TABLE I

CARBOBENZOXY LYSINE TRIPEPTIDE DERIVATIVES

No.	Compound[a]	Molecular formula	Mol. wt.	M.p., °C. (cor.)	Nitrogen, % Calcd.	Found
	Carbobenzoxy tripeptide esters					
1	Z·Gly-Z·Lys-Gly·OBz (L)	$C_{33}H_{38}O_8N_4$	618.7	120–122	9.1	9.2
2	Z·Ala-Z·Lys-Ala·OEt (3L)	$C_{30}H_{40}O_8N_4$	584.7	191–192	9.6	9.7
3	Z·Ala-Z·Lys-Ala·OBz (3L)	$C_{35}H_{42}O_8N_4$	646.7	183–184	8.7	8.7
4	Z·Ala-Z·Lys-Ala·OBz (L-D-L)	$C_{35}H_{42}O_8N_4$	646.7	160–161	8.7	8.8
5	Z·Ala-Z·Lys-Ala·OBz (L-D-D)	$C_{35}H_{42}O_8N_4$	646.7	173–174	8.7	8.8
6	Z_2·Lys-Z·Lys-Z·Lys·OMe (3L)	$C_{51}H_{64}O_{12}N_6$	953.1	142–145	8.8	8.8
7	Z_2·Lys-Z·Lys-Z·Lys·OBz (3L)	$C_{57}H_{68}O_{12}N_6$	1029.2	153–154	8.2	8.3
8	Z_2·Lys-Z·Lys-Z·Lys·OBz (L-D-L)	$C_{57}H_{68}O_{12}N_6$	1029.2	141–142	8.2	8.3
9	Z_2·Lys-Z·Lys-Z·Lys·OBz (L-D-D)	$C_{57}H_{68}O_{12}N_6$	1029.2	151–152	8.2	8.3
	Carbobenzoxy tripeptide hydrazide					
10	Z·Ala-Z·Lys-Ala·$NHNH_2$ (3L)	$C_{28}H_{38}O_7N_6$	570.6	208	14.7	14.6

[a] The following abbreviations are used (*cf.* ref. 2, 3, Table I, footnote *a*): Z: carbobenzoxy, C_6H_5·CH_2OCO; Gly: $NH(CH_2)CO$; Ala: $NH(CHCH_3)CO$; Lys: $NH(CHC_4H_8NH_2)CO$; peptide linkage indicated by hyphen; Me: CH_3; Et: C_2H_5; Bz: $C_6H_5CH_2$; configuration follows compound in parentheses. *E.g.*, α,ε-dicarbobenzoxy-L-lysyl-ε-carbobenzoxy-D-lysyl-ε-carbobenzoxy-L-lysine benzyl ester: Z_2·Lys-Z·Lys-Z·Lys·OBz (L-D-L); L-alanyl-D-lysyl-D-alanine monohydrochloride: H·Ala-Lys-Ala·OH·HCl (L-D-D).

TABLE II

LYSINE TRIPEPTIDES: ANALYTICAL DATA AND SPECIFIC ROTATION IN 0.5 *N* HCl (BASIS: FREE PEPTIDES)

No.	Compound[a]	Molecular formula	Mol. wt.	Nitrogen, % Calcd.	Found	Amino N, % Calcd.	Found	HCl, % Calcd.	Found	Neut. equiv.[b] Calcd.	Found	$[\alpha]^{25}D$ (c = 2)
11	H·Gly-Lys-Gly·OH·HCl (L)	$C_{10}H_{20}O_4N_4$·HCl	296.8	18.9	18.6	..	..	12.3	12.3	148	148	−32.1
12	H·Ala-Lys-Ala·OH·HCl (3L)	$C_{12}H_{24}O_4N_4$·HCl	324.8	17.3	17.2	8.6	8.6	11.2	11.4	162	163	−42.5
13	H·Ala-Lys-Ala·OH·HCl (L-D-L)	$C_{12}H_{24}O_4N_4$·HCl	324.8	17.3	17.1	8.6	8.3	11.2	11.1	162	161	+14.2[c]
14	H·Ala-Lys-Ala·OH·HCl (L-D-D)	$C_{12}H_{24}O_4N_4$·HCl	324.8	17.3	17.1	8.6	8.5	11.2	11.0	162	159	+12.4[d]
15	H·Lys-Lys-Lys·OH·3HCl (3L)	$C_{18}H_{38}O_4N_6$·3HCl	511.9	16.4	16.2	10.9	10.9	21.4	21.4	128	133	− 2.2[d]
16	H·Lys-Lys-Lys·OH·3HCl (L-D-L)	$C_{18}H_{38}O_4N_6$·3HCl	511.9	16.4	16.3	10.9	11.2	21.4	21.2	128	129	+27.7[e]
17	H·Lys-Lys-Lys·OH·3HCl (L-D-D)	$C_{18}H_{38}O_4N_6$·3HCl	511.9	16.4	16.5	10.9	10.9	21.4	21.2	128	130	+54.9[e]

