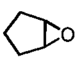
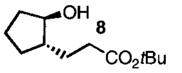
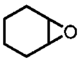
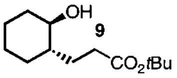
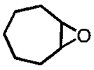
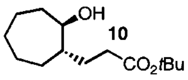
reason for the high selectivity of epoxide opening with **1** seems to stem from its striking structural feature, the almost perfect coplanarity of the benzene rings and the cyclopentadienyl rings, presumably due to π stacking. This interaction seems to lock the ligands in a conformation necessary for highly selective binding of the substrate. The methyl groups of the terpene moiety point towards the homotopic binding sites of the supposed catalytically active titanium(III) complex.[7] These binding sites should be located close to the Cl atoms of the almost C_2-symmetrical titanium (IV) complex, by comparison with other titanocene(III) and titanocene(IV) complexes.[8] Therefore, **1** meets all requirements we believed to be necessary for a succesful catalyst.

Our anticipated mechanism is supported by the reduced enantioselectivity of the opening of **6**. In the case of the *n*-alkyl ethers **2** and **4** the selectivity was similar and high. However, in the case of **6** both *tert*-butyl groups made a rather strong contact with the chiral pocket of **1**, resulting in dimished steric differentiation.

An interesting and demanding problem is the use of bicyclic epoxides in enantio- and diastereoselective C–C bond forming reactions by addition of the *β*-titanoxy radical to *tert*-butyl acrylate. The results of our investigation are summarized in Table 2. With increasing ring size the enantioselectivity of the epoxide opening increases and reaches synthetically useful levels for the six- and seven-membered rings. This indicates a better fit of the larger substrates in the chiral pocket of the catalyst. The diastereoselectivity of the C–C bond forming steps[9] was higher than with $[Cp_2TiCl_2]$ as catalyst[3b,c] (**8**: 86:14 vs. 97.5:2.5; **9**: 60:40 vs. 81:19; **10**: 70:30 vs. 87:13) or with stoichiometric amounts of reagent.[10]

Table 2. Enantioselective C–C bond forming reactions in the presence of 5 mol% of **1** (0.1 M in THF, 48 h).

Substrate	Product	Yield [%]	(*R*,*S*):(*S*,*R*)[a]
	 **8**	68	87:13[b]
	 **9**	61	91:9[c]
	 **10**	65	91:9[d]

[a] Determined by gas chromatography on chiral phases. [b] *trans*:*cis* > 97:3. [c] *trans*:*cis* = 81:19, same *ee* value for the two diastereoisomers. [d] *trans*:*cis* = 87:13.

In summary we have demonstrated for the first time that the catalytic opening of *meso*-epoxides by electron transfer can be performed with high enantioselectivity and high diastereoselectivity with **1** as rationally designed catalyst.

Received: April 23, 1999 [Z13306IE]
German version: *Angew. Chem.* **1999**, *111*, 3112–3114

Keywords: enantioselectivity · epoxides · homogeneous catalysis · radical reactions · titanium

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[7] X-ray crystal structure analysis of $1\cdot CHCl_3$ ($C_{43}H_{55}Cl_5Ti$): $M_r = 797.0$, orthorhombic, space group $P2_12_12_1$, $a = 1290.76(12)$, $b = 1310.0(2)$, $c = 2517.8(6)$ pm, $V = 4.2572$ nm^3, $\rho_{calcd} = 1.244$ g cm^{-3}, 3454 independent reflections, $R1 = 0.0473$ for $I > 2\sigma(I)$, $wR2 = 0.1101$ for all data. The structure was solved by direct methods and refined with anisotropic temperature factors for all non-hydrogen atoms; hydrogen atoms were added in idealized positions and included in the refinement. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-118965. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Noncatalytic Organic Synthesis Using Supercritical Water: The Peculiarity Near the Critical Point

