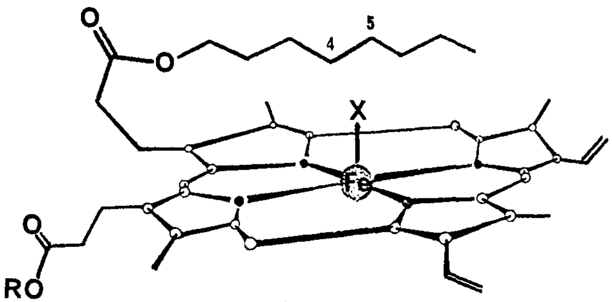
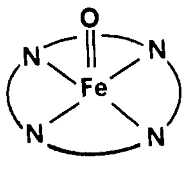


4

The regioselectivity observed for the side-chain hydroxylation of **4** is most easily accommodated by intramolecular oxygen transfer from the locus of the porphyrin-bound iron.

Two general mechanisms consistent with this regioselectivity are (a) oxygen rebound[6a] from iodosylbenzene to the substrate via an iron-oxo intermediate (**5**) and (b) oxygen activation by coordination of iodine to the porphyrin (**6**).



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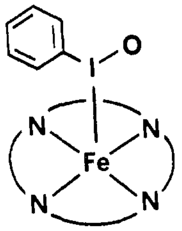

6

While the details of this reaction remain to be elucidated, path a is preferred on the basis of the observed cis olefin selectivity. Molecular models indicate little opportunity for substrate-porphyrin nonbonded interactions with **6**. The scope and mechanism of this porphyrin-catalyzed oxygen transfer, the exact constitution of the catalyst, and the relevance of this oxidation to the mechanism of cytochrome P-450 action are under continued study.

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(10) Under similar conditions, *cis,trans,trans*-1,5,9-cyclododecatriene gave a 2:1 mixture of the trans and cis monoepoxides. We thank Professor L. M. Stephenson for an initial sample of pure cis,trans,trans triene. High selectivity for trans epoxidation has generally been observed for the peroxy acids and alkyl hydroperoxides with this olefin. (a) Y. Kobayashi, *Tetrahedron Lett.*, 5093 (1972); (b) W. Stumpf and K. Rombush, *Justus Liebigs Ann. Chem.*, **687,** 136 (1965).

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(12) The distribution of octanediols in this *intermolecular* oxidation was similar to that observed for the oxidation of octanol by trifluoroperoxyacetic acid; cf. ref 11. GLC analyses of the reaction products were conveniently carried out as described in N. C. Deno and D. G. Pohl, *J. Am. Chem. Soc.*, **96,** 6680 (1974).

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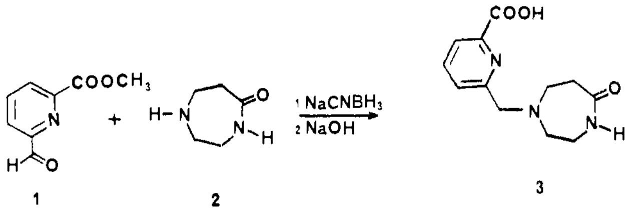
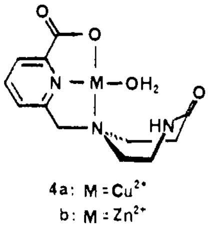
Rapid Amide Hydrolysis Mediated by Copper and Zinc

Sir:

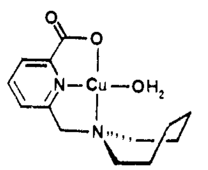
The catalytic role of divalent metal ions in metallohydrolases such as carboxypeptidase A and thermolysin has resisted unambiguous elucidation.[1] Although spectacular rate enhancements have been observed in model systems for ester hydrolysis[2] and nitrile hydration,[3] there has been no demonstration of significant catalysis of amide bond cleavage[4] except those involving Co(III).[5] Either the metal plays only a minor role in enzymic proteolysis or the model systems have failed to achieve some important criterion for catalysis. As part of a program to evaluate geometrical factors in metal catalyzed acyl transfer reactions, we have found very large rate enhancements for amide hydrolysis in copper and zinc complexes in which the metal is forced to lie perpendicular to the amide plane.

