Biomimetic Catalysis

A C_3-Symmetrical Chiral Trisoxazoline Zinc Complex as a Functional Model for Zinc Hydrolases: Kinetic Resolution of Racemic Chiral Esters by Transesterification**

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The key function of the Zn^{2+} cation in the reactive sites of many metalloenzymes is a well-established fact.[1] It normally adopts a tetrahedral coordination geometry and is attached to the protein backbone by three amino acid residues; the fourth coordination site is occupied by a water molecule. In many of the zinc-based peptidases, a tris(histidine)zinc binding site acts as a "tripodal ligand" for the metal ion. These include the Zn-based D-Ala-D-Ala-carboxypeptidase of *Streptomyces albus*[2] and the extensively studied "metzincin" family of endopeptidases.[3,4]

The ubiquity of zinc in metalloenzyme chemistry has been related to its flexible coordination chemistry, substitutional lability, Lewis acidity, intermediate polarizability (and thus moderate softness) combined with a lack of redox activity. Usually, coordination numbers of 4 or 5 are thought to be preferred in enzymes, including bound water molecules, inhibitors or intermediates.[1] To better understand the factors that control the detailed properties of the active sites of zinc enzymes, small molecular models have been studied during the past decade. The extensive work on scorpionate and related tripodal Zn complexes, in particular by the groups of Vahrenkamp and Parkin, has led to the elucidation of key mechanistic features of the activities of Zn enzymes.[5,6] These include biomimetic hydrolyses as well as the modeling of intermediates of peptidase and carboanhydrase catalytic cycles.

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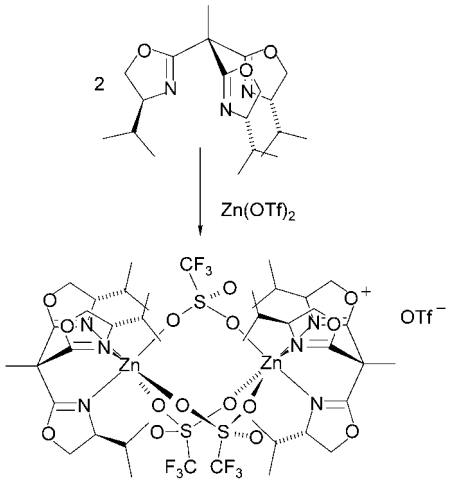
Rendering tripodal metal binding sites chiral may lead to molecular catalysts of C_3 or C_1 symmetry. Their potential in the development of novel enantioselective catalysts remains comparatively underdeveloped.[7] We recently reported a new class of chiral trisoxazoline tripod ligands and have begun studying their properties in asymmetric catalysis.[8] These may be viewed as models emulating both the tris(histidine) binding sites and the chiral environment of the protein skeletal structure. This result provided the opportunity of developing model compounds for hydrolases or transesterases with the potential for stereoselective transformations normally only observed for the enzymatic system. We present herein the first results of this study.

Reaction of the previously reported chiral trisoxazoline ligand 1,1,1-tris{2-[*(S)*-4-isopropyl]oxazolyl}ethane, "*i*Pr-trisox" (**1**)[8b] with $Zn(OTf)_2$ (OTf is trifluoromethanesulfonyl) in dry methanol led to the complete dissolution of the zinc salt and the formation of the *i*Pr-trisox–Zn complex **2a**, which was isolated as a colorless solid and recrystallized from dichloromethane/pentane (Scheme 1).



Scheme 1. Synthesis of the dinuclear complex $[(i\text{Pr-trisox})_2Zn_2(\mu\text{-OTf})_3]OTf$.

Whereas the analytical and ^1H and ^{13}C NMR spectroscopy data are consistent with a tripodal coordination of the trisoxazoline ligand and an overall threefold molecular symmetry, the ESI mass spectrum indicated the presence of a dinuclear complex cation corresponding to the formulation $[(i\text{Pr-trisox})_2Zn_2(\mu\text{-OTf})_3]^+$. A single-crystal X-ray-structure analysis of the salt $[(i\text{Pr-trisox})_2Zn_2(\mu\text{-OTf})_3]OTf$ (**2a**) confirmed this assignment and established the details of the complex structure, which is depicted in Figure 1a.