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As industry is interested in moving away from toxic or environmentally damaging solvents, the finding of an ideal replacement medium for conventional nonpolar solvents offers new opportunities in, for example, reaction engineering, environmental science and technology, and materials science. Supercritical water (scH_2O) heated and pressurized

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beyond its critical point, 374 °C and 22.1 MPa, should be a useful replacement because not only is water the most environmentally acceptable, naturally abundant, and inexpensive solvent, but its physicochemical properties can be changed widely with pressure and temperature;[1] for example, the static dielectric constant of water is about 80 for the liquid phase and dramatically decreases to 6.0 in the supercritical region at 30 MPa and 400 °C.[1b] Supercritical water has such unusual properties compared to those of liquid water or of superheated water that nonpolar organic compounds are very soluble or miscible in scH_2O.[1c] This quality along with its high diffusivity and low viscosity means that scH_2O is expected to function as an ideal replacement for nonpolar organic solvents. Supercritical and superheated H_2O have been used mainly for the "breakdown" of organic reactants, for example, for the oxidative destruction of organic wastes,[2a] pyrolysis and hydrolysis of coal and biomass materials,[2b] and geochemical reactions.[3a] However, there are a few reports on the use of scH_2O as a catalyst or reactant as well as a medium for "organic synthetic reactions".[3] Acid-catalyzed organic syntheses will proceed under a scH_2O atmosphere even in the absence of any acid catalysts. This observation may be expected from studies on the structure of water at high temperatures and high pressures, which indicate that the network of hydrogen bonding is significantly changed relative to that under normal conditions.[4] By using in situ Raman spectroscopy we have shown that the extent and strength of hydrogen bonding decreases peculiarly near the critical point, and promotes the evolution of protons.[4d]

Herein we report interesting examples of an efficient noncatalytic pinacol rearrangement and of a noncatalytic Beckmann rearrangement in the near-critical region of scH_2O; both reactions are known to be catalyzed by strong acids in conventional solutions. The Beckmann rearrangement of cyclohexanone oxime into ε-caprolactam is a commercially important reaction for the production of synthetic fibers and the pinacol rearrangement has attracted attention as a fundamental way of producing aldehydes and ketones. However, both reactions have disadvantages in that highly concentrated monobasic acids or solid acids with short lifetime should be used as catalysts, and by-products of low commercial value are formed frequently.[5]

Although the rate of the rearrangement of pinacol to pinacolone can be improved by introducing acid catalysts at high concentrations,[6] it is still very slow and less selective: for example, the first-order rate constants under distillation conditions are at best $3.0 \times 10^{-3}\,s^{-1}$ [6a] and $2.9 \times 10^{-3}\,s^{-1}$ [6b] with 0.71 M $HClO_4$ and 2.43 M H_2SO_4, respectively. In addition, the selectivity for pinacolone is only 65–72 % even when the reaction is carried out in 6 N concentrated H_2SO_4 solution.[6c]

Figure 1 shows the background-corrected IR spectra for a mixture of the pinacol rearrangement in scH_2O (390 °C, 25 MPa), superheated H_2O (250 °C, 25 MPa), and ordinary water (20 °C, 0.1 MPa) at a constant reaction time of 108.0 s with our real time, in situ FT-IR measurements. A great change is seen in the spectrum obtained in scH_2O (trace C). A new strong band centered at 1701 cm^{-1} appears in the scH_2O spectrum, which can be assigned to the CO stretching (ν_1) of the pinacolone formed in this supercritical region. This band is not observed in the superheated (trace B) and ordinary water (trace A) phases. In addition the band centered at 945 cm^{-1}, which corresponds to the OH bending (ν_2) of pinacol disappears completely in the scH_2O spectrum. This in situ observation demonstrates for the first time that the rearrangement of pinacol to pinacolone proceeds very rapidly in scH_2O in the absence of any acid catalysts and strongly supports the function of scH_2O as an acid catalyst. Further analysis of the reaction mixture at the end of the reaction by GC-MS and ^1H NMR spectroscopy confirmed that the selectivity for the pinacolone reaches 100 % at 390 °C and 25 MPa.