The requisite ligand (**3**) for these studies was prepared by reductive amination of aldehyde **1**[6,7] with azalactam **2**. The spectral and analytical properties of **3** were completely in accord with the assigned structure.[8]





4a: M = Cu^{2+}
b: M = Zn^{2+}
c: M = Co^{2+}
d: M = Ni^{2+}



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Lactam **3** was found to bind readily to divalent cations to form 1:1 complexes (**4**). Titrimetric formation constants (K_f) were found to be $>10^7$ (Cu^{2+}), 1.41×10^5 (Zn^{2+}), 1.23×10^4 (Co^{2+}), and 4.73×10^4 (Ni^{2+}).[9]

Titrations of the metal-amide complexes were consistent with tridentate coordination of the metal by the ligand and ligation of at least one additional water molecule. For the copper complex (**4a**), the pK_a of the metal-bound water was found to be extraordinarily low (7.6). In contrast, complex **5**

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Table I. Formation Constants, Acidity Constants, and Hydrolysis Rate Constants[a]

compd	metal	K_f	pK_a	k_{obsd} (s^{-1}) × 10^5	k_{rel}
3				0.88×10^{-6} M^{-1} [b]	1.0
4a	Cu^{2+}	$>10^7$	7.6	1.39[c]	1.6×10^6
4b	Zn^{2+}	1.41×10^5	$\gtrsim 8.5$	0.167[c]	1.9×10^5
4c	Co^{2+}	1.23×10^4	$\gtrsim 8.5$	<0.1	
4d	Ni^{2+}	4.73×10^4	$\gtrsim 8.5$	$\ll 0.1$	
5	Cu^{2+}		8.5		

[a] Hydrolyses were run in 0.1 M aqueous buffer and 0.5 M sodium perchlorate solutions at 50 ± 0.1 °C. At appropriate time intervals, aliquots or sealed ampules were mixed with freshly prepared *o*-phthalaldehyde–mercaptoethanol solutions in 0.2 M boric acid buffer containing 0.0125 M EDTA at pH 9.8. The formation of primary amine was followed by monitoring absorbance at 330 nm on a Cary 14 spectrophotometer (cf. ref 11). Sodium acetate, Hepes, and borate buffers were used over appropriate ranges. The rates observed were independent of buffer concentration. Suitable first-order plots were obtained over the entire pH range (correlation coefficients ≥0.98). [b] Second-order rate constant (s^{-1} mol^{-1}) extrapolated from data at pH 11–13 (50 °C) which gave a linear pH–rate plot with unit slope. [c] In all cases the product of metal catalyzed hydrolyses was shown by isolation to be the expected amino acid. In the case of **4b**, the progress of the hydrolysis was corroborated by ^{1}H NMR of the reaction mixtures.

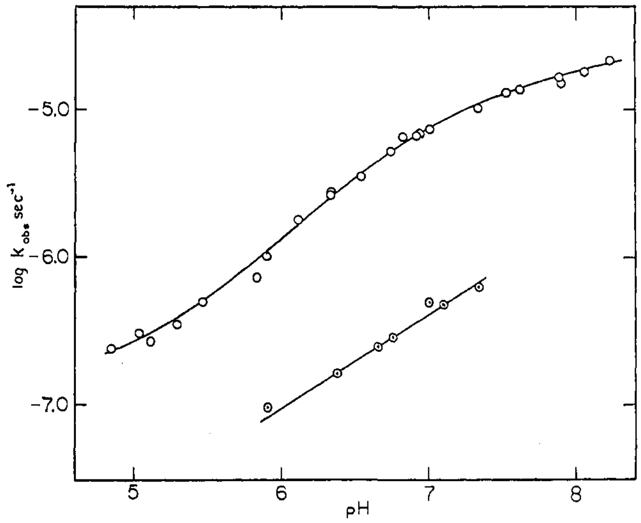


Figure 1. Plot of log k_{obsd} vs. pH for the hydrolysis of **4a** (○) and **4b** (⊙) in water at 50 °C. The solid line depicts calculated values according to eq 1 for **4a**.

was found to have a pK_a of 8.5, much more in accord with typical values for copper-bound water.[10]

The data presented in Table I show that hydrolysis of the copper complex **4a** was *more than a millionfold* faster than the calculated rate for the same lactam without metal at pH 7.6. Similarly, the rate observed for the zinc complex **4b** was a factor of 1.9×10^5 greater than that of the base catalyzed rate.

