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Enantioreversal in the Sharpless Asymmetric Epoxidation Reaction Controlled by the Molecular Weight of a Covalently Appended Achiral Polymer

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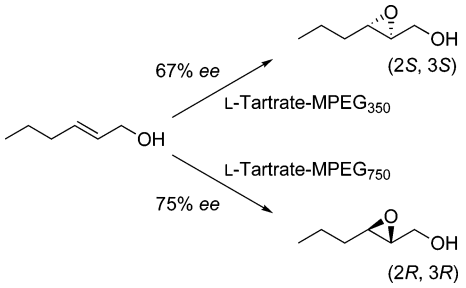

Polymers such as poly(ethylene glycol) (PEG) have proven use in a variety of applications including organic synthesis. We now disclose our investigations into the recently disputed report that PEG tartrate esters can reverse the enantioselectivity of the Sharpless asymmetric epoxidation reaction. The results presented herein have clarified that the enantioselectivity of this reaction can be reproducibly reversed solely as a function of the molecular weight of the appended PEG. By preparing a range of tartrate ligands with varying PEG chains lengths, the reversal was found to occur within a molecular weight change of only 800. As the PEG chain did not affect the inherent chirality of the ligand, the enantioreversal was proposed to occur as a result of two Ti−ligand complexes which differ in their molecularity of ligand, one monomeric in ligand and the other dimeric. Support for this hypothesis was given through equilibrium measurements which revealed that the predominant species in Ti/PEG tartrate ester mixtures is a distinct 2:1 Ti−ligand complex, as opposed to the 2:2 Ti−ligand complex of traditional Sharpless asymmetric epoxidations. In total, these data represent an unrecognized property of PEG-supported catalysts that could open up new venues in the control of asymmetric reactions by means of achiral appended polymers.

Introduction

Poly(ethylene glycol) (PEG) has been extensively studied for synthetic, biological, and industrial applications.[1] In synthetic chemistry, PEG is primarily used as a soluble-polymer support due to the particularly advantageous phase-tagging properties it imparts to the supported compound.[2] While liquid-phase catalysts have been developed that incorporate PEG, it is important to note that the polymer does not appear to play an active role in the catalyst activity or enantioselectivity;[3] rather, the use of PEG in organic synthesis has been traditionally limited to an aid in separation and recovery. To our knowledge, the role PEG plays in affecting catalytically active species has been poorly documented.[4]

Due to our interest in the uses of PEG in organic synthesis we were intrigued to see the report by Guo[5] describing the use of poly(ethylene glycol) monomethyl ether (MPEG) tartrate ester ligands for the Sharpless asymmetric epoxidation.[6] A striking result was noted; the tartrate ester ligand prepared from MPEG 2000 and

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(1) (a) Harris, J. M. *Poly(ethylene glycol) Chemistry. Biotechnical and Biomedical Applications*; Plenum: New York, 1992. (b) Zalipsky, S. *Bioconjugate Chem*. **1995**, *6*, 150−165.

(2) Gravert, D. J.; Janda, K. D. *Chem. Rev*. **1997**, *97*, 489−509.

(3) Dickerson, T. J.; Reed, N. N.; Janda, K. D. *Chem. Rev*. **2002**, *102*, 489−509.

(4) Bergbreiter, D. E.; Kimmel, T.; Caraway, J. W. *Tetrahedron Lett*. **1995**, *36*, 4757−4760.

(5) Guo, H.; Shi, X.; Qiao, Z.; Hou, S.; Wang, M. *Chem. Commun*. **2002**, 118−119.

(6) (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc*. **1987**, *109*, 5765−5780.

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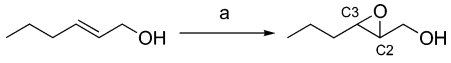
1a MPEG = MW 2000 **1i** MPEG = MW 2000
1b MPEG = MW 750
1c MPEG = MW 550
1d MPEG = MW 350
1e MPEG = $CH_3O(CH_2CH_2O)_4$
1f MPEG = $CH_3O(CH_2CH_2O)_3$
1g MPEG = $CH_3O(CH_2CH_2O)_2$
1h MPEG = $CH_3OCH_2CH_2O$

FIGURE 1. MPEG tartrate ligands.