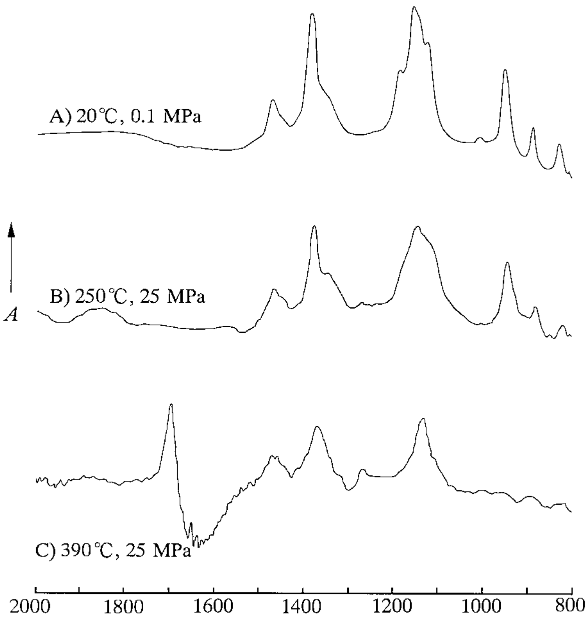


Figure 1. Infrared spectra of the reaction mixture in the noncatalytic pinacol rearrangement in H_2O at different pressures and temperatures. The bands at 1701 and 945 cm^{-1} correspond to CO stretching (ν_1) in pinacolone and OH bending (ν_2) in pinacol, respectively. The reaction time is 108 s.

Since the reaction is kinetically first order in pinacol,[6] the first-order rate constants have been determined by the in situ spectroscopic measurements in the ranges of 20–450 °C and 0.1–35 MPa. The change in the pinacol concentration was monitored by the decrease in the FT-IR absorbance of the ν_2 band of pinacol centered at 945 cm^{-1}. The extinction coefficient of ν_2 determined through the Beer–Lambert law was assumed to be independent of temperature. Variations in pressure did not influence the absorbance at ambient temperatures as evidenced by the unchanged absorptivity of pinacol at a constant concentration of 0.40 M in H_2O over the range of 0.1–35 MPa. Figure 2 shows the first-order rate constants under various conditions: scH_2O, superheated H_2O, and aqueous concentrated acid solutions. A dramatic enhancement in the reaction rate is seen on performing the reaction in scH_2O even in the absence of acid catalysts. The reaction in scH_2O at 25 MPa and 450 °C is over 100 times faster than those in 2.43 M H_2SO_4 [6a] and 0.71 M $HClO_4$[6b] under distillation conditions, and it is also 28 200 times faster than that in 0.871 M HCl at 46.7 MPa and 70 °C.[6d] Quantitative formation of pinacolone from pinacol by a classical method requires

