Table I. Comparison of Photoproducts from Olefins 8 and 9 and Products from Independent Generation of Carbenes 10 and 11

| | Start-ing Olefin | Yield, $\%^a$ | | | | | |
Origin		12	13	14	15	16	17
Olefin 8[b]	25	4	1	9	9	5	13
Olefin 9[b]	21	6	2	30	9	4	5
Carbene 10[c]		7	3	83			
Carbene 11[c]					51	27	22

^{a} Determined by chromatography through silver nitrate impregnated alumina followed by gas chromatographic analysis. ^{b} Irradiations were conducted on 115-ml pentane solutions containing 2.58 g of olefin using a 450-W Hanovia mercury arc and quartz immersion well. ^{c} Generated by treatment of the corresponding tosylhydrazone with sodium hydride in diglyme at 170°.

ther study, it is consistent with the fact that these olefins all afford a mixture of saturated and unsaturated ethers on irradiation in methanol,[1,7] a behavior attributable to reaction via a low-lying $\pi,R(3s)$ excited state.[1] If the proposal is correct, rearrangement to carbenes represents the second observed chemical behavior of the $\pi,R(3s)$ Rydberg excited state in solution, along with nucleophilic trapping in hydroxylic media.[1]

Additional studies are in progress to elucidate further the nature, relative energies, and chemical properties of the various excited states of alkenes.

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(1) For part II see P. J. Kropp, E. J. Reardon, Jr., Z. L. F. Gaibel, K. F. Williard, and J. H. Hattaway, Jr., J. Amer. Chem. Soc., 95, 7058 (1973).
(2) Also formed in both hydroxylic and nonhydroxylic media is the isomer 2,3-dimethyl-1-butene. Simple double bond shifts without concomitant skeletal rearrangement are ubiquitous in olefin photochemistry and will be the subject of a separate report. All of the olefins reported in this communication undergo positional isomerization in competition with the described photochemical behavior.
(3) L. Friedman and H. Shechter, J. Amer. Chem. Soc., 81, 5512 (1959).
(4) Products were identified by direct comparison with commercial specimens or with material independently synthesized. Satisfactory analytical data were obtained for all novel compounds.
(5) Due to poor resolution, the photoproduct yield data from olefins 8 and 9 are only approximate. Moreover, since relative product yields from carbenes are highly dependent on solvent, temperature, and the mode of generation, precise quantitative comparisons between the photochemical data and the data from independent generation of the carbenes are probably not meaningful.
(6) The formation of carbene-derived products from benzene-photosensitized rearrangement of 3-phenylcycloheptene was recently reported; see S. J. Cristol and C. S. Ilenda, 167th American Chemical Society National Meeting, Los Angeles, Calif., April 1974, Abstract ORGN 113. It is not clear what relation, if any, this has with the photobehavior of the tetrasubstituted alkenes reported here, none of which afforded carbene-derived products on sensitization with p-xylene.
(7) P. J. Kropp and H. G. Fravel, in preparation.
(8) Alfred P. Sloan Research Fellow.

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Ligand Displacement of Glycylglycyl-L-histidine from Its Copper(II) Complex. A Proton-Assisted Mechanism Initiated at a Nonterminal Position

Sir:

The presence of L-histidine as the third amino acid residue in tri- and tetrapeptides enhances their ability to bind copper.[1] We find that coordination by the imidazole group causes large differences in the stability, in the pH response, in the electronic spectrum, and in the kinetics behavior of Cu^{II} when it is bound to glyglgy-L-his (structure I) rather
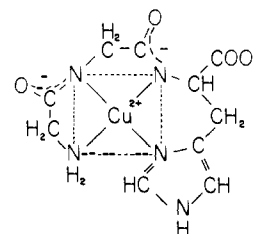
than to glyglygly. This work concerns the reactions of $Cu(H_{-2}glyglgy-L-his)^-$, which is the main species present in solution between pH 5 and 10. (An additional loss of a proton from the pyrrole nitrogen to form $Cu(H_{-3}glyglgy-L-his)^{2-}$ has a pK_a value of 10.7.[2]) Histidine is the third amino acid residue in serum albumin (human, bovine and rat) and it has been proposed that Cu^{II} binds to serum albumin using the same nitrogen donors shown in I.[3-6] We find that the kinetics of transfer of Cu^{II} from glyglgy-L-his to triethylenetetramine (trien) or to EDTA closely parallels the transfer of Cu^{II} from bovine serum albumin to EDTA[7] or from human serum albumin to trien or EDTA. The mechanism of the $Cu(H_{-2}glyglgy-L-his)^-$ reaction (and the parallel reactions of Cu^{II} in serum albumin) is unusual because the displacement process for this tripeptide starts at a central donor group (a peptide nitrogen) rather than at one of the terminal donor groups (the imidazole or the amino nitrogen).