Compound **2a** crystallizes in the cubic space group $P2_13$ and the dinuclear zinc complex cation is aligned along a crystallographic threefold axis, thus rendering it exactly C_3-symmetric (Figure 1b). Both metal centers are coordinated by the tripodal trisoxazoline ligand and are symmetrically linked by three triflato ligands, an arrangement which is unique for the weakly coordinating triflate anion. While there are very few structurally characterized triflato–zinc com-

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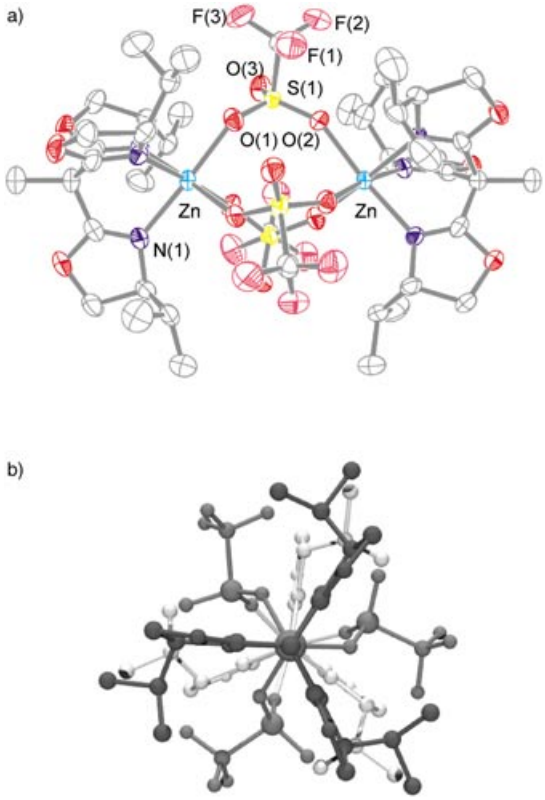
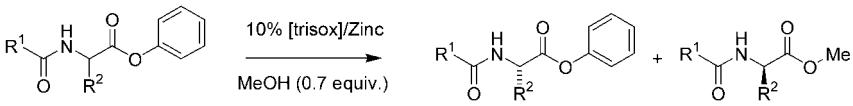


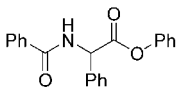
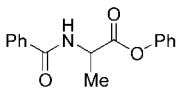
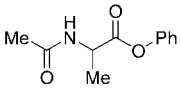
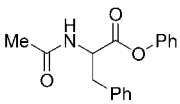
Figure 1. Molecular Structure of the dinuclear zinc complex **2**. a) View perpendicular to the Zn–Zn vector; b) view along the molecular three-fold axis. The principal bond lengths (Å) and angles (°): Zn(1)–N(1) 2.125(4), Zn(2)–N(2) 2.124(4), Zn(1)–O(1) 2.130(4), Zn(2)–O(2) 2.124(4), S(1)–O(1) 1.445(4), S(1)–O(4) 1.444(4), S(1)–O(2) 1.431(4), N(1)-Zn(1)-N(1′) 85.6(2), N(2)-Zn(2)-N(2′) 85.3(2), O(1)-Zn(1)-O(1′) 89.6(2), O(2)-Zn(2)-O(2′) 90.6(2), O(1)-Zn(1)-N(1) 92.6(2), O(1)-Zn(1)-N(1′) 92.1(2), O(4)-Zn(2)-N(2) 87.6(2), O(4)-Zn(2)-N(2′) 96.7(2), O(1)-S(1)-O(4) 113.8(2).

plexes (none of them have the triflate as a bridging ligand),[9] there are several related dinuclear units known in carboxylato–Zn chemistry.[10] We note that bridging triflates have been observed in several other transition-metal complexes, in particular those of the coinage metals.[11] The structural constraints imposed by the relatively rigid tripod ligand lead to a trigonal antiprismatic elongation of the {(*i*Pr-trisox)Zn} unit in the distorted $\{ZnN_3O_3\}$ octahedron [N(1)-Zn(1)-N(1′) 85.6(2), N(2)-Zn(2)-N(2′) 85.3(2) Å], whereas the triflato O atoms are arranged at almost ideal right angles at both Zn centers [O(1)-Zn(1)-O(1′) 89.6(2), O(2)-Zn(2)-O(2′) 90.6(2)°].