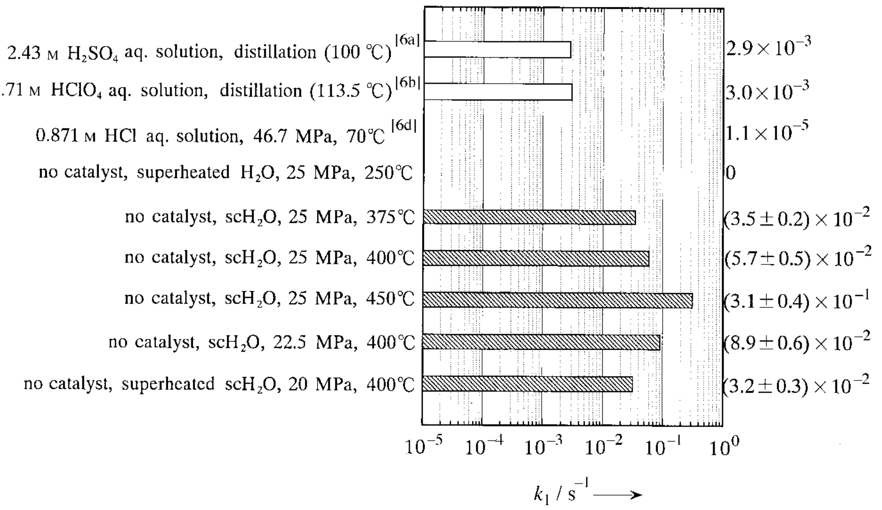


Figure 2. The first-order rate constants k_1 of the pinacol rearrangement to pinacolone. The acid catalyst and its concentration, solvent, pressure, and temperature are stated on the left. For our data 95 % confidence limits are given.

boiling it in 25 % H_2SO_4 for 3 h.[6e] The reaction is significantly accelerated by raising the temperature in the subcritical and scH_2O region; however, the reaction did not occur in superheated H_2O below 300 °C at constant pressures. Up to 60 min were needed to cause quantitative rearrangement of pinacol in superheated D_2O at 275 °C.[6f] Furthermore, no pinacol rearrangement has been reported to have been done in aqueous acid solutions at such high temperatures and pressures that the environment should be changed into the very corrosive state that exists in superheated H_2O,[7] and where the ionic behavior including dynamics should be entirely different from that at ambient conditions.[8] Figure 3 shows the change in the rate constant with pressure at a fixed temperature of 400 °C. It is thus noted that the rate constant in this pinacol rearrangement becomes maximized at the near-critical pressure of 22.5 MPa. For acid-catalyzed reactions the ion product K_w is of importance.[3c,f,i] However, the present results shown in Figures 2 and 3 cannot be explained by the change in K_w. At 400 °C and 5 MPa K_w is $10^{-33.18}$ and increases with increasing pressure; for example, to $K_w = 10^{-19.43}$ at 25 MPa, that is, near the critical pressure.[1d] This pressure dependence is different from the data shown in Figures 2 and 3, and we should consider microscopic/dynamic factors other than macroscopic/static properties, for example, the ionic product. We are sure that a change of hydrogen bonding is a key factor. The extent of hydrogen bonding η of water is also presented in Figure 3, where $\eta = 0$ is the limit of no hydrogen bonds for hot, low-density vapor and $\eta = 1$ corresponds to water at 25 and 0.1 MPa. Our Raman data concerning the hydrogen bonding of water has been successfully converted into the η scale[4d] by applying a linear relation between the NMR chemical shift δ of water and the η value.[9] The η value at the near-critical pressure shows a minimum and is remarkably lower than other superheated or supercritical conditions. It was thus demonstrated that the extent of hydrogen bonding reduces uniquely near the critical pressure, where dimers and/or monomers are predominant,[9] but monomers are, in part, further broken down into protons as a result of the large fluctuations in the structure of water.[4d] The organization of 4–10 water molecules is required to solvate the transferred protons,[10] and hence the water structure near the critical pressure becomes less able to accommodate the ejected protons. That is, the "local" proton concentration would be extremely high when the transferring proton cannot escape. Furthermore, the "local" concentration of pinacol around the protons would be very large near the critical pressure.[11] These effects may explain the observed enhancement of the rate of reaction.

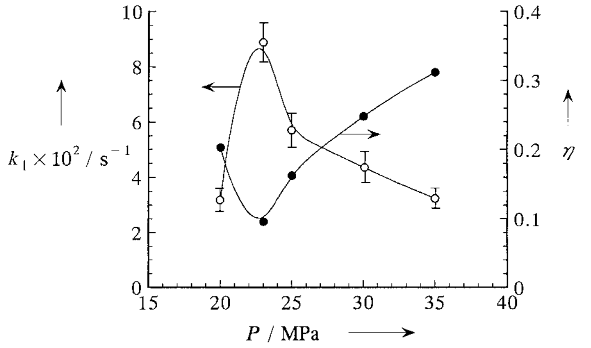


Figure 3. Relationship between the extent of hydrogen bonding η (●) and the first-order rate constant k_1 (○) for the pinacol rearrangement as a function of pressure at a fixed temperature of 400 °C. The 95 % confidence limits for the k_1 values are given by bars.