[a] See Table I, footnote *a*. [b] Neutralization equivalent, obtained by titration in alcohol (Ellenbogen and Brand, Am. Chem. Soc., Philadelphia Meeting, April, 1950, Abstracts p. 56-C). [c] At 19°. [d] At 24°. [e] At 22°.

In the case of Compound 1, 0.025 mole of Z·Gly-Z·Lys·$NHNH_2$ (L, ref. 3, Cmpd. 13) is dissolved in a mixture of 40 cc. of glacial acetic acid, 24 cc. of 5 *N* HCl and 220 cc. of water, treated with 0.028 mole of sodium nitrite and taken up in 250 cc. of cold ether. Following the usual procedure, the azide solution is added in one portion to a cold, dry, ethereal solution of glycine benzyl ester (previously prepared from 0.03 mole of its hydrochloride).

In the case of Compounds 2–5, 0.015 mole of Z·Ala-Z·Lys·$NHNH_2$ (L-L or L-D, ref. 3, Compds. 14, 15) is dissolved in a mixture of 65 cc. of glacial acetic acid, 15 cc. of 5 *N* HCl and 100 cc. of water, treated with 0.018 mole of sodium nitrite, followed by an additional 150 cc. of ice-cold water. The azide is then extracted with 200 cc. of cold ethyl acetate, washed and dried in the usual way, and added in one portion to a cold, dry, ethereal solution of alanine benzyl (or ethyl) ester (previously prepared from 0.024 mole of its hydrochloride).

In the case of Compounds 6–9, 0.06 mole of Z_2.Lys-Z.Lys.$NHNH_2$ (L-L or L-D, ref. 3, Cmpds. 16, 17) is dissolved in a mixture of 70 cc. of glacial acetic acid and 50 cc. of water, treated with 0.075 mole of sodium nitrite, followed by an additional 200 cc. of ice-cold water. The azide is then extracted with 200 cc. of cold ethyl acetate, washed and dried in the usual way, and added in one portion to a cold, dry solution (1:1 ethyl acetate–ether) of ε-carbobenzoxy-lysine benzyl (or methyl) ester (previously prepared from 0.1 mole of its hydrochloride).

In all cases precipitation of the coupling products starts within 30 minutes. After standing for about 20 hours at room temperature, the reaction mixture is cooled to about −10°, the material collected and washed with ether. Compound 1 is recrystallized from ethyl acetate–petroleum ether, Compounds 3–5 from 85% methanol, and Compounds 2, 6–9 from 95% ethanol. The yield of pure recrystallized carbobenzoxy tripeptide esters is 70–80% based on the hydrazide use.

Carbobenzoxy Tripeptide Hydrazide (Compound 10).—Z·Ala-Z·Lys-Ala·$NHNH_2$ (3L) is prepared in the usual manner[2] from Compound 2, except that refluxing with hydrazine hydrate in alcohol is carried out for one and a half hours instead of one hour. The yield of pure recrystallized (95% ethanol) product is 75% based on the ester used.

Tripeptides (Compounds 11–17).—The tripeptides are isolated as hydrochlorides, which are all more or less hygroscopic.

Hydrogenolysis of 0.005 mole of a carbobenzoxy tripeptide benzyl ester is carried out in 100 cc. of 85% acetic acid, containing the amount of *N* HCl required for the epsilon amino groups, with palladium black as catalyst in a rapid stream of hydrogen. After cessation of CO_2 evolution, hydrogenolysis is continued for another two hours. Concentration of the filtrates *in vacuo* (bath temperature at 40°) results in oils which are dried over P_2O_5 in high vacuum. The glass-like solids (though sometimes crystals appear at this stage) crystallize from warm 95% methanol upon the addition of absolute ethanol. Recrystallization from the same solvents results in pure peptide hydrochlorides in 70–80% yield. For analysis and rotation measurements, the tripeptide hydrochlorides are dried at 56° in high vacuum.

