)_3$], 65.62 (CH_2OH), 73.06 (CH—N), 117.50, 126.02, 126.23, 126.99, 129.30, 129.50, 136.46, 137.90, 137.97, 157.98 (C—OH), 166.94 (CH═N). IR $\nu_{C=N}$: 1625 cm^{-1}. Found: C, 78.22; H, 9.13; N, 3.71. $C_{24}H_{33}NO_2$ requires C, 78.43; H, 9.05; N, 3.81.

2.1.2. (S)-2-(N-3,5-di-tert-Butylsalicylidene)-amino-3-methyl-1-butanol (L²)

Yield 81%, m.p. 106–108°C (from hexane). NMR spectra, δ_H: 0.94 d and 0.98 d [6H, $(CH_3)_2CH$], 1.34 s [9H, $C(CH_3)_3$], 1.46 s [9H, $C(CH_3)_3$], 1.93 m [1H, $(CH_3)_2CH$], 3.04 m (1H, CH—N), 3.77 m (2H, CH_2OH), 7.14 d (1H), 7.42 d (1H), 8.38 s (1H, CH═N); δ_C: 18.61 and 19.70 [2C, $(CH_3)_2CH$], 29.99 [$(CH_3)_2CH$], 29.39 and 31.39 [6C, $C(CH_3)_3$], 34.02 and 34.94 [2C, $C(CH_3)_3$], 64.54 (CH_2OH), 77.71 (CH—N), 117.67, 126.01, 126.97, 136.67, 140.06, 158.08 (C—OH), 166.66 (CH═N). IR $\nu_{C=N}$: 1625 cm^{-1}. Lit. [9] m.p. 107–108°C.

*2.1.3. (S)-2-(N-3,5-di-tert-Butylsalicylidene)-amino-3,3-dimethyl-1-butanol (**L³**)*

Yield 67%. NMR spectra, δ_H: 0.97 s [9H, CHC(CH_3)$_3$, 1.32 s and 1.44 s [18H, C(CH_3)$_3$], 2.91 dd (1H, NCH), 3.72 dd and 3.90 dd (2H, CH_2O), 7.14 d (1H), 7.42 d (1H), 8.38 s (1H, CH═N); δ_C: 27.04 [3C, (CH_3)$_3$CCH], 29.47 and 31.43 [6C, (CH_3)$_3$C], 33.19, 34.08 and 35.01 [3C, (CH_3)$_3$*C*], 62.59 (CH_2O), 81.40 (NCH), 117.78, 126.11, 127.02, 136.80, 140.16, 158.16 (COH), 167.02 (C═N). IR $\nu_{C=N}$: 1625 cm^{-1}. Found: C, 75.49; H, 10.63; N, 4.21. $C_{21}H_{35}NO_2$ requires C, 75.62; H, 10.57; N, 4.20.

2.2. Oxidation of sulfides

2.2.1. Fast addition of oxidant (method A)

Sulfide **1** (4.26 mmol) was added to a magnetically stirred (120 rpm) solution of vanadyl acethylacetonate (11 mg, 0.042 mmol) and Shiff base (**L¹**–**L³**) (0.064 mmol) in 10 ml of methylene chloride. Resulting solution was thermostated at 1°C and 4.7 mmol of 30% hydrogene peroxide were introduced at once (the temperature rose to no more than 1–2°C at that moment). Temperature was elevated to 20°C within 1 h and stirring was continued for another 15 h. Resulting sulfoxides **2** were purified as described in Ref. [4].

2.2.2. Stepwise addition of oxidant (method B)

The same proportions of reagents were used, and hydrogene peroxide was added as 15 equal portions in 15-min intervals to the solution of sulfide **1** and vanadium catalyst stirred at 20°C. Stirring was continued for another 12 h, and then sulfoxides **2** were purified.

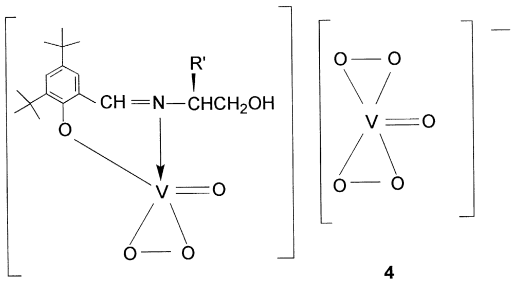
3. Results and discussion

The data on oxidation of thioanisol **1a** and methyl phenylthioacetate **1b** are shown in the Table 1. Even if a milder temperature regime is used for method A, remarkably higher chemical and optical yields of sulfoxides **2** are achieved in all the cases at the portionwise addition of hydrogen peroxide by method B. Hypothetically, the observed effect can be attributed to the following reasons. Probably, asymmetric oxidation of sulfides **1a,b** is catalyzed by chiral monoperoxo complexes **3** (Scheme 2). In the presence of some excess of the oxidant, these complexes loose their optically active ligand and are transformed into a vanadium (V) diperoxocompound **4**. The latter oxidizes sulfides to achiral sulfoxides. As a result, the optical yield of the reaction product decreases if the reaction is conducted at fast addition of the whole portion of hydrogen peroxide. At the portionwise addition of the oxidant, formation of undesirable diperoxocompounds becomes less probable, and the optical yield of the target sulfoxides can be remarkably improved (see Table 1).