Previous studies[8-11] of the displacement reactions of Cu^{II} from glycyl, L-alanyl, and L-leucyl tripeptide complexes have shown the existence of two main reaction pathways: (1) proton transfer to a peptide nitrogen followed by rapid solvent or ligand displacement, but with no rate dependence on the attacking ligand, and (2) nucleophilic attack by chelating ligands which show a high degree of steric selectivity. The nucleophilic pathway, when it is not sterically hindered, predominates over the proton-transfer mechanism even in neutral solutions. As a result the rates of displacement of Cu^{II} (and Ni^{II}) from the tripeptide complexes increase with increasing pH because the less-protonated chelating ligands are better nucleophiles. Thus, for the trien reactions with the gly, L-ala, and L-leu tripeptides, the reactivity is $H_2trien^{2+} \ll Htrien^+ < trien$. On the other hand, a ligand such as EDTA, with sterically hindered tertiary nitrogens, is a relatively poor nucleophile, so that solvent dissociation and various catalyzed pathways become important. The rate contribution of $HEDTA^{3-}$ with $(Cu(H_{-2}glyglgy)^-$ is not significant and the rate constant for $EDTA^{4-}$ is quite small (600 M^{-1} sec^{-1}) compared to the rate constant for trien (1.1 × 10^7 M^{-1} sec^{-1}) with $Cu(H_{-2}glyglgy)^-$.

The kinetics behavior of $Cu(H_{-2}glyglgy-L-his)^-$ is very different from the glycyl, L-alanyl, and L-leucyl tripeptides. Table I compares the rate constants for a number of reactions of the copper complexes of glyglgy and glyglgy-L-his. The presence of histidine as the third group in the tripeptide reduces the rate of the acid dissociation pathway by a factor of 25 and reduces the rate of solvent dissociation by a factor of 160. (The solvent and acid pathways cause partial dissociation of the tripeptides from copper and are followed by rapid reaction of additional acid or other complexing agents.) However, the most striking difference is in the rate of direct attack by trien which is a factor of 2 × 10^7 slower for glyglgy-L-his. This is consistent with the behavior of other reactions of peptide complexes which show the importance of the accessibility of equatorial sites for nucleophilic

displacement.[11] When histidine is present as the third amino acid residue, the reaction rate increases as the pH decreases. This effect of pH on the trien reactivity is the reverse of that found for $Cu(H_{-2}glyglygly)^-$ The rate expression in eq 1 holds from pH 6.5 to 8.3, and k equals 6.3

$$\frac{-d[Cu(H_{-2}glygly-L-his)^-]}{dt} =$$

$$k[H^+][H_2trien^{2+}][Cu(H_{-2}glygly-L-his)^-] \quad (1)$$

$\times 10^8\ M^{-2}\ sec^{-1}$. Similar rate expressions are found for EDTA and for histidine. The proton-assisted rate for the $HEDTA^{3-}$ reaction and for the $Hhis^{\pm}$ reaction are almost as large as the proton-assisted rate for H_2trien^{2+} (Table I). Thus, for $Cu(H_{-2}glygly-L-his)^-$ the large steric selectivity factor favoring trien over EDTA is not present in the pathway which combines ligand and proton attack.