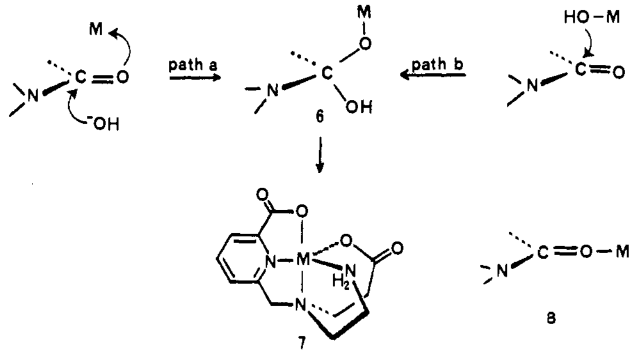
A pH–rate profile for the copper complex **4a** (Figure 1) gave a good fit to eq 1 where k_1 (1.41×10^{-7} s^{-1}) is the rate constant of a Cu^{2+}–OH_2 catalyzed reaction, k_2 (1.74×10^{-5} s^{-1}) is the rate constant of a Cu^{2+}–OH catalyzed reaction, k_{OH} (3.0 M^{-1} s^{-1}) is a base catalyzed reaction of Cu^{2+}–OH, and K_a ($10^{-7.13}$) is the acidity constant associated with the metal-bound water molecule. Any reasonable accommodation of the data required a kinetic pK_a significantly lower than the titrimetric value.

$$k_{obs} = \frac{k_1 a_H + k_2 K_a + k_{OH} K_a [^{-}OH]}{K_a + a_H} \tag{1}$$

Two mechanisms can reasonably be considered for this process: electrophilic activation of the carbonyl group toward hydroxide ion attack (path a) and nucleophilic addition of a metal-bound hydroxide ion (path b) (Scheme I).[12]

Although it is not possible to choose unambiguously between these kinetically equivalent mechanisms, path b is favored on several grounds. Space-filling CPK models indicate that a metal-bound water molecule in **4** would be within the van der Waals radius of the acyl carbon. The very low pK_a of water in the copper complex could be readily attributed to the electrophilic effect of the acyl carbon. The overall pH dependence is very similar in *absolute rate* as well as shape to the cyclization of 2-aminomethylbenzamide which can only proceed via a nucleophilic mechanism.[13] The distinct sigmoid shape of the pH-rate profile with a kinetic pK_a substantially lower than the titrimetric value is strongly suggestive of a change in the rate-limiting step from formation of tetrahedral intermediate **6** below pH 7 to its decomposition at high pH. The lack of a plateau for the hydrolysis of **4b** in the accessible pH range is thus consistent with the higher pK_a of water bound to zinc.

Scheme I



Another important feature of this model is the possible intervention of stereoelectronic effects in the decomposition of the tetrahedral intermediate **6**. Lone pairs are oriented antiperiplanar to nitrogen on *both* oxygens in **6**, a situation which favors expulsion of nitrogen.[14]

Thus, copper and, more interestingly, zinc are highly effective in promoting amide bond cleavage at physiological pH when the metal is placed above the amide π bond. In contrast, situations in which the metal is forced to lie in the plane of the amide bond (**8**) have shown limited acceleration or even inhibitory effects.[15]

Clearly, subtle geometric factors which lead to such spectacular rate changes must be carefully considered in relating metal catalyzed model reactions to the role of metals in metalloenzymes.

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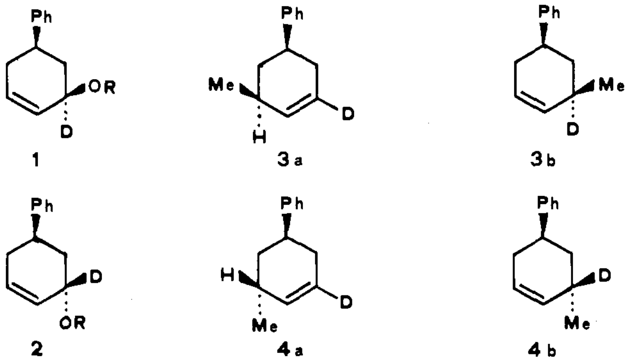
Conversion of Allylic Carbamates into Olefins with Lithium Dimethylcuprate. A New Formal S_N2' Reaction

Sir:

Coupling of $LiCuMe_2$ with acetates of cyclic allylic alcohols was shown by Goering[1] to proceed with anti attack and competitive α/γ substitution at the allylic system. An allylic cyclopentenyl lactone[2] and cyclohexenyl mesitoates,[3] where α/γ substitution appears to be controlled by steric factors, were found to react accordingly. Previous work on noncyclic allylic esters[4] showed that α/γ attack is little affected by the nature of the leaving group and primarily controlled by the degree of substitution of the two ends of the allylic system.[5] We report that coupling of *cis*- and *trans*-1-deuterio-5-phenyl-2-cyclohexenylcarbamates **1a** and **2a** (R = CONHPh) with $LiCuMe_2$ gives the syn S_N2' products, **3a** and **4a**, respectively. Exclusive syn γ attack on the allylic system has been thus achieved.



