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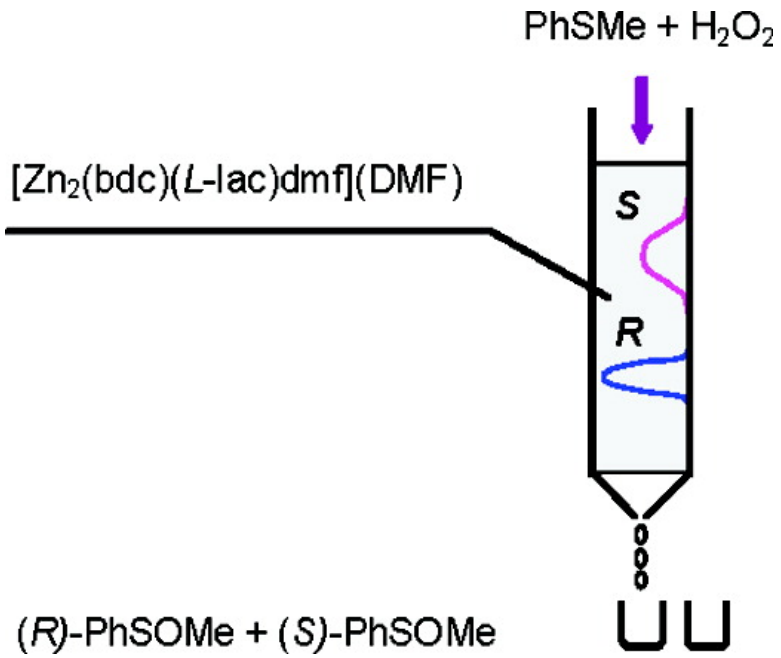
J. Am. Chem. Soc., **2007**, 129 (43), 12958-12959• DOI: 10.1021/ja076276p • Publication Date (Web): 09 October 2007



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Published on Web 10/09/2007

Enantioselective Chromatographic Resolution and One-Pot Synthesis of Enantiomerically Pure Sulfoxides over a Homochiral Zn−Organic Framework

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The growing interest to porous metal-organic frameworks (MOFs), especially with respect to their potential applications (such as sorption and storage[1] as well as catalysis and separation)[2] is apparent in the literature in the past few years. The incorporation of enantiomerically pure homochiral building blocks into microporous materials has been an ambitious goal and creates potential opportunities for separation of enantiomers as well as for chiral synthesis and catalysis. However, examples of enantioselective sorption and/or enantioseparation are still rather rare in the literature,[2a,3] and no preparative chromatographic enantioseparations over enantiopure MOFs have been reported so far. Recently, we published the synthesis of 3D porous Zn-organic framework [Zn_2(bdc)(L-lac)(dmf)]·DMF (**1**)[4a] (where bdc = *p*-benzenedicarboxylic acid, dmf = *N*,*N*′-dimethylformamide), possessing the intrinsic chirality due to the chiral L-lac (= L-lactic acid)[4b] and displaying both catalytic and enantioselective sorption properties. In this study, we present the more detailed quantitative study of the enantioselective sorption properties of **1**, as well as the first example of chiral chromatographic column for the separation of racemic mixtures of chiral alkyl aryl sulfoxides over the enantiopure porous metal−organic framework as the stationary phase. Ultimately, by combining both chromatographic and catalytic properties of **1** we developed a unique one-pot process for the synthesis of enantiomerically pure sulfoxides.

The synthesis of **1** was carried out by a published procedure.[4] The details of sorption constants measurements are described in the Supporting Information. In Table 1, one can see the sorption constants for the (*R*)- and (*S*)-enantiomers of several sulfoxides and the highest measured sorption values. The concentrations of the sulfoxides were 0.1−0.34 M, CH_2Cl_2 being the best solvent (i.e., leading to the highest sorption and ee values).[5] The high stereoselectivity parameter values α of 2.1−4.5 (which in the end relates to the K_S/K_R ratio)[6] suggest an idea of using **1** as a chiral stationary phase for enantioselective liquid chromatography.

For column chromatographic separations, a glass tube with 8 mm inner diameter was charged with a suspension of **1** (14 g) in 10% solution of DMF in CH_2Cl_2 to obtain a 33 cm high column. Each probe contained ca. 0.15 mmol of the sulfoxide in 0.2 cm^3 of CH_2Cl_2. The experimental chromatograms can be seen in Figure 1, one of the sulfoxides (PhSOMe) demonstrating a clear peak resolution that allowed the complete separation of enantiomers.