SCHEME 1. Epoxidation of *trans*-Hex-2-en-1-ol Using MPEG Tartrate Ligands[a]



2 **3a** (2*S*, 3*S*)
3b (2*R*, 3*R*)

[a] Reagents and conditions: (a) ligand **1**, $Ti(OiPr)_4$, CH_2Cl_2, 4 Å molecular sieves, −20 °C.

L-(+)-tartaric acid gave the enantioselectivity *opposite* that of L-(+)-diethyl tartrate or the L-(+)-tartrate ligand prepared from MPEG 750, although no rationale was provided and no further examples were investigated. Given the extraordinary nature that a mere change in molecular weight of 1250 could completely change the enantioselectivity, this finding may represent an unprecedented new property of PEG. However, since this phenomenon is so contrary to our own experience with the behavior of PEG, we felt compelled to repeat the procedures as described by Guo. During our own investigations into this purported phenomenon, a report on the synthesis of an MPEG tartrate library from the same laboratory appeared.[7] In this study, a brief statement retracting their original findings was included wherein the observed enantioselectivity switch apparently could not be reproduced using MPEG 2000-derived tartrate esters. The only explanation given for this was a misinterpretation of the experimental optical rotation data and the value reported in the literature. Herein, we describe our investigations into clarifying the reproducible effect of MPEG on the enantioselectivity of the Sharpless asymmetric epoxidation.

Results and Discussion

In accordance with the original report, we appended two molecular weights of MPEG (2000 and 750) to L-(+)-tartaric acid to give ligands **1a** and **1b** (Figure 1). In addition to these two ligands, we prepared seven tartrate ester ligands, **1c**−**1i**, to survey the effect of chain length on the enantioselectivity. The ligands **1c**−**1h** were prepared from L-(+)-tartaric acid and MPEG 550, MPEG 350, monomethoxy tetraethylene glycol, monomethoxy triethylene glycol, monomethoxy diethylene glycol, and monomethoxy ethylene glycol, respectively, while ligand **1i** was prepared from MPEG 2000 and D-(−)-tartaric acid (Scheme 1). Treatment of 2 equiv of MPEG with tartaric acid and catalytic *p*-TsOH in benzene with azeotropic removal of water provided the tartrate esters. Ligands

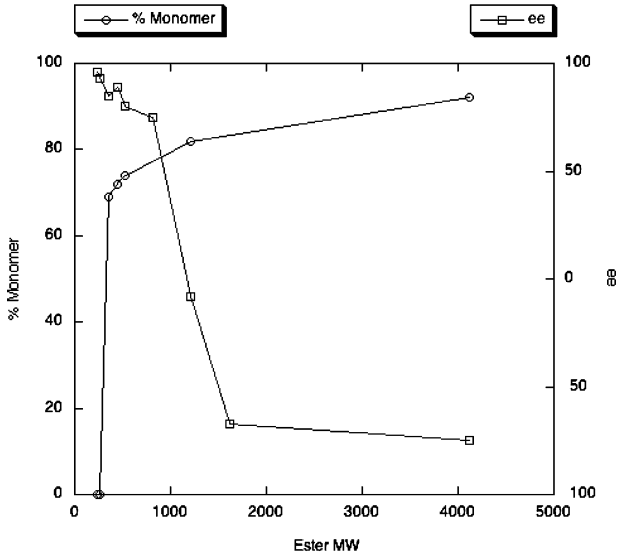


FIGURE 2. Effect of MPEG length on the enantioselectivity of the Sharpless asymmetric epoxidation and on the proportion of monomeric species: circles, monomer proportion (%); squares, ee (%).

1a, **1b**, and **1i** were purified by precipitation from diethyl ether and further dried by azeotropic removal of water from refluxing benzene or toluene. The ligands prepared from lower molecular weights of MPEG (**1c**−**1h**) were oils; hence, they were purified by treatment with basic ion-exchange resin in water and lyophilized to dryness, followed by azeotropic removal of water from refluxing toluene.