To demonstrate that this type of nucleophilic rearrangement in scH_2O is triggered by a decrease in the extent of hydrogen bonding in the near-critical region we have further attempted a Beckmann rearrangement of cyclohexanone oxime into ε-caprolactam without acid catalysts in superheated and scH_2O conditions by using a flow system. A new band of CO stretching assigned to the ε-caprolactam formed is found in the IR spectrum obtained near the critical point (not shown), whereas no bands for cyclohexanone, which is the hydrolysis product of cyclohexanone oxime, were observed. Furthermore, the ^1H NMR spectrum of the purified chief product obtained at 22.1 MPa and 375 °C is in agreement with that of the authentic sample. Therefore, in analogy to the pinacol rearrangement, the Beckmann rearrangement can also proceed without acid catalysts in scH_2O. Figure 4 shows the first-order rate constant versus temperature profile for the formation of ε-caprolactam at the critical pressure. One can also see an interesting temperature dependence. In this Beckmann rearrangement the ε-caprolactam is found, peculiarly, to be synthesized in the limited temperature range where the rate greatly increases as the temperature approaches the critical temperature. In Figure 4 the extent of hydrogen bonding η in water based on the Raman data[4d] is also represented. The η value shows a significant decrease above 370 °C and shows a minimal value at the critical

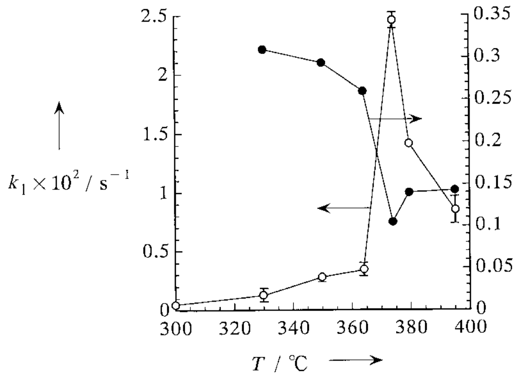
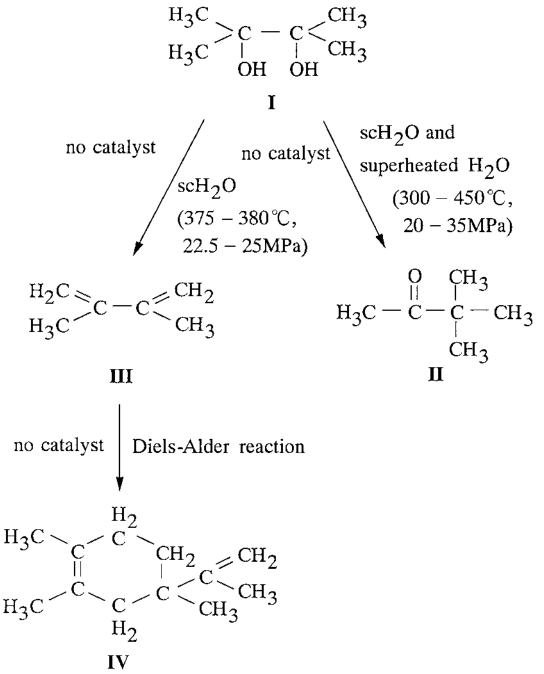


Figure 4. Relationship between the extent of hydrogen bonding η (●) and the first-order rate constant k_1 (○) for the Beckmann rearrangement to ε-caprolactam as a function of temperature at the critical pressure of 22.1 MPa. The 95 % confidence limits for the k_1 values are given by bars.

temperature. One can thus believe that a marked loss in the ability of water to accept a proton near the critical point is an important cause for the promotion of the Beckmann rearrangement as well as the pinacol rearrangement.