One can see that additional electron-withdrawing substituents (Br- and NO_2-) in the aromatic ring of the sulfoxides reduced both the sorption constants and ee's of sorption (Table 1, entries 1, 4). Plausibly, it is mainly electronic effects that reduce the coordinating ability of the sorbate. Introduction of an electron-donating substituent (cf. *p*-MePhSOMe and PhSOMe in Table 1) resulted in higher sorption constants but lower stereoselectivity factor (apparently, additional substituent in *p*-MePhSOMe molecule decreases α for steric reasons) that, along with the slower internal diffusion of *p*-MePhSOMe, led to poorer enantioseparation (Figure 1b). Steric effect was also probed by the use of PhSO*i*-Pr which showed the same α as PhSOMe. The enantioseparation was incomplete (Figure 1d), probably owing to the higher diffusion obstacles because of the bulkier *i*-Pr substituent at the sulfur atom. Apparently, it is the methyl phenyl sulfoxide molecule that has the most appropriate size and hence fits the inner pore space of **1** in the best way. As far as we know, although analytical-scale resolutions of chiral sulfoxides on modified polysaccharide-type and other chiral stationary phases are reported,[6b−d] this is the first semipreparative scale chromatographic separation of chiral sulfoxides and the first documented use of metal−organic frameworks as chiral stationary phases for preparative liquid chromatography.

Table 1. The Apparent Sorption Constants of Enantiomerically Pure Sulfoxides on **1**[a]

entry	sulfoxide	K_S M^{-1}	K_R M^{-1}	α[b]	*ee*, %[c] (sorption)
1	*p*-BrPhSOMe	11	10	1.1	7 (0.15)
2	PhSOMe	68	15	4.5	60 (0.30)
3	*p*-MePhSOMe	326	129	2.5	38 (0.53)
4	*p*-NO_2PhSOMe	n.m.	n.m.		∼0 (0.13)
5	PhSO*i*-Pr	54	12	4.5	55 (0.20)

[a] Measured by method B (see Supporting Information) unless otherwise stated. n.m. = not measured (negligible). [b] Stereoselectivity factor, α = K_S/K_R. [c] The highest measured ee's of the sorbate, and the respective sorption values, in molecules per formula unit [Zn_2(bdc)(L-lac)(dmf)].

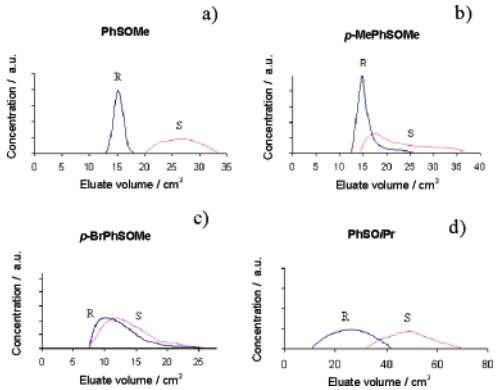

Figure 1. Separation of alkyl aryl sulfoxides using **1** as the chiral stationary phase. Eluents: (a, b) 12 cm^3 of 0.01 M DMF solution in CH_2Cl_2, then 1% DMF in CH_2Cl_2; (c, d) 20 cm^3 of 0.01 M DMF solution in CH_2Cl_2, then 1% DMF in CH_2Cl_2. Elution rate = 2 cm^3/h.

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10.1021/ja076276p CCC: $37.00

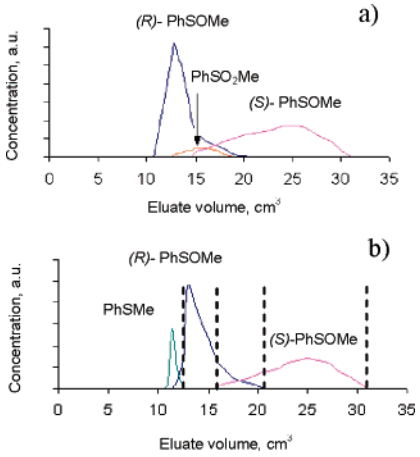

Figure 2. Catalytic oxidation of PhSMe/enantiomeric separation of PhSOMe over a column with **1**·DMF, using 5-fold (a) and 1.5-fold (b) excess of the oxidant. Elution rate = 2 cm^3/h; eluent CH_2Cl_2/CH_3CN = 85:15.