The diester MPEG ligands **1a** and **1b** were then used in the Sharpless asymmetric epoxidation reaction of *trans*-hex-2-en-1-ol (**2**) to form *trans*-3-propyloxiranemethanol (**3**) (Scheme 1).[6] These reactions were generally slower than epoxidations using simply L-DIPT (6−8 h for the MPEG ligands versus 2−3 h for DIPT) and did not go to completion, stopping at 60−95% conversion. As expected, control epoxidations using L-DIPT as the ligand instead of MPEG ligands **1a**−**1i** under identical reaction conditions gave **3a** in greater than 95% yield. Spectral data of glycidol **3a** agreed with literature values.[6] After purification of the epoxy alcohols, the enantioselectivities were determined by conversion to the corresponding Mosher esters and quantitation of the individual isomers using ^1H NMR (Figure 2).[8] Upon examination of the NMR spectra it was readily apparent that ligands **1a** and **1b** exhibited the *same* enantioselectivity, and furthermore, both ligands give the (2*R*,3*R*) isomer **3b** in nearly identical enantiomeric excesses (63% and 67%). These results can be contrasted with those of the L-DIPT-catalyzed reaction (Table 1, entry 8), which yields the expected (2*S*,3*S*) isomer **3a** in 96% ee. Ligands **1d**−**1h** (Table 1, entries 4−8) also gave **3a**, however, in decreasing enantiometric excess as the MPEG length was increased, while ligand **1c** gave a nearly racemic mixture (8% ee), slightly favoring **3b** (Table 1, entry 3). Ligand **1i**, prepared from D-(−)-tartaric acid, exhibited the op-

(7) Guo, H.-C.; Shi, X.-Y.; Wang, X.; Liu, S.-Z.; Wang, M. *J. Org. Chem.* **2004**, *69*, 2042−2047.
(8) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549.

TABLE 1. Yields and Enantioselectivities of Epoxidations

entry	ligand	MPEG MW	yield (%)	ee (%)	product
1	**1a**	2000	54	75	**3b** (2*R*,3*R*)
2	**1b**	750	66	67	**3b** (2*R*,3*R*)
3	**1c**	550	89	8	**3b** (2*R*,3*R*)
4	**1d**	350	95	75	**3a** (2*S*,3*S*)
5	**1e**	207	93	80	**3a** (2*S*,3*S*)
6	**1f**	163	83	89	**3a** (2*S*,3*S*)
7	**1g**	119	72	85	**3a** (2*S*,3*S*)
8	**1h**	75	75	93	**3a** (2*S*,3*S*)
9	**1i**	2000	63	78	**3a** (2*S*,3*S*)
10	L-DIPT[a]		96	87	**3a** (2*S*,3*S*)
11	L-DIPT		96	96	**3a** (2*S*,3*S*)

[a] A 2 equiv sample of poly(ethylene glycol) dimethyl ether (MW 2000) was added to the reaction.

TABLE 2. Molecular Weight Determination of Tartrate Esters[a]

entry	ligand	monomer MW[b]	dimer MW[b]	MW found	% monomer[c]
1	L-DIPT	398	796	840	0
2	**1h**	446	892	930	0
3	**1g**	584	1052	690	77
4	**1f**	890	1212	775	79
5	**1e**	980	1392	875	81
6	**1c**	1664	2760	1630	85
7	**1a**	4564	8560	4642	92

[a] Apparent molecular weights were determined using the Signer method after equilibration for a minimum of 7 days. [b] Monomer = $Ti_2L(OR)_6$ and dimer = $Ti_2L_2(OR)_4$, where L = ligand and R = *i*Pr. [c] Calculated assuming a two-state equilibrium between monomer and dimer and the presence of 1 equiv of free tartrate ligand in monomer-containing solutions.

posite enantioselectivity, yielding product **3a** (Table 1, entry 9). The effect of PEG as an additive in the Sharpless asymmetric epoxidation reaction was also examined.[9] Addition of 2 equiv of poly(ethylene glycol) dimethyl ether to a control reaction using L-DIPT as the ligand (Table 1, entry 10) gave the expected product **3a** with only a minor degradation of enantioselectivity.