One enantiomer only shown

The esters **1a-f** and **2a-e**[6] (Table I) were obtained by standard procedures from alcohols **1** and **2** (R = H).[7] Experimental details of the coupling with $LiCuMe_2$ and results are reported in Table I. Control experiments on 3-*d* isomers and nondeuterated **1d** and **2d** are in accordance with the reported data. Products were >99% pure by GLC,[8] and gave mass, IR, and ^1H NMR spectra in accordance with the expected alkenes.[9] Cis and trans configurations were attributed according to the stereochemistry of conversion of allylic cyclohexenyl acetates[1] and mesitoates[3] with $LiCuMe_2$. Hydrogenation of the individual alkenes gave *cis*- and *trans*-1-methyl-3-phenylcyclohexane whose ^1H NMR spectra agree with the shielding properties of equatorial and axial methyl groups.[10] The ratios of **3a/3b** and **4a/4b** were obtained by evaluating the abundance of the vinylic protons relative to the aromatic protons through careful integration of their NMR signals; CH_3CD signals in the middle of the CH_3CH doublet could not be observed for the products obtained from **1a** and **2a.**

Table I. Reaction of 1-Deuterio-5-phenyl-2-cyclohexenyl Esters with $LiCuMe_2$[a]

R	cis esters	products		trans esters	products	
		3a/3b	**4a/4b**		**3a/3b**	**4a/4b**
CONHPh[b]	**1a**	>98/2		**2a**		>98/2
HCO[c]	**1b**		58/42	**2b**	45/55	
MeCO[c]	**1c**		51/49	**2c**	47/53	
PhCO[c]	**1d**		50/50	**2d**	50/50	
EtOCO[c]	**1e**		53/47	**2e**	46/54	
Me(Ph)NCO[c]	**1f**		54/46			

[a] 0.10 M solutions of $LiCuMe_2$ were prepared at 0 °C under nitrogen from CuI (Fluka) purified by extraction with THF (Posner, G. H.; Whitten, C. R.; Sterling, J. J., *J. Am. Chem. Soc.* **1973,** *95,* 7789–7800) and ~2 M ethereal LiMe (Fluka). Esters (2 mmol) were allowed to react for 24 h. Products (80–90% isolated yield) were obtained by quenching with 20% NH_4Cl, washing with 2 N HCl, 1 N $NaHCO_3$, and water, and distillation at 90 °C (bath) and 18 mm. [b] 3 equiv of $LiCuMe_2$ was used; reaction mixture was allowed to warm to 25 °C. [c] 2 equiv of $LiCuMe_2$ was used; reaction temperature was 0 °C.

As shown in Table I, anti attack and little preference for α or γ substitution were observed for esters **1b-f** and **2b-e,** while carbamates **1a** and **2a,** bearing an active hydrogen atom, gave exclusive γ substitution with syn attack on the allylic system within experimental error.

Complete control of regio- and stereochemistry of this conversion promises to be of value in synthetic work since the method appears of general applicability. For example, *N*-phenylcarbamates of nerol and linalol could be converted into the product of γ substitution without any detectable (GLC) contamination of the complementary regioisomer. Moreover, the allylic carbamates required are in general configurationally stable and easily available starting materials.[11] A brief study of the method was therefore undertaken. Addition of **1a** to 1 equiv of $LiCuMe_2$ immediately afforded a yellow precipitate (probably CuMe). No conversion was observed even on warming at 25 °C and the carbamate could be recovered after quenching. Displacement took place only when a second equivalent of $LiCuMe_2$ was present. These findings strongly suggest that lithium carbamates and $LiCuMe_2$ are involved in the syn γ substitution. On the other hand, the carbamate **1e** lacking active hydrogen atoms behaves like the other esters.

To our knowledge, (i) conversion of lithium carbamates is the first example of $LiCuMe_2$ coupling with syn attack to the allylic substrate; (ii) only one precedent (without stereochemical evidence) of γ displacement in which the concurrent α displacement is forbidden by factors different from substitution and/or steric hindrance is known at present;[11] (iii) displacement of a very poor leaving group has been achieved with $LiCuMe_2$ under mild conditions. These findings appear to be of high mechanistic interest both in the field of the controversial S_N2' reaction and of the copper reagents.

Neither steric arguments considered by Goering nor the orbital distorsion technique[12] as applied to $LiCuMe_2$ coupling with allylic epoxides[13] seem to satisfactorily explain our results. In our opinion, the exclusive syn γ substitution of lithium carbamates should be regarded as a consequence of a preferred concerted process, possibly occurring by an electron-transfer[14] mechanism, which results in a formal syn S_N2' reaction. The behavior of the other esters may now be accommodated by assuming that an anti α/γ attack of the reagent follows a rate-limiting allylic carboxylate ion-pair formation. An analogous hypothesis was considered in the case of allylic ep-

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