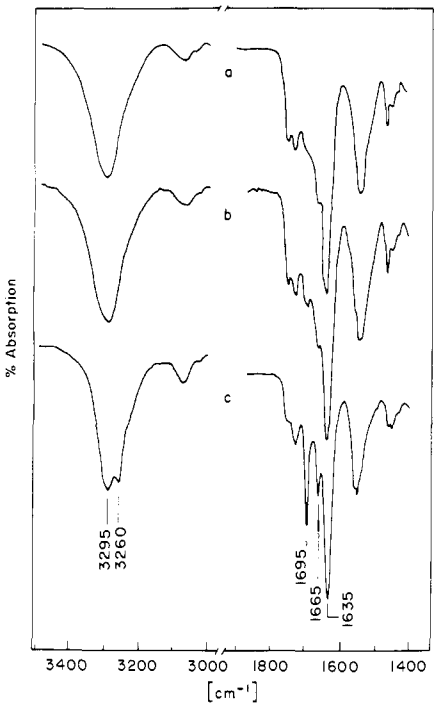

Figure 3. Infrared spectra of films of Cbz-Gly-L-Ser-(*O*-Bu^t)-L-Ser-Gly-*O*-stearyl ester cast from various concentrations in cyclohexane: (a) 3.54 mg/mL; (b) 0.290 mg/mL; (c) 0.060 mg/mL.

1695 cm^{-1} became more pronounced (Figure 3b,c). As the 1695-cm^{-1} band increases, the 1665-cm^{-1} band decreases while simultaneously there is a greater splitting between the 3295- and 3260-cm^{-1} bands. As the 1695-cm^{-1} absorption band is that found for the antiparallel β sheet, it would also be expected to exist for the β bend. Thus, under the conditions of high dilution, where the maximum CD values were observed, one finds a splitting of the amide A band at 3295 and 3260 cm^{-1} and in the amide I region one finds an extremely large 1695-cm^{-1} band in comparison with an extremely small 1665 and a large 1635-cm^{-1} band. Therefore, it is suggested that this IR spectrum is that of a β bend, while at higher concentrations intermolecular association exists. It appears that the ratio of the 1695-cm^{-1} band to the 1635-cm^{-1} band is larger in the β bend than that found in the antiparallel β sheet. For the tetrapeptide *N*-Cbz-Gly-L-Pro-L-Leu-Gly, which has been shown to be a type I β bend by x-ray crystallography,[14] when examined in Nujol mulls, the ratio of (r) 1687/1638 = 0.83. For the tetrapeptide studied therein, *N*-Cbz-Gly-L-Ser-(*O*-Bu^t)-L-Ser-Gly-*O*-stearyl ester, the ratio 1695/1635 = 0.68 was observed. For antiparallel β sheets, lower ratios of these two bands have been reported: poly-(L-Glu-ONa), β form, r = 0.41;[15] poly(L-Thr), r = 0.29;[11] (L-Glu-L-Val-L-Glu)$_n$, r = 0.10;[16] and (L-Glu-L-Glu-L-Val-L-Glu)$_n$, r = 0.13.[16] Thus, the magnitude of the 1695/1635 ratio may be indicative of β bends.

The infrared spectrum of a Nujol mull of crystalline *N*-Cbz-Gly-L-Pro-L-Leu-Gly, known to exist as a type-I β bend in the crystal,[14] showed the following bands: amide A region, 3360 (s), 3330 (m), and 3270 cm^{-1} (m); amide I region, 1687 (s), 1655 (m), and 1638 cm^{-1} (s). Thus the similarity of the IR spectrum shown in Figure 3c with that found for the type-I β bend establishes the conformation of the tetrapeptide synthesized therein.

On the basis of the IR spectra, the probability of β-turn formation for this sequence,[9] Gly-L-Ser-L-Ser-Gly, and the similarity of the CD spectrum to that calculated for a β bend,[7] it is believed that a type I β turn exists at high dilution in cyclohexane. Thus, the CD spectrum shown in Figure 1 is that for the type-I β turn. As 42% of identified β turns in proteins[9] are of the type-I β turn, and another 15% of β turns are found to be type-II β turns,[9] a total of 57% of β turns in proteins might be expected to display this spectrum, as Woody[7] has calculated that both type-I and type-II turns would display similar CD spectra. It may now be possible to calculate the conformation of proteins in solution with greater accuracy utilizing CD measurements if this β-turn spectrum is used in combination with those of other known conformations. Such studies are in progress.

