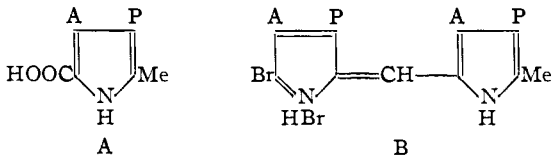
252–253°. This m.p. was not depressed by an authentic synthetic specimen, and the identity was confirmed by solubility, crystal form, visible and infrared spectra.



A = $CH_2 \cdot COOH$
P = $CH_2CH_2 \cdot COOH$

The m.p. of the synthetic porphin-1,3,5,7-tetraacetic acid-2,4,6,8-tetrapropionic acid octamethyl ester was not depressed by the purest uroporphyrin I methyl ester,[6] and their identity was confirmed by comparison of their visible spectra, infrared spectra, and X-ray powder photographs.

DIVISION OF PURE CHEMISTRY
THE NATIONAL RESEARCH COUNCIL S. F. MACDONALD
OTTAWA, CANADA R. J. STEDMAN[7]

RECEIVED MAY 21, 1953

(6) C. Rimington and P. A. Miles, *Biochem. J. (London)*, **50**, 202 (1951).

(7) National Research Council of Canada Postdoctoral Fellow.

A METHOD FOR THE SYNTHESIS OF CYCLIC POLYPEPTIDES

Sir:

The recognition of the cyclic nature of several of the antibiotic polypeptides has focused attention on the paucity of methods for the synthesis of cyclic peptides with rings larger than those of diketopiperazines. It is the purpose of this communication to report a procedure for the synthesis of such "cyclopeptides" by the catalytic hydrogenolysis of carbobenzoxypeptide azides. The method is exemplified by the synthesis of cyclo-DL-phenylalanylglycylglycine.

Carbobenzoxy-DL-phenylalanylglycylglycine hydrazide, m.p., 170–171° (*Anal.* Calcd. for $C_{21}H_{25}O_5N_5$: N, 16.4. Found: N, 16.0 (Dumas)), was converted to the azide in the usual manner. A solution of the azide (from 0.54 g. of the hydrazide) in 500 ml. of dry ethyl acetate was introduced slowly (at room temperature over a period of 26 hours) into 750 ml. of dry ethyl acetate containing *ca.* 2 g. of palladium black,[1] hydrogen being bubbled through the solution After 29 hours, the catalyst was removed by filtration, the solution was allowed to stand at room temperature overnight, and it was then concentrated *in vacuo* to a small volume. The resulting solid product was collected, washed with ethyl acetate, and reprecipitated from ethanol with ether; yield, 0.1 g. The cyclic tripeptide decomposed at 177–179° (*Anal.* Calcd. for $C_{13}H_{15}O_3N_3$: C, 59.8; H, 5.8; N, 16.1. Found: C, 60.0; H, 6.0; N, 15.6 (Dumas)). A determination of the molecular weight by the method of Cottrell[2] gave a value of 250, as compared with the theoretical value of 261. The Van Slyke nitrous acid method gave a value of 0.045 per cent. NH_2-N, indicating the absence of free amino groups. The product gave no color with ninhydrin (3 mg. heated with 2 ml. of 0.25 per cent. solution in 1:1 pyridine–water). Hydrolysis with 6 *N* hydrochloric acid at 100° for 24 hours, followed by chromatographic examination of the hydrolysate, gave a molar ratio of glycine to phenylalanine of 1.9:1. The cyclic peptide is soluble in methanol, ethanol, glacial acetic acid, and hot water; it is sparingly soluble in ethyl acetate, ether, cold water, or aqueous acid or alkali. When a suspension of the product in aqueous picric acid-sodium carbonate is heated, a permanent orange-red color is produced. 2,5-Diketopiperazine also gives a positive reaction,[3] but the color fades on standing. The infrared spectrum of the cyclic tripeptide differs from that of glycycl-L-phenylalanine anhydride.

While this work was in progress, the report of Boissonas and Schuman[4] appeared on the preparation of a cyclic peptide from D-leucylglycylglycine by treatment with ethyl chloroformate in dimethylformamide; no quantitative analytical data were presented, however, to establish the identity of the product with the desired cyclopeptide.

(1) C. A. Dekker and J. S. Fruton, *Methods in Medical Research*, **3**, 280 (1950).

(2) F. G. Cottrell, THIS JOURNAL, **41**, 721 (1919).

(3) E. Abderhalden and E. Komm, *Z. physiol. Chem.*, **139**, 181 (1924).

(4) R. A. Boissonas and I. Schuman, *Helv. Chim. Acta*, **35**, 2229 (1952).

