rate of cleavage =

$$\frac{k_{1k2}[\mathrm{ApA}][\mathrm{ImH^+}][\mathrm{Im}]}{k_{-1}[\mathrm{ImH^+}] + k_2[\mathrm{Im}] + k_3 + k_w} + k'[\mathrm{Im}] + k''[\mathrm{ImH^+}] \quad (1)$$

$$\text{rate of isomerization} = \frac{k_1k_3[\mathrm{ApA}][\mathrm{ImH^+}] + k_w}{k_{-1}[\mathrm{ImH^+}] + k_2[\mathrm{Im}] + k_3 + k_w} \quad (2)$$

appears in both numerator and denominator of eq 1, but for isomerization [Im] appears only in the denominator of eq 2. An increase in [Im] at constant [ImH^+] diverts the common intermediate I toward cleavage; this decreases the steady-state concentration of I and thus the rate of isomerization.

Such a negative kinetic effect would not be seen if the cleavage and isomerization paths did not branch from a common intermediate whose concentration is decreased when we catalyze one of the branches; the kinetic data are at early times, so Im does not appreciably decrease the concentration of the starting material itself. The effect is intellectually related to the demonstration that an isotope effect on one path affects the rate of another path,[6,7] first used by Katz[6] to show that two paths diverge from a common intermediate. Our kinetic version of it does not seem to be widely known or used. In any case, this work shows that the mechanistic conclusions from our previous studies of UpU reactions are indeed soundly based.

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A Planar Oxocuprate(II) Array via Heterometallic Alkoxide Chemistry

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Application of the molecular precursor method[1,2] to the synthesis of copper-based high-temperature superconductors[3] rests on our ability to produce copper-containing heterometallic alkoxides.[4] We have reported recently[5,6] on the chemistry of the anion $Zr_2(O^iPr)_9^-$, which is related to recent reports by the group of Mehrotra.[7,8] We report here our investigation of the coupling of this and related anions to $CuCl_2$ of relevance to hydrolytic routes to copper/oxo superconductors.

The reaction of $K_4Zr_2O(O^iPr)_{10}$,[6] $CuCl_2$, and water (2:4:1 mole ratio) in a refluxing THF solution produces a deep olive green solution. Workup (i.e., removal of solvent, extraction with pentane, concentration, and layering with 2-propanol) yields a blue-green solid (25% yield), which was established[9] to have the formula $Cu_4^{II}Zr_4^{IV}O_3(O^iPr)_{18}$ (**1**), eq 1. The centrosymmetric structure

$$2K_4Zr_2O(O^iPr)_{10} + 4CuCl_2 + H_2O \rightarrow Cu_4Zr_4O_3(O^iPr)_{18} + 8KCl + 2HO^iPr \quad (1)$$