As the trien concentration is increased at constant pH, the rate initially increases in accord with eq 1, but then levels off and eventually becomes independent of trien in accord with eq 2. The k_H value of $1.1 \times 10^7\ M^{-1}\ sec^{-1}$ corre-

$$\frac{-d[Cu(H_{-2}glygly-L-his)^-]}{dt} =$$

$$k_H[H^+][Cu(H_{-2}glygly-L-his)^-] \quad (2)$$

sponds to the rate constants found[10] for proton transfer to the peptide nitrogen with seven different $Cu(H_{-2}tripeptide)^-$ complexes where the k_H values are $(0.5-1.2) \times 10^7$ $M^{-1}\ sec^{-1}$. Hence, proton transfer to a peptide group of the glygly-L-his complex occurs prior to the trien reaction and greatly enhances the ability of trien to react with this complex. Furthermore, this proton addition activates the copper complex sufficiently to permit $HEDTA^{3-}$ to become an effective nucleophile. The proposed reaction mechanism using trien as an example is given in Figure 1, where path ABFG represents the combined proton and nucleophilic attack. The direct nucleophilic path AEG and the solvent dissociation path ADG are seen only at high pH (>8.5), where the rate is very slow. Below pH 6.5 the acid dissociation path ABCG contributes to the rate of formation of $Cu(trien)^{2+}$. This rate constant was determined by direct acid dissociation reactions below pH 5. The combined proton and trien attack predominates from pH 6 to 8.5. The intermediate species B is highly reactive toward nucleophilic displacement by trien, EDTA, or L-histidine and it is not sterically selective. The reactions cannot proceed by a complex in which the imidazole group is protonated and the carboxylate group is coordinated in its stead, because the reactions of other tripeptides[9-11] show that such a species would be unreactive with $HEDTA^{3-}$. The formation of this species also would be inconsistent with the proton-transfer limiting
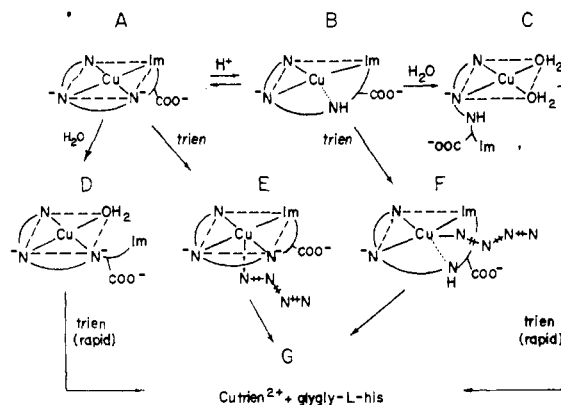

Figure 1. Proposed mechanism for the transfer of Cu^{II} from glygly-L-his to trien. Water molecules coordinated in the axial positions of Cu^{II} and the variable degree of protonation of trien are not shown. The pathway for the transfer depends upon pH, and the reactions at the left are observed at high pH while those at the right are observed in neutral solution and at low pH. Species B, C, D, E, and F are all reaction intermediates and are not present in appreciable concentrations. The predominant pathway in neutral solutions is the combined proton and nucleophilic attack shown in path ABFG, in which the displacement of the tripeptide starts at a middle rather than terminal dentate group. ADG is the solvent dissociation path observed at high pH with excess trien present. (This is from the trien-independent rate and the rate-limiting step is AD.) AEG is the direct nucleophilic attack by trien observed only at high pH. AB is the proton-transfer rate constant observed with excess trien in neutral solutions (independent of trien). ABCG is the proton-assisted solvent path observed at low pH in the presence of trien (but independent of trien concentration). ABC is the same proton-assisted solvent path observed by the direct reaction with acid below pH 5.

rate at high trien concentrations. On the other hand the proposed ABFG mechanism agrees with known proton-transfer rate constants of peptide complexes and with the steric effects of peptide complexes. Coordination rearrangement has been observed previously[12] to reduce steric hindrance to EDTA attack in the bis(tripeptide) complexes of Cu^{2+}.