Using circular dichroism, L-DIPT and tartrates **1a**−**1e** displayed the same influence on circularly polarized light, implying that the direction of the optical rotation played no significant role in the enantioselectivity of the reaction. Likewise, D-DIPT and ligand **1i** also displayed similar profiles in their respective CD spectra, despite the production of opposite enantiomers induced by the ligands. To directly detect chemical exchange processes between various conformers,[10] ROESY ^{1}H NMR was used to determine if MPEG tartrates contain additional structure relative to nonpolymeric tartrate esters that could explain the anomalous enantioreversal. Although an unusual chemical exchange cross-peak was observed in the mixtures containing Ti(O*i*Pr)$_4$ and ligand **1a**, the relationship of this phenomenon to catalyst enantioselectivity is unclear.

Achiral and meso ligands have proven utility in asymmetric catalysis, especially in the context of large, flexible ligands.[11] Here, achiral additives that do not possess chiral conformations can enhance catalyst activity and enantioselectivity by serving as ligands, thereby altering the metal geometry of the catalyst. Although we felt it unlikely that MPEG could serve as a ligand in this sense of chirality transmittal, these studies do provide an attractive explanation for the observed enantioselectivity switch; that is, the reversal might arise from two structurally distinct Ti−ligand species found within the low and high molecular weight MPEG tartrates influenced directly by the presence of the appended MPEG. Monomeric Ti−ligand complexes for the Sharpless epoxidation reaction have been proposed,[12] and we postulated that epoxidations using ligand **1a** and DIPT proceed via complexes that differ in the molecularity of Ti and ligand. Indeed, a monomeric 2:1 Ti−tartrate complex has been proposed by Sharpless in which the enantioselectivity of the reaction is reversed.[12a] In this model, the Ti atoms are chelated between the tartrate alcohol and carbonyl oxygen, thereby altering the asymmetric environment about the metal, generating the opposite enantiomer compared to the corresponding 2:2 Ti−tartrate complex.

Our initial attempts to observe a monomeric species using mass spectrometric techniques (e.g., MALDI, ESI) in Ti/MPEG ligand mixtures were not successful due to the inherent lability of the Ti−ligand complex. However, the isopiestic Signer method[13] has been previously employed to provide evidence for dimeric complexes in traditional Sharpless asymmetric epoxidations. Using this method, the major species in reactions containing DIPT or **1h** were found to be dimeric,[14] whereas mixtures of **1a** and Ti(O*i*Pr)$_4$ were comprised of monomeric species (Table 2). Surprisingly, equilibrations conducted with ligands **1f** and **1g** in which three and two appended PEG units are present, respectively, were also observed to be principally monomeric (Table 2). Given a two-state equilibrium between monomeric and dimeric species,[15] these experiments contained 79% and 77% monomer, respectively. The relative proportion of monomer present gradually increased with MPEG molecular weight to a maximum of 92% monomer present in Ti−**1a** complexes (Figure 2).

The discovery that the Ti−**1h** complex is dimeric while the Ti−**1g** complex is largely monomeric is particularly amazing as the difference between these two ligands is the addition of only three atoms, that is, one ethylene glycol unit. A plausible explanation for this phenomenon can be made in that **1h** cannot chelate to the metal due to the single ethylene oxide unit, while **1g** is of suitable

(9) Rudolph, J.; Hermanns, N.; Bolm, C. *J. Org. Chem*. **2004**, *69*, 3997−4000 and references therein.

(10) Bain, A. D. *Prog. Nucl. Magn. Reson. Spectrosc*. **2003**, *43*, 63−103.

(11) Walsh, P. J.; Lurain, A. E.; Balsells, J. *Chem. Rev*. **2003**, *103*, 3297−3344 and references therein.