Supercritical water could also be used as a more profitable acid catalyst for dehydration and other reactions if its own "acidity" could be changed. Pinacolone was the sole product under scH_2O and superheated H_2O reaction conditions as described above; however, in the very limited near-critical region of 375–380 °C at 22.5–25 MPa, the formation of to 1,2,4-trimethyl-4-isopropenyl-cyclohexene (**IV**) rather than of pinacolone (**II**, Scheme 1) from pinacol (**I**) was observed for the first time. The conversion of **I** to **IV** is 50–70%. The analytical result obtained by GC-MS is in accord with that of the authentic sample. We think that pinacol is completely dehydrated into 2,3-dimethyl-1,3-butadiene (**III**), and then the intermolecular Diels–Alder reaction of **III** results in the formation of **IV**. Diels–Alder reactions have already been confirmed to occur in scH_2O in the absence of acid catalysts.[3e] The complete dehydration of **I** to **III** can be achieved with relatively weak acids such as HBr[12] by a mechanism different from that in the above-mentioned pinacol–pinacolone rearrangement. Thus, not only the "local" concentration of protons but also the "acidity" of scH_2O itself can be adjusted, especially in the near-critical region. Hence scH_2O is expected to find more important potential applications in organic synthesis. In a very compressible medium such as a supercritical fluid it may be possible, by controlling pressure and temperature, to adjust the mean distance between a solvent and a more massive solute species within a range where the mutual pair function is significantly varied.[13] It appears that the alternate path for dehydration may be associated with the tuning of the average distance between the protons generated and the substrate molecules, which results in a change in the solvation energy of the substrate.



Scheme 1. Noncatalytic reaction paths producing pinacolone (**II**, rearrangement) and 1,2,4-trimethyl-4-isopropenyl-cyclohexene (**IV**; Diels–Alder reaction) in scH_2O.

Experimental Section

The reactions were carried out under ambient to scH_2O conditions by using a high-pressure, high-temperature flow reaction system with a short path length (20 μm) FT-IR cell operable at 500 °C and 50 MPa (Figure 5), wherein the reactions could be conducted and monitored. The cell was constructed from Hastelloy C-276 and type II a diamond windows. This new development of the cell with the short path length diamond windows has

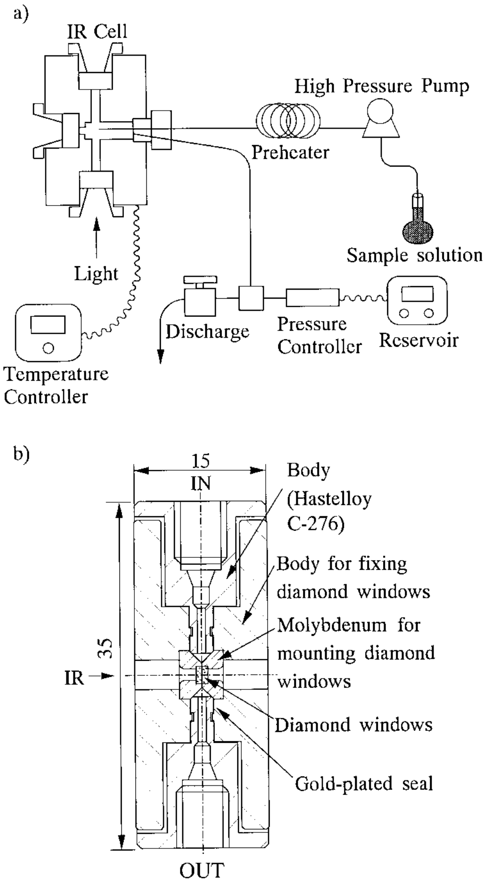


Figure 5. a) Schematic diagram of a high-temperature and high-pressure FT-IR flow reaction system. b) Cross-sectional view of a high-pressure and high-temperature optical IR cell. 15 mm and 35 mm represent the diameter and length, respectively.