While this work was in progress, the CD spectrum of another material believed to be in the β-turn conformation, poly(L-Ala$_2$Gly$_2$) was published,[17] which was similar to that calculated by Woody,[7] but with much larger magnitudes. As the extrema (227, 207.5 nm) are slightly displaced from those reported herein, as well as having lower magnitudes, it is not known whether this is the spectra of a different β turn, or whether there are interactions between β turns. Further research will be necessary to evaluate these possibilities.

References and Notes

(1) This is Publication No. 1197 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Mass. 02154. This work is supported in part by grants from the U.S. Public Health Service (GM17533) and the National Science Foundation (PCM76-21856).
(2) N. J. Greenfield and G. D. Fasman, *Biochemistry*, **8**, 4108 (1969).
(3) Y. H. Chen, J. T. Yang, and H. M. Martinez, *ibid.*, **11**, 4120 (1972); Y. Chen, J. T. Yang, and K. H. Chau, *ibid.*, **13**, 3350 (1974).
(4) A. J. Adler, N. J. Greenfield, and G. D. Fasman, *Methods Enzymol.*, **27**, 675 (1973).
(5) (a) P. N. Lewis, F. A. Momany, and H. A. Scheraga, *Proc. Natl. Acad. Sci. U.S.A.*, **68**, 2293 (1971); (b) I. D. Kunz, *J. Am. Chem. Soc.*, **94**, 4009 (1972); (c) P. N. Lewis, F. A. Momany, and H. A. Scheraga, *Biochim. Biophys. Acta*, **303**, 211 (1973); (d) J. L. Crawford, W. N. Lipscomb, and C. G. Schellman, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 538 (1973); (e) P. Y. Chou and G. D. Fasman, *Biochemistry*, **13**, 222 (1974); (f) P. Y. Chou, A. J. Adler, and G. D. Fasman, *J. Mol. Biol.*, **96**, 29 (1975); (g) P. Y. Chou and G. D. Fasman, *ibid.*, **115**, 135 (1977).
(6) C. M. Venkatachalam, *Biopolymers*, **6**, 1425 (1968).
(7) R. W. Woody in "Peptides, Polypeptides and Proteins", E. R. Blout, F. A. Bovey, M. Goodman, and L. Lotan, Ed., Wiley, New York, N.Y., 1974, p 338.
(8) D. M. Urry, M. M. Long, T. Ohnishi, and M. Jacobs, *Biochem. Biophys. Res. Comm.*, **61**, 1427 (1974).
(9) P. Y. Chou and G. D. Fasman, *J. Mol. Biol.*, **115**, 135 (1977).
(10) J. C. Howard, A. Ali, H. A. Scheraga, and F. A. Momany, *Macromolecules*, **8**, 607 (1975).
(11) For review see S. Kubota and G. D. Fasman, *Biopolymers*, **14**, 605 (1975).
(12) T. Miyazawa and E. R. Blout, *J. Am. Chem. Soc.*, **83**, 712 (1961).
(13) J. E. Shields, S. T. McDowell, J. Paulos, and G. R. Gray, *J. Am. Chem. Soc.*, **90**, 3549 (1968).
(14) T. Ueki, T. Ashida, M. Kakudo, Y. Sasada, and Y. Katsube, *Nature*, **216**, 205 (1967); *Acta Crystallogr., Sect. B*, **25**, 1840 (1969).
(15) G. D. Fasman, H. Hoving, and S. N. Timasheff, *Biochemistry*, **9**, 3316 (1970).
(16) K. D. Fraser, B. S. Harrap, T. P. MacRae, F. H. C. Stewart, and E. Suzuki, *J. Mol. Biol.*, **12**, 482 (1960).
(17) S. Brahms, J. Brahms, G. Spach, and A. Brack, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 3208 (1977).