(12) (a) Lu, L. D.-L.; Johnson, R. A.; Finn, M. G.; Sharpless, K. B. *J. Org. Chem*. **1984**, *49*, 731−733. (b) Corey, E. J. *J. Org. Chem*. **1990**, *55*, 1693−1694.

(13) (a) Clark, E. P. *Ind. Eng. Chem., Anal. Ed*. **1941**, *13*, 820−821. (b) Burger, B. J.; Bercaw, J. E. In *Experimental Organometallic Chemistry: A Practice in Synthesis and Characterization*; Wayada, A. L., Darensbourg, M. Y., Eds.; ACS Symposium Series 357; American Chemical Society: Washington, DC, 1987; pp 94−96.

(14) (a) Woodard, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc*. **1991**, *113*, 106−113. (b) Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc*. **1991**, *113*, 113−126.

(15) The Signer method measures the total amount of solute in a given solution. As such, monomer-containing solutions were assumed to contain 1 equiv of 2:1 Ti−MPEG ligand species and 1 equiv of free ligand. Thus, the apparent molecular weight of these solutions is the average of the molecular weights of these two species.

length to complex the metal and favor a 2:1 Ti−ligand complex. As the MPEG length increases, a statistically greater number of oxygen atoms are present that can interact with the metal, thereby increasing the relative proportion of monomeric species. Interestingly, using MPEG tartrate esters, a 2:1 Ti−ligand complex forms even when the reactions are prepared as 2:2 mixtures of metal to ligand. In contrast, the previously reported analogous complex[12a] was prepared in the presence of 2 equiv of metal and 1 equiv of ligand. That the transition from monomer and dimer is different from the observed enantioselectivity reversal is not surprising. In accordance with the Curtin−Hammett principle, different catalyst reactivities would be expected for rapidly interconverting catalysts. Indeed, on the basis of our findings the monomeric Ti−tartrate complex is approximately 5−6 times less active than the corresponding dimeric species, corresponding with previously reported data.[12a]

Conclusion

Our investigations into the nature of Sharpless asymmetric epoxidations catalyzed by MPEG tartrate esters have revealed several interesting details regarding the mechanism of catalysis, including the finding that a mere change in molecular weight of 800 leads to a complete reversal in the enantioselectivity, apparently through a 2:1 Ti−ligand complex. The addition of PEG dimethyl ether had no effect on the enantioselectivity of the reaction, indicating that simple coordination of metal and MPEG is not important in establishing a monomeric species. We hypothesize that the addition of long MPEG chains onto the tartrate prevents dimer formation by raising the energy barrier for assembly, thereby reducing the population of dimeric species. This could be the result of many factors including the known helicity of PEG in solution[16,17] or other steric-based effects. Furthermore, the enantioselectivity and molecular weight data agree with those of the previously reported 2:1 Ti−tartrate complex,[12a,14] suggesting this may be a plausible mechanism for our observations.

Our findings are counterintuitive; however, they clearly demonstrate a reproducible reversal in enantioselectivity directly dependent on PEG chain length. As the observed enantioreversal occurs using the *same* isomer of tartaric acid, the change in catalyst structure is consummate with two fundamentally different transition states leading to monomeric and dimeric transition states. These data could be indicative of a more general phenomenon in which designed polymers displaying defined secondary and/or tertiary structure (e.g., foldamers[18]) could result in changes in catalyst selectivity. We are currently investigating the nature of this fascinating effect and will report our results in due course.

Experimental Section

General Procedure for the Preparation of MPEG Tartrate Ligands. Ligands were prepared according to previously published procedures.[5,7] Briefly, either D- or L-tartaric acid (2.0 g, 13.32 mmol), the appropriate MPEG (127.60 mmol), 0.5 mol % TsOH, and toluene (60 mL) were mixed and refluxed in a Dean−Stark apparatus for 2 days, after which the residue was distilled to remove excess MPEG. The resulting oil was purified by flash chromatography with CH_2Cl_2/MeOH (9:1) to obtain the desired ligands in pure form.