DEPARTMENT OF BIOCHEMISTRY
YALE UNIVERSITY MILTON WINITZ
NEW HAVEN, CONN. JOSEPH S. FRUTON

RECEIVED MAY 7, 1953

EVIDENCE FOR COBALT HYDROCARBONYL AS THE HYDROFORMYLATION CATALYST

Sir:

It has been postulated[1] and indirect evidence has been presented[2,3] that cobalt hydrocarbonyl, a strong acid, is the catalyst for the reactions that occur under hydroformylation conditions (90–200° and 100–300 atmospheres of synthesis gas (mixtures of hydrogen and carbon monoxide) in the presence of cobalt). However, the presence of the hydrocarbonyl, $HCo(CO)_4$, during or after the reaction has been difficult to demonstrate. This communication presents experimental work which shows that (a) cobalt hydrocarbonyl is formed under hydroformylation conditions, and (b) pure hydrocarbonyl in the absence of carbon monoxide and hydrogen reacts with certain substrates at room temperature and 1 atmosphere to give products that are also secured from the same substrates under hydroformylation conditions.

(a) Treatment of a solution of dicobalt octacarbonyl in pyridine with synthesis gas at 120° and 230 atmospheres resulted in the conversion of all of the cobalt to the pyridinium salt of cobalt hydrocarbonyl, $[C_5H_5NH]^+[Co(CO)_4]^-$. The same salt was obtained by adding pure cobalt hydrocarbonyl to pyridine at room temperature.

(b) The products from experiments involving

(1) (a) O. Roelen, Office of Tech. Services, U. S. Dept. Commerce, PB 81383; (b) H. Adkins and G. Krsek, THIS JOURNAL, **70**, 383 (1948); (c) I. Wender and M. Orchin, U. S. Bureau of Mines Rep. of Investigations 4270 (1948).

(2) I. Wender, S. Metlin and M. Orchin, THIS JOURNAL, **73**, 5704 (1951).

(3) I. Wender, H. Greenfield, S. Metlin and M. Orchin, *ibid.*, **74**, 4079 (1952).

treatment of selected substrates with cobalt hydrocarbonyl at atmospheric pressure are compared in Table I with the products secured by reaction of the same substrates under hydroformylation conditions. The experiment at atmospheric pressure with cyclohexene is typical: Cobalt hydrocarbonyl (4.0 g., 0.023 mole) was collected in a liquid-nitrogen trap containing 7.0 g. (0.085 mole) of cyclohexene. On warming, the cobalt hydrocarbonyl dissolved in the olefin without noticeable decomposition. At about 15°, the solution began to darken, a small amount of gas was given off, and a noticeable amount of heat was evolved. Upon addition of 2,4-dinitrophenylhydrazine, the 2,4-dinitrophenylhydrazone of cyclohexanecarboxaldehyde was obtained from the reaction mixture; it melted at 167.5–168.3°[4] after one recrystallization from ethanol. The yield of cyclohexanecarboxaldehyde, determined from the weight of hydrazone obtained, was 16 per cent., based on cobalt hydrocarbonyl added.

Further, it has now been found that bases suppress the hydroformylation reaction. Thus, the hydroformylation of a mixture of 2,3-dimethylbutene-1 and -2 at 135° and 230 atmospheres of synthesis gas was completely inhibited in the presence of triethylamine. The hydrogenation of benzhydrol, which proceeds readily under the usual hydroformylation conditions,[5] failed to occur when pyridine was used as a solvent.

These results strongly support the hypothesis that cobalt hydrocarbonyl catalyzes the variety of reactions that occur under hydroformylation conditions.

TABLE I

PRODUCTS SECURED FROM VARIOUS SUBSTRATES BY HYDROFORMYLATION AND BY REACTION WITH COBALT HYDROCARBONYL

Substrate	Products: Hydroformylation conditions	Products: Cobalt hydrocarbonyl
Cyclohexene	Cyclohexanecarboxaldehyde[a]	Cyclohexanecarboxaldehyde[b]
Hexene-1 (excess)	Heptaldehyde[c]	C_7 aldehydes[d]
	2-Methylhexanal[c]	
	Hexene-2[d]	Hexene-2[d]
	Hexene-3[d]	Hexene-3[d]
	No hexene-1[d]	No hexene-1[d]
α-Methylstyrene	Isopropylbenzene[e]	Isopropylbenzene[f]
	3-Phenylbutyraldehyde[g]	C_{10} aldehyde[d,f]
Benzyl alcohol	Toluene[h]	Toluene[f]
	2-Phenylethanol[h]	
Benzhydrol	Diphenylmethane[h]	Diphenylmethane[d,i]
Triphenylcarbinol	Triphenylmethane[h]	Triphenylmethane[j]