Undoubtedly, supporting this hypothesis needs elucidation of the true nature of vanadium

Table 1
Asymmetric oxidation of sulfides **1** to sulfoxides **2** (experimental data)

Entry	Ligand	Sulfide (**1**)	Method of H_2O_2 addition	Chemical yield of sulfoxide (**2**), %	e.e., %
1	**L¹**	**a**	A	60	27
2	**L¹**	**a**	B	93	39
3	**L¹**	**b**	A	65	24
4	**L¹**	**b**	B	92	32
5	**L²**	**b**	A	50	29
6	**L²**	**b**	B	90	44
7	**L³**	**a**	A	82	40
8	**L³**	**a**	B	61	47
9	**L³**	**b**	A	75	46
10	**L³**	**b**	B	66	51



Scheme 2.

compounds involved in the oxidation process. This problem has not been as yet resolved [4,6] but the research in the field is in progress. For example, ^{51}V NMR spectrum recorded for the system $V^{IV}O(acac)_2/L_1 = 1{:}1.5$ in CH_2Cl_2 at 20°C exhibits weak signals from unidentified complexes of vanadium (V) existing in a small amount in the solution (Fig. 1A). The treatment of this sample with H_2O_2 gives rise to the appearance of another three complexes of vanadium (V) (**a**–**c**) with ^{51}V NMR signals at −512, −645 and −687 ppm, respectively (Fig. 1B). Complexes **a**–**c** are unstable and their concentrations decrease with time (Fig. 1C). The further treatment of the sample shown in Fig. 1c with hydrogen peroxide restores partially the concentration of complexes **a**–**c**. Besides, the other ^{51}V NMR signals grow, which belong to the products of the catalyst degradation (Fig. 1D).

Complex **c** is diperoxovanadium $[VO(O_2)_2]^-$ (**4**) present in the aqueous phase. Its identity was reliably confirmed by the previous studies [10–12].

The concentration of unstable complexes **a**,**b** increases with the H_2O_2 concentration in the solution (Fig. 1D). Similar behavior is characteristic of peroxovanadium compounds. Formation of complexes **a** and **b** was not observed in the catalytic system $VO(acac)_2 + H_2O_2$ without L_1. In this case only complex **c** was detected. Thus, complexes **a** and **b** comprise L_1 as a ligand (or ligands). ^{51}V NMR chemical shift of complex **a** (−512 ppm) is very close to that (−522 ppm) observed for the solution of well characterized monoperoxo complex $VO(O_2)$-$Pic(H_2O)_2$ (**5**) in CH_3CN, where Pic is picolinic acid [13]. ^{51}V NMR chemical shifts observed for complex **5** in CH_3CN (−522 ppm) and H_2O (−590 ppm) differ markedly. Probably, complex **5** exists in the form of $VO(O_2)$-$Pic(H_2O)CH_3CN$ in CH_3CN and in the form of $VO(O_2)Pic(H_2O)_2$ **5** in water [13]. Based on these data, we suppose that complex **a** is monoperoxo complex $VO(O_2)L_1H_2O \cdot S$, where S is the solvent or vacancy. As for **b**, we have spectroscopic evidence that it could be monoperoxocomplex $[VO(O_2)(L_1)]$ with tridentate mode of L_1 coordination to vanadium, the extra coordination bond formed between V and OH group of the aminoalcohol fragment of L_1. ^{13}C NMR spectroscopic study of complexes **a** and **b** is to be presented in subsequent publication.

According to the literature data, both mono and diperoxocomplexes of vanadium are reactive towards the sulfide [14,15]. The presence of the latter achiral species would decrease the enantioselectivity. It is natural to explain the beneficial effect of the portionwise addition of the oxidant (method B) by a smaller concentration of diperoxo complexes in the solution. In

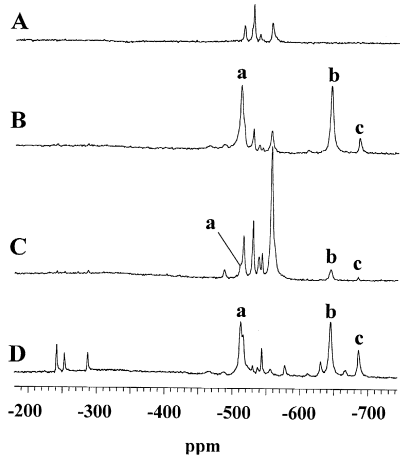


Fig. 1. ^{51}V NMR spectra of the solution of $VO(acac)_2$ (2.5 mg) and L_1 (7 mg) in CH_2Cl_2 (0.6 ml) recorded at various moments of time after treatment with 30% H_2O_2(0.003 ml): before reaction (A), in 3 min (B), in 60 min (C), 3 min after the treatment with an additional portion of H_2O_2 (0.03 ml) (D).

full agreement with this assumption, ^{51}V NMR spectra show that the relative concentration of complex **c** is higher in the case of the fast addition of the oxidant (method A).

Thus, we suggest a new procedure for conducting asymmetric oxidation of sulfides into sulfoxides in the presence of a chiral vanadium catalyst. The procedure is based on the portionwise, long in time, addition of the oxidant. This version of the process seems more convenient to increase the chemo and stereoselectivity than the temperature decrease. Supposedly, this approach can be used in the future to increase the substrate to catalyst ratio at no lower chemical and optical yields of the target products.

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