MPEG 550 Tartrate Ligand (1c). ^{1}H NMR ($CDCl_3$): δ 4.70 (s, 2H), 4.48−4.44 (m, 4H), 3.81−3.79 (m, 8H), 3.72 (br s, 104H), 3.63−3.59 (m, 8H), 3.44 (s, 8H). ^{13}C NMR ($CDCl_3$): δ 171.6, 72.9, 72.8, 72.0, 70.6, 70.2, 68.9, 64.7, 64.7, 61.6, 59.1.

General Procedure for Asymmetric Epoxidations. A solution of Ti(O*i*Pr)$_4$ (0.05 equiv, 0.5 mmol, 150 μL), MPEG tartrate (0.06 equiv, 0.6 mmol), and 3 Å molecular sieves (300 mg) in CH_2Cl_2 (35 mL) was stirred at room temperature for 5 min. We found that mixing the Ti(O*i*Pr)$_4$ and tartrate at −20 °C without warming did provide an active enantioselective catalyst.[19] After the mixture was cooled to −20 °C, TBHP (2.9 M in isooctane, 2 equiv, 6.9 mL, dried over 4 Å molecular sieves for 2 h) was added dropwise and stirring continued for 1 h. *trans*-Hex-2-en-1-ol (**2**) (1 equiv, 10 mmol, 1.17 g, dried over molecular sieves for 1 h) in CH_2Cl_2 (5 mL) was added dropwise and the resulting mixture stirred at −20 °C for 12 h. The reaction was warmed to 0 °C, an ice-cold solution of $FeSO_4 \cdot 9H_2O$ (3.3 g) and L-(+) tartaric acid (1.0 g) in water (10 mL) was added, and the mixture was stirred for 1 h at 0 °C. The layers were separated, the aqueous layer was extracted with diethyl ether (2 × 100 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated. Remaining MPEG tartrate was precipitated from diethyl ether. Chromatography (4:1 hexane/ethyl acetate) provided the pure glycidol **3**. It should be noted that this workup is slightly different from the one used by Guo, since the precipitation step is after the aqueous workup. This simplifies the workup procedure; however, precipitation of the MPEG tartrate before quenching the peroxide provides a slightly higher mass recovery. No transesterification between the allylic alcohol product and the MPEG tartrates was observed. Given the propensity for MPEG to form peroxy ethers, the MPEG ligand was not recycled.[20]

Preparation of the MTPA Esters. (*R*)-(−)-α-Methoxy-α-trifluoromethylphenylacetyl chloride was prepared according to the procedure of Mosher.[8] Freshly prepared (*R*)-(−)-MTPA-Cl (90 μL, 0.48 mmol) was added to a solution of the epoxy alcohol **3a** or **3b** (0.4 mmol, 46 mg), *i*Pr$_2$EtN (300 μL), and DMAP (54 mg) in CH_2Cl_2 (1.5 mL) at room temperature and the resulting solution stirred until complete as determined by gas chromatography. Elution through a plug of SiO_2 (5 g of SiO_2, 4:1 hexane/ethyl acetate) provided the pure Mosher ester. Enantiomeric excess was determined by integration of the C1 methylene protons in the ^{1}H NMR spectrum. For all ^{1}H NMR experiments, the recycle delay was set to 10 s to ensure complete relaxation of all observed resonances.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **1c**−**1h**, procedures for ROESY experiments, and molecular weight determinations (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO048009X

(16) (a) Takahashi, Y.; Tadokoro, H. *Macromolecules* **1973**, *6*, 672−675. (b) Liu, K.-J. *Macromolecules* **1968**, *1*, 213-217.

(17) It is possible that upon reaching lengths long enough to form helices the appended MPEG could impart a defined secondary and/or tertiary structure on the catalyst.

(18) (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173−180. (b) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893−4012.

(19) M. G. Finn, personal communication.

(20) Hamburger, R.; Azaz, E.; Donbrow, M. *Pharm. Acta Helv*. **1975**, *50*, 10−17.