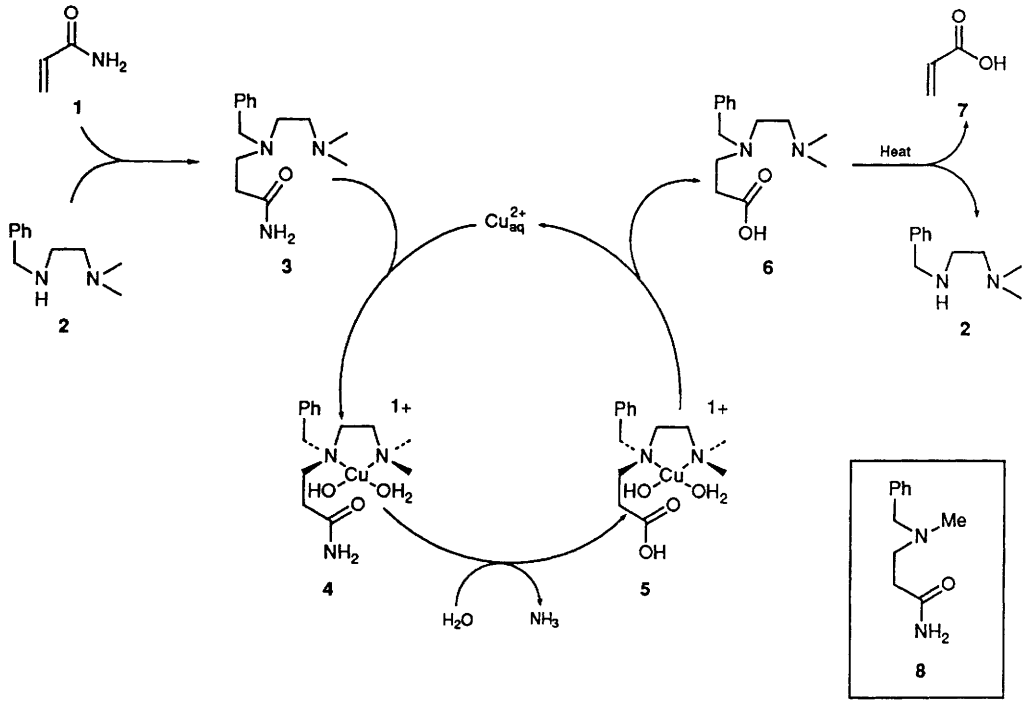
Copper(II)-catalysed Hydrolysis of an Unactivated Amide. Application of the Groves' Rule to the Hydrolysis of Acrylamide

Brook F. Duerr and Anthony W. Czarnik*

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210-1173, USA

Conjugate addition of *N*-benzyl-*N*′,*N*′-dimethylethylenediamine to acrylamide affords a chelating amide in which the amide carbonyl can coordinate to the bound metal only *via* a *six*-membered chelate; this compound demonstrates copper(II)-catalysed amide hydrolysis, in which each metal acts on at least five equivalents of substrate.

The hydrolysis of unactivated amides is exceptionally slow,[1] yet subject to efficient catalysis by enzymes.[2] This combination of properties makes the amide ideal as a mortar for the construction of proteins.[3] For several decades now, chemists have set their sights on the duplication of protease activity using abiotic means. Several divalent metals promote peptide hydrolysis.[4] Other examples of promoted (*i.e.*, stoichiometric) amide hydrolyses yielding large ($>10^5$-fold) increases in the rate of amide hydrolysis have been reported with the use of a variety of metals and their complexes.[5] A properly



Scheme 1

oriented carboxylate group can also promote amide hydrolysis.[6] Nevertheless, catalytic (*i.e.*, non-stoichiometric)† amide hydrolysis in an abiotic systems remains elusive. We now report what we believe to be the first observation of abiotic metal accelerated amide hydrolysis in which the metal is a catalyst: that is, it displays turnover behaviour.