is shown in Figure 1. The molecule contains a planar central

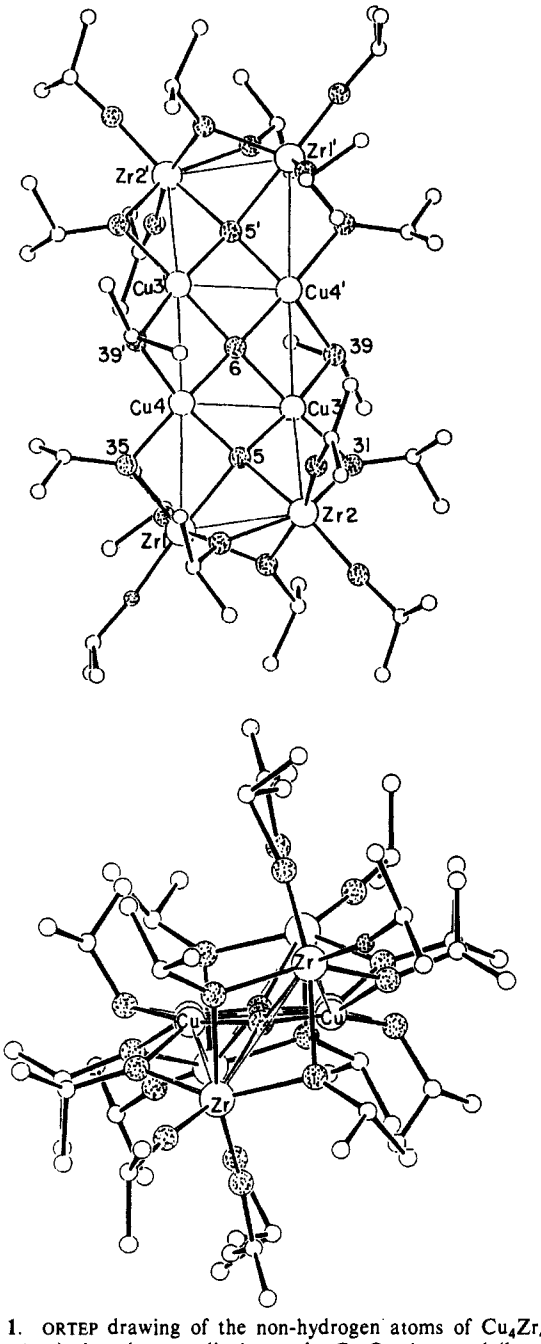

Figure 1. ORTEP drawing of the non-hydrogen atoms of $Cu_4Zr_4O_3(O^iPr)_{18}$ (top) viewed perpendicular to the Cu_4O_3 plane and (bottom) viewed along the edge of the Cu_4O_3 plane. Oxygen atoms are stippled. Lines between metals are for clarity and are not bonds. Primes indicate atoms related by a center of symmetry. Selected structural parameters (distances, Å; angles, deg): Cu3–O6, 1.968 (3); Cu4–O6, 1.966 (2); Cu3–O5, 1.880 (18); Cu4–O5, 1.896 (11); Cu3–O39, 1.892 (12); Cu4–O39′, 1.901 (12); Cu3–O31, 1.965 (11); Cu4–O35, 1.966 (11); Cu3′–Cu4 = Cu3–Cu4, 2.781 (8); cis angles O–Cu–O range from 84.5 (5)° to 104.0 (5)°.

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(9) Crystal data (−92 °C) for $Zr_4Cu_4C_{54}H_{63}O_{21}\cdot C_5H_{12}$: a = 12.673 (8) Å, b = 17.482 (13) Å, c = 10.877 (8) Å, α = 104.85 (3)°, β = 113.52 (3)°, γ = 75.65 (3)° with Z = 1 in space group $P\bar{1}$. $R(F)$ = 0.0798, $R_w(F)$ = 0.0777 for 3101 reflections with $F > 2.33\sigma(F)$.

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$Cu_4O_3(O^iPr)_2$ unit capped on two opposite ends by $Zr_2(O^iPr)_8$ units. At the crystallographic center of symmetry is an unusual four-coordinate *planar* O^{2-} ion. Only two other examples of this geometry are known.[10,11] An alternative description of the structure is that two face-shared bioctahedral $Zr_2O(O^iPr)_8^{2-}$ units bind through a pseudotetrahedral μ-O and two terminal O^iPr groups to a central planar $Cu_4O(O^iPr)_2^{4+}$ unit. This view leads to the idea that the $Zr_2(O^iPr)_8O^{2-}$ unit is a template (via $2O^iPr$ and the oxide) for growth of the planar ribbon of composition $Cu_4O(O^iPr)_2^{4+}$. Growth of this ribbon into a sheet [i.e., growth perpendicular to the $(\mu_4\text{-O})_3$ direction] is prevented by the isopropyl groups on the oxygens which bridge the coppers.

Spectroscopic analysis confirms the chemical formula and structure. IR spectra lack any O–H stretches, thus excluding the presence of hydroxyl or coordinated alcohol. The NMR spectra[12] of **1** lack the expected shifting and broadening associated with paramagnetic species. The methine region of the $^{13}C\{^1H\}$ NMR spectrum shows that the solid-state structure is maintained in solution: the expected five chemical shifts with approximately the correct integral ratio of 2:2:2:2:1 are found.[12] This conclusion is further supported by the methyl group ^1H and ^{13}C NMR peaks. These are sufficiently complex to indicate the retention of the solid-state structure (with diastereotopic methyls) in solution.

On the basis of the lack of paramagnetic characteristics in the NMR spectra, the magnetic susceptibility was investigated. This reveals that, while there are unpaired electron spins, these spins are coupled antiferromagnetically. The solution magnetic susceptibility (Evans method, 295 K, THF) yields a μ_{eff} of 0.9 μ_B/Cu. A variable-temperature (56–230 K) solid-state study shows the μ_{eff} to remain clearly constant at 1.1 μ_B/Cu from 230 to 100 K and then drop to 0.4 μ_B/Cu by 56 K. A mononuclear Cu^{2+} ion would have μ_{eff} = 1.73 μ_B. Our initial exploration of the parameter space of the three J values (two J_{cis} and one J_{trans}) of a Heisenberg Hamiltonian model appropriate to a centrosymmetric Cu_4^{8+} unit shows a singlet ground state. There are another singlet, a set of three triplets, and a quintet state at higher energies; one or more of the triplets become appreciably populated by 100 K, causing the rise in μ_{eff} from 56 to 100 K, but up to now it has not been possible to simulate the magnetic susceptibility data, and further work is in progress. The μ_{eff} fails to rise further even at 300 K because a quintet state lies too high to be significantly populated.