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Generation of Stable Acidic Solutions of Copper(III) Chelates from Basic Copper(II) Solutions

Sir:

The discovery by Margerum and co-workers[1-3] of water-stable copper(III) chelates containing peptide linkages has generated much interest especially considering the proposed role of copper(III) in galactose oxidase and tyrosinase.[4-5] The major problem in the study of copper(III) chelates is their relative instability in neutral and basic solutions. In Table I it is quite apparent that, as the pH is raised, the decomposition

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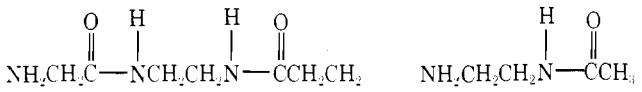
of copper(III) chelates increases dramatically.[6] To generate the copper(III) chelates the peptide protons of the chelating agent must be ionized; in many systems this requires a neutral to basic solution depending on the chelating agent. Since the copper(III) chelates are unstable at these pH values and apparently undergo internal redox reactions with some destruction of the ligand,[2] a method to generate stable (acidic) solutions of copper(III) chelates from basic copper(II) solutions is needed. We now wish to report a convenient method for the above. By passing (gravity flow or pump) basic solutions of copper(II) chelates through a continuous electrolytic cell with a packed graphite electrode,[7] acidic solutions of the copper(III) chelates were obtained by using excess current from a constant current source. The excess current oxidizes H_2O to produce H^+ and O_2 concomitantly with the copper(III) chelates. Furthermore, it is possible to adjust the current and/or flow rate to produce solutions of copper(III) chelates at various pH values.

For example, the copper(II) chelates of diglycylethylenediame (DGEN) and bis(*N*-acetylethylenediamine) (Aen) undergo amide deprotonation only in neutral (DGEN) or very basic (pH > 10) (Aen) solutions. As seen in Table I, the corresponding copper(III) chelates are not stable at these pH values. $[Cu(H_{-1}Aen)_2^+]$ is so unstable above pH 10 that cyclic voltammograms indicate a chemically nonreversible system. However, acidic solutions of $[Cu(H_{-1}Aen)_2^+]$ are stable enough (Table I) to allow the initiation of spectral or kinetic studies.



DGEN (I) Aen (II)

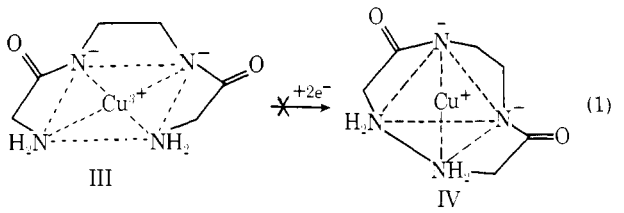
The two systems reported here were chosen for two reasons: (1) cationic copper(III) chelates were generated in contrast to those (neutral or anionic) reported by Margerum and coworkers[2] and (2) the donor set consists of two amino and two amide groups. The $E°$ value for $[Cu(H_{-2}DGEN)^+]$ is 0.77 V[8] in agreement with the prediction of Margerum and coworkers[2] that a system containing two amino and two ionized amide groups would have a potential of ~0.78 V. The estimated $E°$ value for $[Cu(H_{-1}Aen)_2^+]$ generation is 1.15 V,[9] possibly indicating the importance of a chelate effect and/or the nonplanarity of chelate rings in $[Cu(H_{-1}Aen)_2]$ compared with di-, tri-, and tetrapeptide copper(II) chelates.

The presence of copper(III) was confirmed by the loss of copper(II) bands at 520 $[Cu(H_{-2}DGEN)]$ and 550 $[Cr(H_{-1}Aen)_2]$ and the appearance of an intense absorption at 390 $[Cr(H_{-2}DGEN)^+]$[10] and 360 nm $[Cr(H_{-1}Aen)_2^+]$.[10] The four-line ESR spectra characteristic of the copper(II) chelates was lost upon electrochemical oxidation. The addition of ascorbic acid or catechol resulted in a reappearance of the copper(II) bands as well as the four-line ESR spectra, and, as previously noted above, the oxidized chelates are fairly stable in acid solution to substitution reactions which is characteristic of d^8 square-planar complexes.