The search for the new applications of porous metal−organic frameworks in catalytic processes is also highly important for this branch of chemistry. Earlier, we announced the highly chemo- and size-selective oxidation of alkyl aryl sulfides by H_2O_2 using **1** as the heterogeneous catalyst[4a] (for more details see the Supporting Information). The oxidation process was nonstereoselective, resulting in racemic mixtures of the corresponding sulfoxides. Now, we present the use of the unique combination of catalytic and adsorption properties of the porous structure **1** for the isolation of both (*R*)- and (*S*)-enantiomers of PhSOMe in a one-pot procedure, starting from the corresponding sulfides. Here, the microporous homochiral Zn−organic coordination polymer **1** acts as both the catalyst and at the same time the chiral stationary phase for column liquid chromatography.

First, we examined the catalytic activity of Zn-containing catalysts toward the oxidation of alkyl aryl sulfides with H_2O_2 in more detail (see Supporting Information). Surprisingly, the simple $Zn(NO_3)_2$ was found to act as an effective catalyst for the alkyl aryl sulfides oxidation by H_2O_2 in polar solvents, featuring the quantitative conversion and up to 100% selectivity in some cases. It is worth noting that because of the obvious nonporous nature of the Zn^{2+} aquacomplex, there is no size limit for the substrate in the homogeneous oxidation process. In turn, the heterogeneous nature of the porous framework **1** leads to very low oxidation conversions for the bulky *p*-NO_2PhSOMe and $PhSCH_2Ph$. It has also been found that the heterogeneous selective oxidation of alkyl aryl sulfides by **1** could be carried out in CH_3CN or CH_2Cl_2/CH_3CN (Supporting Information). The observed selectivity toward the size of the substrate corroborates the robust porous structure of **1** and supports the heterogeneous nature of the catalysis.

The combined oxidation/separation experiments were made on the same column as mentioned above. For the reasons of better enantioselective separation effectiveness, PhSMe was chosen as substrate. The mixture of the sulfide and H_2O_2 in the corresponding organic solvent was loaded directly onto the top of the column, and the products were slowly eluted with CH_2Cl_2/CH_3CN mixture. The resulted chromatograms are shown in the Figure 2. The (*R*)-isomer of PhSOMe comes out first during the elution, followed by a peak of the (*S*)-isomer. Despite some peak overlap, the major part of the sulfoxides could be collected separately as optically pure (*R*)- or (*S*)-enantiomers. The use of 5-fold excess of H_2O_2 results in slight overoxidation of PhSOMe, with preferable formation of the sulfoxide PhSOMe (ca. 5% of the sulfone is formed). The yield of enantiopure (ee = 100%) fraction of (*S*)-PhSOMe was estimated ca. 35% (based on the starting PhSOMe). On the other hand, the 1.5-fold excess of H_2O_2 left some sulfide unreacted (conversion 91%) (Figure 2b). The sulfide does not display any significant sorption in the pores of **1** and thus comes out from the column before the (*R*)-PhSOMe. Hence, in this case, both (*R*)- and (*S*)-sulfoxides could be isolated with relatively high yields (yields of pure enantiomers were ca. 35% each based on the starting PhSOMe, i.e., 70% isolated net yield of pure enantiomers (Figure 2b)). Apparently, using 1.5-fold excess of the oxidant, one could obtain both enantiomers of the chiral sulfoxide PhSOMe in optically and chemically pure form, provided that the column used is long enough.

In conclusion, we present the first successful liquid chromatographic resolution of enantiomers (sulfoxides) using **1** as the chiral stationary phase and the combined selective oxidation of thioethers and enantioselective separation of the resulting sulfoxides in a one-pot process, MOF **1** acting as both the heterogeneous catalyst and the chiral stationary phase.

Acknowledgment. The authors thank the Russian Foundation for Basic Research, Grants 06-03-32214 and RFBR-JSPS 07-03-91208, for financial support.

Supporting Information Available: Experimental procedures for the sorption constant measurements, oxidation, and chromatographic separations procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) The stereoselection is due to the interaction of the sorbate with the inner pore space of **1** rather than the outer surface. This is supported by the facts that (1) coordination to the surface Zn atoms could account for less than 0.01 adsorbed sulfoxide molecules per formula unit and (2) bulkier sulfoxide molecules (e.g., $PhSOCH_2Ph$) cannot enter the pores and hence display zero sorption.

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JA076276P