A significant aspect of the proposed mechanism is that the displacement of the multidentate ligand (glygly-L-his) is initiated by protonation and coordinate bond disruption at a nonterminal dentate group. This is most unusual for multidentate ligand displacement reactions.[13] The ability of the protonated peptide group to be readily displaced by other multidentate ligands removes severe effects of steric hindrance.

If the data[8] for the reaction of H_2EDTA^{2-} reacting as an acid with copper-triglycine were reinterpreted in terms of a combined proton and $HEDTA^{3-}$ mechanism, the rate would equal $k[H^+][HEDTA^{3-}][Cu(H_{-2}glyglygly)^-]$ where k is $5.4 \times 10^9\ M^{-2}\ sec^{-1}$. However, this is the maxi-

Table I. Rate Constants for Reactions with $Cu(H_{-2}tripeptide)^-$, 25°

Reactants	L = glyglygly	L = glygly-L-his	Fig. 1 pathway
H_2O (partial dissoc)	$0.12\ sec^{-1}$ [a]	$0.75 \times 10^{-3}\ sec^{-1}$	AD
H^+ (proton transfer)	$4.9 \times 10^6\ M^{-1}\ sec^{-1}$ [a]	$1.1 \times 10^7\ M^{-1}\ sec^{-1}$	AB
H^+ (partial dissoc)	$4.9 \times 10^6\ M^{-1}\ sec^{-1}$ [a]	$1.8 \times 10^5\ M^{-1}\ sec^{-1}$	ABC
trien	$1.1 \times 10^7\ M^{-1}\ sec^{-1}$ [b]	$0.5\ M^{-1}\ sec^{-1}$	AEG
his$^-$	$2.3 \times 10^5\ M^{-1}\ sec^{-1}$ [c]	$\sim 0.3\ M^{-1}\ sec^{-1}$	
EDTA^{4-}	$6 \times 10^2\ M^{-1}\ sec^{-1}$ [d]		
H^+, H_2trien^{2+}		$6.3 \times 10^8\ M^{-2}\ sec^{-1}$	ABFG
H^+, $HEDTA^{3-}$	$<5 \times 10^9\ M^{-2}\ sec^{-1}$ [e]	$2.2 \times 10^8\ M^{-2}\ sec^{-1}$	
H^+, $Hhis^{\pm}$		$\sim 4 \times 10^8\ M^{-2}\ sec^{-1}$ [f]	

[a] Reference 8. [b] Reference 9. [c] G. R. Dukes and D. W. Margerum, *Inorg. Chem.*, **11**, 2952 (1972). [d] G. R. Dukes, G. K. Pagenkopf, and D. W. Margerum, *ibid.*, **10**, 2419 (1971). [e] The maximum possible value was obtained from the H_2EDTA^{2-} rate constant in ref 8. [f] This third-order rate constant, similar to the ABFG path, is found at pH 9-10 with histidine concentrations above 0.05 M. At pH 7-8 the apparent third-order rate constant is $1.6 \times 10^7\ M^{-2}\ sec^{-1}$, but the reaction mechanism is more complex and the rate constant represents a different rate-determining step.

mum possible value for k with $Cu(H_{-2}glyglygly)^-$ because the proton-transfer reactions from general acids with pK_a values near that of H_2EDTA^{2-} are known to contribute to the rate. Hence, this third-order rate constant with the tri-glycine complex must be less than $5 \times 10^9 \ M^{-2} \sec^{-1}$ as indicated in Table I. Such proton-assisted nucleophilic pathways for $Cu(H_{-2}glyglygly)^-$ are much too slow to be observed with the trien or L-histidine reactions because the direct nucleophilic pathways are much more favorable for tri-glycine. The proton-assisted nucleophilic pathway is, however, the predominant one for the reactions of Cu^{II} bound to bovine and to human serum albumin. We find the third-order rate constants corresponding to k in eq 1 are 2×10^7 $M^{-2} \sec^{-1}$ for H_2trien^{2+} and ca. $2 \times 10^6 \ M^{-2} \sec^{-1}$ for $HEDTA^{3-}$ with copper bound to human serum albumin.