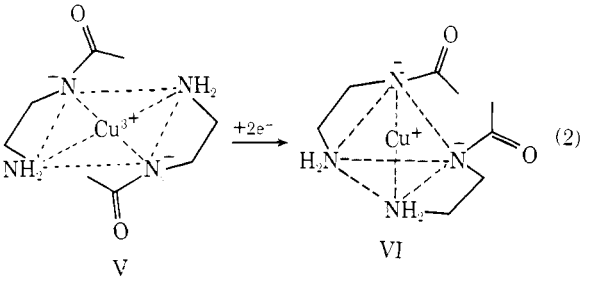
We originally intended to investigate copper(III) chelates as potential $2e^-$ transfer agents as first proposed by Hamilton and co-workers.[4,5] However, cyclic voltammograms of $[Cu(H_{-2}DGEN)]$ solutions indicate that reduction of the metal complex does not occur prior to that of solvent (0.1 M KNO_3). This may be a result of the usually observed geometries of copper(II) and copper(I) complexes (eq 1).[11,12] $[Cu(H_{-2}DGEN)]$ with its ionized amide groups requires a planar ligand geometry which is highly unusual for copper(I) (d^{10} systems) which tend to be tetrahedral or octahedral.[11] Therefore, it appears that peptide-containing chelating agents that require square-planar ligand geometries, i.e., di-, tri-, and tetrapeptides and their respective amides, will not be capable of copper(III) → copper(I) electron-transfer reactions. However, square-planar to tetrahedral stereochemical changes should be possible in systems in which the ionized amide groups do *not* force the ligand system into a planar geometry. For this reason, we also examined $[Cu(H_{-1}Aen)_2]$ which does, indeed, undergo reduction at −0.47 V (eq 2). For this particular system, the $E°$ value (copper(III) → copper(II)) of ~1.1 V is too large for the study of model biochemical oxidations; however, it should be noted that in enzymes the influence of the extensive protein network on electrochemical potentials may be quite large.[13] Finally, $[Cu(H_{-2}DGEN)^+]$ and $[Cu(H_{-1}Aen)_2^+]$ solutions are reduced by ascorbic acid and catechol; the systems are noncatalytic (with respect to copper(III)) in the presence of molecular oxygen.

Table I. Pseudo-First-Order Rate Constants for the Decomposition of Copper(III) Chelates at Various pH Values

$[Cu(H_{-2}DGEN)^+]$		$[Cu(H_{-1}Aen)_2^+]$	
pH	k_{obsd} (10^4 s^{-1})	pH	k_{obsd} (10^4 s^{-1})
4.00	2.24	2.1	2.8
5.00	2.44	3.0	3.5
6.50	3.41	4.0	fast
7.00	6.96		
8.00	fast		



III IV (1)



V VI (2)

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References and Notes

(1) G. L. Burce, E. B. Paniago, and D. W. Margerum, *J. Chem. Soc., Chem. Commun.*, 261 (1975).
(2) D. W. Margerum, K. L. Chellappa, F. P. Bossu, and G. L. Burce, *J. Am. Chem. Soc.*, **97**, 6894 (1975).
(3) K. P. Bossu, K. L. Chellapa, and D. W. Margerum, *J. Am. Chem. Soc.*, **99**, 2195 (1977).
(4) G. A. Hamilton, R. D. Libby, and C. R. Hartzell, *Biochem. Biophys. Res. Commun.*, **55**, 333 (1973).
(5) G. R. Dyrkacz, R. D. Libby, and G. A. Hamilton, *J. Am. Chem. Soc.*, **98**, 626 (1976).
(6) The rates of copper(III) chelate decomposition were studied at 25 °C and 0.1 M (KNO_3) by following the disappearance of the copper(III) peak at ~360 nm.
(7) W. J. Blaedel and J. H. Strohl, *Anal. Chem.*, **36**, 1248 (1964).
(8) $E°$ vs. NHE; the separation of peaks is 88 mV with a peak current ratio of 0.95.
(9) $E°$ vs. NHE; the system at pH > 10 is chemically nonreversible.
(10) $\epsilon_{max} = 7 \times 10^3$ M^{-1} cm^{-1} $[Cu(H_{-2}DGEN)]$ and $\epsilon_{max} = 6 \times 10^3$ M^{-1} cm^{-1} $[Cu(H_{-1}Aen)_2^+]$ based on extrapolations using rate constants in Table I.
(11) Although d^{10} systems are nonstereoselective, tetrahedral geometries are