We found that the zinc triflate complex **2a** displays catalytic activity in the transesterification of various phenyl esters. It should be noted that the use of non-enzymatic catalysts for asymmetric acylation of substrates is now well-established, in particular, kinetic resolutions by using chiral nucleophilic catalysts have recently proved to be an effective tool in organic synthesis.[12–14] On the other hand, the use of non-enzymatic catalysts for an asymmetric transesterification of activated esters remains, to our knowledge, unexplored.[15,16] This contrasts with the fact that several enzymes have been reported to catalyze the kinetic resolution of carboxylic acid derivatives[17] and the first report of a kinetic resolution by transesterification, with yeast lipase and porcine pancreatic lipase, involved α-halogen-substituted carboxylic acid derivatives.[18]

The chiral zinc complex **2a** showed modest but significant enantioselectivity in the kinetic resolution of various phenyl ester derivatives of *N*-protected amino-acids by transesterification with methanol (Scheme 2). The catalyst is characterized by only modest selectivity factors, in the range of $S = 1.3–2.0$ for substrates listed in Scheme 2.[19] However, upon going from the zinc triflato complex **2a** to the acetate complex **2b** and further to the trifluoroacetate **2c**, there was an increase of the selectivity factor for all the substrates, notably to $S = 5.1$ for entry 3 in the table in Scheme 2. The importance of the tripodal-zinc environment for the observed stereoselectivity is inferred from the observation that the coordination of the classical bidentate dimethyl-bisoxazoline 2,2′-bis[2-((4*S*)-(isopropyl)-1,3-oxazolinyl)]-propane to a zinc salt does not induce kinetic resolution. These first data prove the concept and indicate that non-enzymatic catalysts of this family may prove to be useful in asymmetric transesterifica-



Entry	Substrate	Selectivity factor (s)		
		$Zn(OTf)_2$	$Zn(OAc)_2$	$Zn(OCOCF_3)_2$
1		1.8	3.5	3.8
2		1.3	2.7	3.0
3		2.0	4.5	5.1
4		1.8	2.6	4.3

All reactions were performed in CH_2Cl_2 at room temperature in the presence of 10 mol% of Zinc precursor/ *i*Pr-trisox for 2-3 days.

Scheme 2. Partial kinetic resolution of activated aminoacid esters by stereoselective {trisox–Zn} catalyzed transesterification.

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tion after further development. Ongoing studies are directed at providing mechanistic information, at developing more efficient zinc-based molecular catalysts for this reaction, and at extending the use of these biomimetic systems to other transformations.

Experimental Section

Preparation of complex **2a**: A mixture of *i*Pr-trisox (**1**) (44 mg, 0.12 mmol) and $Zn(OTf)_2$ (40 mg, 0.11 mmol) in methanol (1 mL) was stirred under nitrogen at room temperature for one hour. The solvent was removed in vacuo and the white solid washed with pentane. Recrystallization from dichloromethane/pentane yielded 45 mg (56%) of colorless crystals (suitable for X-ray diffraction). ^{1}H NMR (300 MHz, CD_2Cl_2): $\delta = 4.56$–4.44 (m, 6H), 4.41 (m, 3H), 2.18 (m, 3H), 2.02 (s, 3H), 1.03 (d, $J = 6.9$ Hz, 9H), 0.93 ppm (d, $J = 6.8$ Hz, 9H); ^{13}C NMR (75.5 MHz, CD_2Cl_2): $\delta = 167.3$ (C=N), 119.7 (quad., $J_{(C\text{-}F)} = 318.2$ Hz, CF_3), 71.4 (*C*H*i*Pr), 70.3 (CH_2), 45.1 ($C_{quat.}$), 30.5 ($CH(CH_3)_2$), 17.9 ($CH(CH_3)(CH_3)$, CH_3), 15.2 ppm ($CH(CH_3)(CH_3)$); ^{19}F (282.4 MHz, CD_2Cl_2): $\delta = -78.6$ ppm; HRMS (ESI): *m*/*z* (%): 1305.2194 ($[L_2Zn_2(OTf)_3]^+$; calculated for the most abundant isotopomer: 1305.2186 amu); Elemental analysis (%) calcd. for $C_{44}H_{66}F_{12}N_6O_{18}S_4Zn_2$: C 36.34, H 4.58, N 5.78; found C 36.49, H 4.75, N 5.85.