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# $[_2\pi + _6\pi]$ Cycloaddition Reactions between Ligands Coordinated to an Iron Atom

Sir:

Both $[_2\pi + _4\pi]$ and $[_2\pi + _6\pi]$ concerted cycloaddition reactions are calculated to be exothermic processes and, on the basis of thermodynamic considerations alone, both processes might then be expected to occur with roughly similar facility. In practice, however, whereas there are hundreds of examples of the first of these processes known (i.e., the Diels-Alder reaction), there is to our knowledge not a single example of the second of these reactions reported. The reason for this striking difference is that the latter reaction is a "forbidden" one according to the Woodward-Hoffmann classification of concerted reactions and associated with this is an additional high energy term in the reaction coordinate of the process.

It has earlier been shown in these laboratories that cycloaddition reactions can apparently take place between two ligands simultaneously bonded to a transition metal;[1] fur-

thermore, from theoretical considerations[2] and the experimental results from other types of reactions,[3] we consider that "forbidden" reactions may become "allowed" when a transition metal is involved in the reaction. It therefore seemed possible that intramolecular cycloaddition reactions between a triene and trienophile, each being appropriately coordinated to a transition metal, may take place as indicated in eq 1. We now report examples of $[_2\pi + _6\pi]$ reactions which apparently are occurring by such a process.

(1)
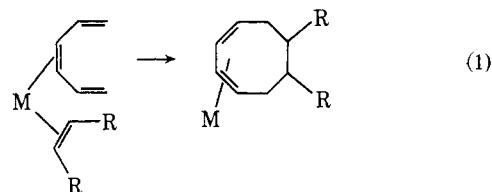
Irradiation of solutions of cycloheptatrieneiron tricarbonyl (1) and acetylene dicarboxylic ester in THF at 0° produced the complex 2 as yellow crystals, mp 109° (10%).[4,5] The structure of 2 was determined by X-ray analysis.[6] Of particular significance, in addition to demonstrating that $[_2\pi + _6\pi]$ addition had taken place, the X-ray study indicates that the acetylene moiety has added to the triene on the same face to which the iron atom is bonded, strongly suggesting that at some point in the reaction the acetylene was bonded to the Fe atom even though it is not in the product 2.
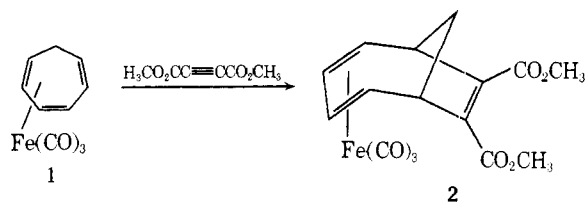
The iron tricarbonyl complex of tropone ethylene ketal (3), upon similar irradiation at 0° in THF with acetylene carboxylic ester, produced the complex 4 (20% yield) as well as the uncomplexed free ligand 5 (5%).

3

4   5
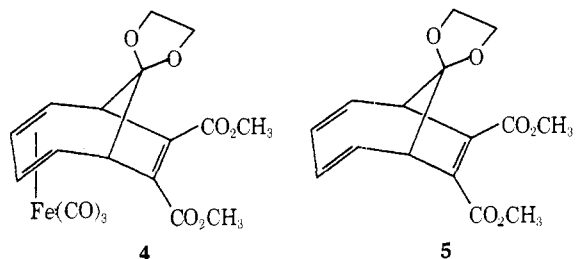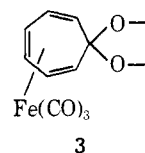
When solutions of the triene complex 3 in THF were irradiated at −78°, the lamp then turned off, and the acetylene added followed by warming to room temperature, the free [2 + 6] adduct 5 was isolated. This demonstrates that the formation of the new carbon bonds in the [2 + 6] process is a thermal, not photochemical, process.

The cycloaddition reaction of triene $Fe(CO)_3$ complexes and the acetylenic trienophiles under such conditions appears to be fairly general and offers promise of synthetic utility. Thus irradiation of complex 1 in THF at −78°, removal of the light source followed by addition of diphenyla-