The reactions shown in Scheme 1, including the well known reversible conjugate addition of amines to enones,[7] can be effected entirely in 0.2 mol dm^{-3} pH 7.50 HEPES buffer. Compounds **3** and **6** were synthesized independently,‡ and each step of the reaction sequence was studied separately. The presence of the UV-active benzyl group in diamine **2** allowed us to obtain kinetic measurements using reverse-phase HPLC. Without added metals the hydrolysis of the amide **3** (8 mmol dm^{-3}) to give the acid **6** is too slow at pH 7.50 to measure readily; no (≤2%) reaction had occurred after 650 h at 50 °C. As one basis for comparison, Still has measured the rate of peptide hydrolysis at 25 °C and pH 6–8 as $k_{obs} = 3 \times 10^{-9}$ s^{-1} ($t_{1/2}$ *ca.* 7 years).[1b]

With 1 equivalent of $Cu(ClO_4)_2$ at pH 7.5 and 23 °C, the hydrolysis of **3** (8 mmol dm^{-3}) occurs to at least 97% completion with $k_{obs} = 3.4 \times 10^{-6}$ s^{-1}. By comparison, no (<2%) hydrolysis of the control **8** is observed under these reaction conditions after 5 months, consistent with the expectation for a simple, noncoordinating amide. Attempts to use 1 equivalent of Cu^{II} above room temperature led to metal precipitation. However, the reaction of **3** (8 mmol dm^{-3}) with Cu^{II} (0.5 equiv.) at pH 7.5 and 50 °C proceeded to >97% completion and showed biphasic kinetics: $k_{obs} = 8.7 \times 10^{-6}$ s^{-1} (first half) and 4.6×10^{-6} s^{-1} (second half).

While observations of metal ion promotion of amide hydrolysis have been made before, the reaction shown in Scheme 1 is catalytic with respect to copper ion. The use of 8 mmol dm^{-3} **3** and 2 mmol dm^{-3} Cu^{II} (0.25 equiv.) at pH 7.5 and 50 °C resulted in 80% conversion to acid **6** after 10 days. Likewise, the use of 1.2 mmol dm^{-3} Cu^{II} (0.15 equiv.) at pH 7.0 and 50 °C resulted in 74% conversion to acid **6** after 15 days. These reactions, while not of enzyme-like speed, represent the first examples of metal-catalysed† amide hydrolysis in a synthetic system.

How can we rationalize catalysis using amide **3** when the effect of added M^{II} ions on other chelating amides is to give either no acceleration[8] or relatively inefficient, stoichiometric hydrolysis?[5a,b,e] Groves has demonstrated that amide chelates that do not involve carbonyl ligation to the M^{II} centre are hydrolysed more rapidly than amides in which oxygen coordination occurs. This idea, which we characterise as the 'Groves' rule,' has obvious implications for the mechanisms of metalloproteases, which themselves utilize divalent metal centres. Based on previous work, we know that the complexation of Cu^{II} to acid **6** is reversible;[9] the complexation of amide **3** will be weaker still.

Our working hypothesis follows. α-Amino amides such as glycinamide bind Cu^{II} tightly in 1:1 and 1:2 complexes; in either complex, the attack of hydroxide must occur externally. The external attack of hydroxide is fast if the metal centre is trivalent (*e.g.*, Co^{III})[5c] but not if the metal is divalent. In addition, the five-membered chelate is correctly sized for optimal stability; dissociation to glycine and Cu^{II}_{aq} does not occur quickly. Conversely, Cu^{II}_{aq} complexation by **3** leads to an equilibrating mixture of chelates in which amide coordination is not complete because the required six-membered chelate will be less stable than the five-membered chelate formed by glycinamide. Thus, while the hydrolysis of **4** can benefit from intracomplex metal hydroxide attack, the chelate of glycinamide and Cu^{II} presumably cannot. For the same

† The term catalytic may be defined narrowly or broadly. In our view, a *promoted* reaction involves an upper-limit stoichiometry of 'catalyst' to substrate; that stoichiometry may be 1:1 (as in $AlCl_3$ 'catalysed' Friedel–Crafts acylation) or 2:1 (as in Cu^{II}-promoted hydrolysis of glycinamide). Conversely, our view of metal ion *catalysis* requires that the product dissociates from the metal at a kinetically meaningful rate.

‡ Compound **3** gave suitable ^1H and ^{13}C NMR, and mass spectra, and satisfactory elemental analyses. Compound **6** has been reported previously (ref. 9).

reason, complex **5** is labile;[9] dissociation produces **6** and Cu^{II}_{aq}, which can act on another equivalent of amide **3**.

This is, in essence, one solution to the Groves' imperative for facilitated amide hydrolysis that provides for the possibility of turnover. Our conclusion that chelate ring size is of critical importance for the M^{II}-catalysed hydrolysis of chelating amides is clearly of relevance to the design of synthetic amidases with improved catalytic activity; such work is ongoing in this and in other groups.

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