Complexes **2b** and **2c** were prepared in a similar way. Selected spectroscopic data for **2b**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.55$–4.24 (m, 6H), 4.16 (m, 3H), 2.18 (m, 3H), 1.98 (s, 6H), 1.95 (s, 3H), 0.86 (d, $J = 6.9$ Hz, 9H), 0.82 ppm (d, $J = 6.8$ Hz, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 179.2$ (C=O), 165.5 (C=N), 70.4 (*C*H*i*Pr), 69.9 (CH_2), 44.3 ($C_{quat.}$), 30.3 ($CH(CH_3)_2$), 22.5 (CH_3-C=O), 18.6 ($CH(CH_3)(CH_3)$), 15.3 ($CH(CH_3)(CH_3)$), 14.0 ppm (CH_3); HRMS (ESI): *m*/*z*: 1035.3877 ($[L_2Zn_2(OAc)_3]^+$; calculated for the most abundant isotopomer: 1035.4025 amu). Selected spectroscopic data for **2c**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.45$ (m, 6H), 4.25 (m, 3H), 2.15 (m, 3H), 1.99 (s, 3H), 0.91 (d, $J = 6.9$ Hz, 9H), 0.82 ppm (d, $J = 6.8$ Hz, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 166.2$ (*C*=N), 162.5 (quad., $J_{(C\text{–}F)} = 37.2$ Hz, *C*O–CF_3), 116.3 (quad., $J_{(C\text{–}F)} = 289.3$ Hz, CF_3), 70.6 (CH_2), 70.4 (*C*H*i*Pr), 44.8 ($C_{quat.}$), 30.6 ($CH(CH_3)_2$), 21.8 (CH_3), 18.4 ($CH(CH_3)(CH_3)$), 15.5 ppm ($CH(CH_3)(CH_3)$); ^{19}F (282.4 MHz, $CDCl_3$): $\delta = -75.4$ ppm; HRMS (ESI): *m*/*z*: 1197.3001 ($[L_2Zn_2(CF_3CO_2)_3]^+$ (calculated for the most abundant isotopomer: 1197.3177 amu).

Crystal data for **2a**: $C_{44}H_{66}F_{12}N_6O_{18}S_4Zn_2$; CF_3O_3S, colorless, crystal dimensions $0.13 \times 0.10 \times 0.08$ mm, $M_r = 1454.01$, cubic, space group $P2_13$, $a = 18.433(2)$ Å, $V = 6263.1(12)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.542$ g cm^{-3}, $\mu = 1.004$ mm^{-1}, $F(000) = 2992$, number of data measure: 5862 ($2.47 < \theta < 30.01°$) at 173(2) K, number of data with $I > 2\sigma(I)$: 3730, number of variables: 260, $R = 0.0678$, $Rw = 0.1617$, GOF = 1.042, largest peak in final difference: 1.42 e Å^{-3}. CCDC-233158 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Representative general procedure for the kinetic resolutions; transesterification of N-benzoyl-phenylglycine phenyl ester: A suspension of zinc triflate (9.0 mg, 0.025 mmol) and *i*Pr-trisox (**1**; 9.5 mg, 0.026 mmol) was stirred in dry methanol (0.5 mL) until complete dissolution of the zinc salt (ca. 1 h). The solvent was then evaporated to dryness and a solution of *rac*-*N*-benzoyl-phenylglycine phenyl ester (83.0 mg, 0.25 mmol) in dry CH_2Cl_2 (1.0 mL) was added followed by dry methanol (7.0 μL, 0.17 mmol). After two days stirring, the mixture was passed through a short plug of silica to separate the esters derivatives from the catalyst. A ^{1}H NMR spectroscopy study showed a conversion of 52% into the methyl ester derivative. HPLC analysis (AD daicel, 95:5 hexane/isopropanol, 0.8 mL min^{-1}) analysis revealed an *ee* of 20.0% for the starting material and 19.5% for the product. These *ee* values correspond to a selectivity factor (s) of 1.8 at 51% conversion.[20]

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Keywords: asymmetric catalysis · biomimetic synthesis · chirality · tripodal ligands · zinc

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[20] Conversion (%) calculated = *ee* (starting material)/[*ee* (starting material) + *ee* (product)]; see reference [12]. The difference between the conversion (%) calculated by this method and the value measured by ^{1}H NMR was less than 2% in all cases.

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