[a] 35% yield. 2,4-Dinitrophenylhydrazone, m.p. 167.5–168.5°; see reference 4. [b] 16% yield. 2,4-Dinitrophenylhydrazone, m.p. 167.5–168.3°; a mixed melting point of the hydrazones from both sources gave no depression. [c] H. Adkins and G. Krsek, THIS JOURNAL, 71, 3051 (1949). [d] Identified by infrared analysis. We wish to thank Dr. R. A. Friedel for the spectra determinations. [e] 69% yield; $n^{25}D$ 1.4910. [f] Identified by mass spectrometric analysis. [g] 9% yield. The aldehyde was reduced to the corresponding alcohol; the infrared spectrum of this alcohol was identical with that of an authentic sample. [h] See ref. 5. [i] Reaction run in acetone. Product isolated by chromatographic adsorption on alumina in 33% yield; benzophenone (12%) was present. [j] Reaction run in acetone. Product obtained in 95% yield, m.p. 92–93°, not depressed when mixed with an authentic sample.

(4) G. Natta, P. Pino and E. Mantica, *Gazz. chim. ital.*, **80**, 680 (1950).

(5) I. Wender, H. Greenfield and M. Orchin, THIS JOURNAL, **73**, 2656 (1951).

SYNTHETIC FUELS RESEARCH BRANCH
BUREAU OF MINES
BRUCETON, PENNSYLVANIA
I. WENDER
H. W. STERNBERG
M. ORCHIN

RECEIVED APRIL 14, 1953

SYNTHESIS OF A REVERSIBLY CONTRACTILE AMPHOTERIC POLYPEPTIDE

Sir:

K. H. Meyer[1] has suggested that the contraction and relaxation of muscle may be attributed to the electrostatic attraction and repulsion of the ionized ammonium and/or carboxyl groups in the molecule of myosin. Recently Kuhn, Katchalski and their collaborators[2–6] have synthesized such mechanochemical systems composed of vinyl-type polyanions. Such systems are, of course, very useful and instructive, but the polypeptide-type polyampholyte is more desirable. We have now synthesized a three-dimensional amphoteric polypeptide network, composed of L-glutamic acid, L-lysine and DL-cystine residues and realized its reversible contraction and extension.

A mixture of anhydro-α-N-carboxy-ε-N-carbobenzoxy-L-lysine (8 millimoles), anhydro-α-N-carboxy-γ-benzyl L-glutamate (8 millimoles) and bis-(anhydro-N-carboxy)-DL-cystine (0.4 millimole) was dissolved in dry chlorobenzene–pyridine mixture and polymerized. After being precipitated with petroleum ether, the polymer was obtained quantitatively as a white powder. *Anal.* Calcd. for $[(C_{12}H_{13}NO_3)_{20}(C_{14}H_{18}N_2O_3)_{20}(C_6H_8N_2O_2S_2)_1]_n$: N, 8.8. Found: N, 8.7.

The reduction of this polymer by phosphonium iodide gave the hydriodide of a linear polypeptide consisting of L-glutamic acid, L-lysine and DL-cysteine residues, the amino acid composition of which was approximately the same as that derived from the starting monomer mixture. *Anal.* Calcd. for $[(C_5H_7O_3N)_{20}(C_6H_{12}ON_2\cdot HI)_{20}(C_3H_5ONS)_2]_n$: I, 32.2; N, 10.9; amino-N, 3.54. Found: I, 32.1; N, 10.8; amino-N, 3.46. This polypeptide hydroiodide was soluble in water, methanol and ethanol, and gave positive biuret and nitroprusside reaction.

When the foil, made on the glass plate from its methanolic solution, was soaked in commercial (not purified) ether overnight, it became insoluble in water and colored yellowish brown, due to the liberation of iodine (this color vanished by soaking in very dilute alkali). This insoluble matter is considered to be a network polypeptide in which cysteine residues were converted into cystine ones.

(1) K. H. Meyer, *Biochem. Z.*, **214**, 253 (1929); *Experientia*, **7**, 361 (1951).

(2) W. Kuhn, B. Hargitay, A. Katchalski and H. Eisenberg, *Nature* **165**, 514 (1950).

(3) A. Katchalski and H. Eisenberg, *ibid.*, **166**, 267 (1950).

(4) W. Kuhn, *Experientia*, **5**, 318 (1949).

(5) A. Katchalski, *ibid.*, **5**, 319 (1949).

(6) J. W. Breitenbach and H. Karlinger, *Monatsh. Chem.*, **80**, 311 (1949).