enabled broad-range optical access for the first time in the near- and mid-IR region even in a scH$_2$O atmosphere. Aqueous solutions of pinacol (0.40 M) and cyclohexanone oxime (0.15 M) were introduced into the system with flow rates in the range of 0.07 to 2.0 mL min^{-1} (the reaction time varied from 4 to 215 s) using a high-pressure liquid pump, and pressure control was achieved by a back-pressure regulator. The temperature was then raised to the desired value. Once the system had stabilized, 50 spectra (4 cm^{-1} resolution) were summed in one destination file. Each file was normalized against the spectrum of pure H$_2$O under the same conditions. Furthermore, all of the products were identified qualitatively by ^{1}H NMR spectroscopy and GC-MS.

The frequency precision at the band center of the Raman OH symmetric stretch (ν_1) in the spectrum depends on changes in the optical pixel width of the charge-coupled device, and the resulting frequency error of the ν_1 mode is within 2.0 cm^{-1}.[8]

Received: March 22, 1999 [Z13199IE]
German version: *Angew. Chem.* **1999**, *111*, 3087–3091

Keywords: rearrangements · solvent effects · supercritical fluids · vibrational spectroscopy

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A 10^{10} Rate Enhancement of Phosphodiester Hydrolysis by a Dinuclear Aminopeptidase—Transition-State Analogues as Substrates?**

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The studies of metal complex based chemical models for hydrolytic metalloenzymes[1–3] have provided insight into the mechanistic roles of the metal ion(s) at the active-site and the coordinated nucleophilic water molecule in those enzymes.[4] However, these model complexes lack specific recognition and catalysis toward peptide substrates over phosphoester substrates, or vice versa, as a result of the absence of a well-defined active site. Conversely, enzymes have evolved to recognize one particular type of substrate and are able to stabilize the corresponding transition state,[5] such as the tetrahedral transition state in peptide hydrolysis which is very different from the trigonal bipyramidal transition state in phosphoester hydrolysis.[4] As a result each class of hydrolytic metalloenzymes can perform only one type of hydrolysis despite the presence of a highly activated ($>10^7$ in terms of pK_a) coordinated water molecule that is ready for nucleophilic attack on the substrate. Moreover, anionic tetrahedral phosphoesters,[6] phosphonates,[7] phosphoamidates,[8] and semiacetals,[9] resemble the transition-state *gem*-diolate of peptides, esters, and amides formed during hydrolysis and can serve as potential inhibitors for the corresponding enzymes. Thus, it seems unlikely that an enzyme with a single active site can hydrolyze both phosphoester and peptide substrates because the specific recognitions and hydrolytic pathways for these two types of substrates are quite different.

Herein we report a unique example of an "alternative" enzyme catalysis in which a dizinc aminopeptidase from *Streptomyces griseus* (sAP) exhibits remarkable hydrolytic activities toward both peptide and phosphodiester substrates. Thus, this enzyme can serve as an alternative dinuclear model system to provide further insight into the catalytic mechanism of metal-centered dinuclear hydrolysis.

The activity profiles obtained during the purification of the sAP[10, 11] and its thermo-deactivation at 69 °C show that the activity toward the hydrolysis of the phosphodiesterase substrate bis-*p*-nitrophenylphosphate (BNPP)[12] is always parallel to the activities toward the aminopeptidase substrates Leu-*p*-nitroanilide (Leu-*p*NA) and Lys-*p*NA (see data in ref. [13] and Table 1). This observation suggests that these two different types of hydrolytic reactions are possibly carried out by a single enzyme, and the decrease in both activities is attributable to thermo-denaturation of the sAP. Both activities are competitively inhibited by the dizinc aminopeptidase inhibitors bestatin,[14] 1-aminobutylphosphonate,[7] and Leu-

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[**] This work was partially supported by a PYF award (1996) from the University of South Florida.