This heterometallic oxo alkoxide contains a planar Cu_4 array previously unknown in the chemistry of Cu(II). This work suggests that electropositive partner metals in heterometallic species can "guide" the growth of Cu/O patches which mimic some of the structural features of high T_c superconductors.[13] We believe that the thermodynamically favored unit (i.e., Zr_2X_9) of a "partner metal" in a heterometallic alkoxide can serve as a structural template for the planar Cu_4O array. In the present case, three colinear donor sites (i.e., one terminal alkoxide on each Zr together with the μ-O^{2-}) of two $Zr_2(O^iPr)_8O^{2-}$ units are complementary to the growth of a copper(II) oxide "ribbon" *two* coppers wide. Further growth along the ribbon direction (i.e., the O5–O5′ axis) would require insertion of the repeat unit $Cu_2O(O^iPr)_2$.

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Supplementary Material Available: A table of positional and thermal parameters for compound **1** (1 page). Ordering information is given on any current masthead page.

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(12) ^1H NMR (500 MHz, 20 °C, C_6D_6): methine peaks at δ 5.51 (septet, J = 6 Hz), 5.03 (br), 4.34 (septet, J = 6 Hz), 4.21 (m); methyl peaks at δ 2.53, 2.09, 1.47, 1.26 (all overlapping doublets), and 1.32 (d, J = 6). $^{13}C\{^1H\}$ NMR (125 MHz, 20 °C, C_6D_6): δ 72.0, 71.3, 70.0, 66.3, 66.2 (*C*H, int = 2:2:2:2:1), 33.2 (br), 29.0, 28.4, 27.3 (m), 26.7 (*C*H_3, int = 1:1:1:5:1).
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General Method for Incorporation of Modified N^{ω}-Cyanoguanidino Moieties on Selected Amino Functions during Solid-Phase Peptide Synthesis

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In peptide chemistry, incorporation of unusual or unnatural amino acids into bioactive peptides is an important tool in structure–activity relationship (SAR) studies and in the ultimate development of more stable and effective analogues.[1] It is desirable that unusual amino acids be easily prepared or readily available from optically active amino acids through derivatization and that the method be compatible with solid-phase peptide synthesis (SPPS). We describe herein a general method for the preparation of N^{ω}-cyano-$N^{\omega'}$-alkyl- or -arylhomoarginine-containing peptides as well as heterocyclic N^{ϵ}-lysine derivatives via modification of the ϵ-amino of lysine residues in orthogonally protected, resin-bound peptides.

In studies directed toward the development of potent and long-acting gonadotropin-releasing hormone[2] (GnRH) analogues, extensive use has been made of unusual amino acid substitutions to improve its therapeutic index.[3] Substitution of basic amino acids such as D-Arg in position 6 significantly increased potency of GnRH antagonists which contained a hydrophobic aromatic N-terminus.[4] Unfortunately this structural combination has been implicated in the deleterious histamine-mediated flare and wheal response seen when the peptides were injected subcutaneously in rats.[5] Our approach to this problem was to attenuate the basicity of various guanidino-containing residues of active analogues by modifying the guanidine moiety with an electronegative N^{ω}-cyano substituent.[6] This strategy proved successful in the development of the potent guanidino-containing histamine H_2 receptor antagonists (of which cimetidine is a member) where introduction of electron-attracting substituents such as cyano or nitro groups improved the effectiveness of the analogues in inhibiting gastric acid secretion.[7]

Peptides were synthesized by standard SPPS methodology either manually or on a Beckman 990 peptide synthesizer.[8] The ϵ-amino groups of lysine residues to be modified were protected as the (9*H*-fluorenylmethoxy)carbonyl (Fmoc) derivatives. The fully assembled peptide resin was treated with a 20% piperidine/DMF solution (10 min) to remove the Fmoc from the lysine side chain(s) followed by addition of diphenyl cyanocarbonimidate (PCI) in DMF at room temperature (Scheme I) to form intermediate A.[9]

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