usually favored over square-planar ones: G. Wilkinson and F. A. Colton, "Advanced Inorganic Chemistry", 2nd ed, Interscience, New York, N.Y., 1966, Chapter 29-H.
(12) Molecular models indicate that C–C bond breaking will occur if attempts are made to change III and IV.
(13) For a discussion of the role of "extrinsic" effects in the determination of redox potentials of $[Fe_4S_4(SR)_4^{x-}]$ systems, see C. L. Hill, J. Renaud, R. H. Holm, and L. E. Mortenson, *J. Am. Chem. Soc.*, **99**, 2549 (1977).

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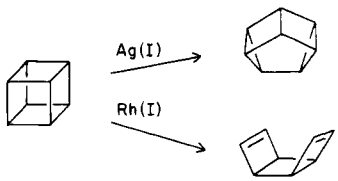
Octahydro- and Perhydro[0.0]paracyclophane

Sir:

Transition metal catalyzed reactions of strained polycyclic compounds offer special opportunities for the synthesis of new ring systems. Rearrangements of the cubane → cuneane type (eq 1) induced by silver(I) are most familiar and have certainly been used profitably.[1] We have also been considering the

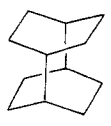


(1)

(2)

mechanistically important, but synthetically less appreciated, conversion of the type cubane → *syn*-tricyclooctadiene (eq 2) brought about by rhodium(I).[2] In this communication we describe the critical use of just this kind of metal-induced reaction for the tactical synthesis of octahydro- and perhydro[0.0]paracyclophanes.

The frame of the title system, **1**, tricyclo[4.2.2.2^{2,5}]dodecane, is constructed of two cyclohexane rings joined by single bonds at their 1 and 4 positions. This seems simple enough; yet the system is hardly known at all. Although at the core of the common anthracene photodimers (e.g., **2**), its properties there



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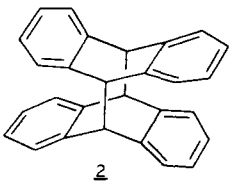
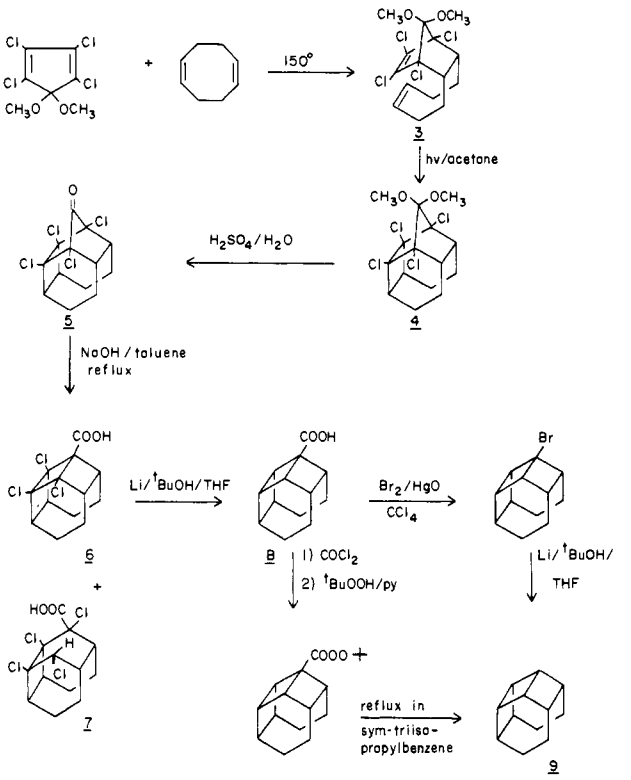


2

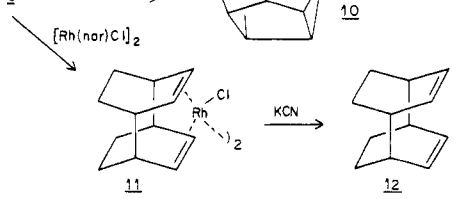
are totally obscured by the four fused benzene rings. More open examples have been obtained by Yang at Chicago by photoadditions of *cis*-1,2-dihydrophthalic anhydride to anthracene, naphthalene, and even benzene.[3] Until now, however, no other approach has been used successfully,[4] and there has been no report of any synthesis of the unsubstituted system.

Reaction of 5,5-dimethoxytetrachlorocyclopentadiene[5] with an eightfold excess of 1,5-cyclooctadiene at reflux gave a single 1:1 Diels–Alder adduct (**3**, 80%), mp 71–72 °C (lit.[6] mp 71–72 °C). It is assigned endo stereochemistry, for on ultraviolet irradiation in dilute (~0.1 M) solution in acetone it was closed to the cage isomer (**4**, 70%), mp >230 °C dec.[7] Deketalization in strong acid freed the corresponding ketone (**5**, 95%), mp >250 °C dec. Boiling **5** with dry, powdered sodium hydroxide suspended in toluene gave, after acidification, the carboxylic acids **6**, mp >270 °C (methyl ester mp 161.5–162 °C),[8] and **7** (methyl ester mp 170.5–171 °C)[9] in 55 and 42% yield, respectively. Dechlorination of **6** with lithium and *tert*-butyl alcohol in THF gave **8** (66%), mp 142–143 °C. Decarboxylation was achieved, as illustrated, by way of the Hunsdiecker



reaction and subsequent reduction or by thermolysis of the *tert*-butyl perester. The hydrocarbon **9**, pentacyclo[6.4.0.0^{2,7}.0^{3,12}.0^{6,9}]dodecane, was obtained pure in 25–30% yield by preparative gas chromatography on OV-17: mp >210 °C dec; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.87 (8 H, br s, $W_{1/2h}$ ~5 Hz), 1.92 (4 H br d, J ~ 9 Hz), 1.53 ppm (4 H, br d, J = 9 Hz); ^{13}C NMR (22.63 MHz, $CDCl_3$) δ 33.6 (4 C, d, J = 143 Hz), 31.3 (4 C, d, J = 136 Hz), 17.3 ppm (4 C, t, J = 128 Hz).

Reaction of **9** with a catalytic amount of silver tetrafluoroborate in benzene at 70 °C resulted in slow, quantitative rearrangement to cyclopropane **10**: IR ($CDCl_3$) ν 3030 cm^{-1}; ^{13}C NMR δ 56.5 (1 C), 54.2 (2 C), 34.8 (2 C), 28.7 (2 C), 25.8 (2 C), 23.3 (1 C), 19.3 ppm (2 C). The assignment of structure is based on precedents established for simpler systems[1] and is consistent with the NMR data. As expected, the reaction with rhodium(I) complexes took a different course. Treatment of **9** (0.56 M in $CDCl_3$) with an equivalent of [Rh(norbornadiene)Cl]$_2$ at room temperature gave free norbornadiene and rhodium complex **11** quantitatively in <30 min.[10] Diene **12** was



liberated by destruction of the complex with potassium cyanide in aqueous Me_2SO. It ligates rhodium(I) very strongly; it was not displaced significantly from complex **11** even by a high concentration of norbornadiene.

Diene **12**, octahydro[0.0]paracyclophane, is a colorless solid: mp 149.5–150 °C; IR ν 3040 cm^{-1}; ^{1}H NMR δ 5.93 (4 H, m), 2.72 (4 H, m), 2.15 (4 H, br d, J = 9 Hz), 1.38 ppm (4 H, br d, J = 9 Hz); ^{13}C NMR δ 134.3 (4 C, d, J = 160 Hz), 37.4 (4 C, d, J = 132 Hz), 22.6 ppm (4 C, t, J = 128 Hz). Ultraviolet irradiation in the presence of a sensitizer resulted in fairly ef-

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