This work was aided by a contract between the Office of Naval Research, Department of the Navy, and Columbia University (NR 122-260).

DEPARTMENT OF BIOCHEMISTRY
COLLEGE OF PHYSICIANS AND SURGEONS
COLUMBIA UNIVERSITY
NEW YORK 32, N. Y.

RECEIVED APRIL 16, 1951

The Magnetic Susceptibility of $Co^{+++}aq.$

BY HAROLD L. FRIEDMAN, JOHN P. HUNT, ROBERT A. PLANE AND HENRY TAUBE

Co(III) in solid K_3CoF_6 has a magnetic moment corresponding to 4 unpaired electrons[1] while $Co(NH_3)_3F_3$, $Co(NH_3)_6Cl_3$ and $K_3Co(CN)_6$ are dia-

(1) Cartledge quoted (p. 109) in "The Nature of the Chemical Bond," Pauling, Cornell University Press, Ithaca, N. Y., 1939.

magnetic.[2] It is of particular interest to compare the magnetic moments of the ions in the series $CoF_6^{\equiv}$, $Co(H_2O)_6^{+++}$ and $Co(NH_3)_6^{+++}$. Water is intermediate in polarizability between F^- and NH_3, and no theoretical basis exists for predicting whether the aquo complex in the ground state will be a non-penetration complex of the type of $CoF_6^{\equiv}$, or a penetration complex of the type of $Co(NH_3)_6^{+++}$. Bommer[3] reports measurements on solids with compositions $Co_2(SO_4)_3 \cdot 18H_2O$ and $RbCo(SO_4)_2 \cdot 12H_2O$. Within the limits of his rather large experimental error, due to the unavoidable presence of Co(II), he concluded that Co(III), which in the alum presumably exists as $Co(H_2O)_6^{+++}$, is diamagnetic.

The lability observed for the exchange of water between the aquo cobaltic ion and the solvent,[4] led us to a study of the magnetic moment of the ion in solution. A modified Quincke method was used for the measurement of the susceptibility, comparisons being made of susceptibilities of pairs of solutions identical in composition except that one member of each pair contained Ga(III) or Al(III) instead of Co(III). The solutions were strongly acid and contained perchlorate ion as the only anion. It seems unlikely that effects due to complex ion formation or hydrolysis are important in this environment. The measurements are complicated however due to the formation of the paramagnetic substances Co(II) and O_2 as products of the reduction of Co(III) by water. To correct for the magnetic effects due to these products, reference solutions were made up to contain them at concentrations equal to those in the cobaltic solutions. The rate of oxidation of water by Co(III) was reduced by making the measurements at 1°.

Experimental

The solutions of cobaltic perchlorate were prepared by electrolytic oxidation of a solution of cobaltous perchlorate in *ca.* 4 *M* $HClO_4$. The cobaltous perchlorate was purified by recrystallization from water.

Total cobalt was determined (±0.3%) by electrodeposition as metal,[5] perchlorate (to ±0.3%) by the tetraphenylphosphonium chloride method,[6] Al^{+++} and Ga^{+++} by using 8-hydroxyquinoline as the precipitating agent.[7] In the first set of experiments, Co(III) was determined by adding a weighed amount of the solution containing it, to an excess of ferrous sulfate solution, the excess ferrous ion being titrated with potassium dichromate solution. In the second set of experiments, the cobaltic solution was discharged into excess potassium iodide solution and the iodine titrated. The two methods agree to within 0.3% on oxygen-free samples. The oxygen error in the iodide method was tested using Ce(IV) as oxidizing agent, having the solutions otherwise identical with those used in the cobaltic analyses, and was found to amount to 0.2%. In the second set of experiments, the cobaltic concentrations were determined before and after making magnetic readings, and were found to be identical within the limits of precision of the analyses.

In making the magnetic susceptibility readings, the zero position of the meniscus in the field was fixed by viewing with a cross-hair telescope. The pressure required to return the meniscus to the zero position when the field was applied was measured with a water manometer, which was read to ±0.001 cm. All solutions were saturated with oxygen before the magnetic measurements were made. The field strength was determined before and after each group of measurements using distilled water or a solution of nickel chloride as the calibrating liquid. The field strength was observed to be 2.420 ± 0.005 × 10^4 oersted. In no case did it change outside experimental error during a set of measurements.

In one set of experiments an aluminum perchlorate solution was used as the reference liquid. Six comparisons yielded for (χ_M of Co^{+++}aq. − χ_M of Al^{+++}aq.) the average value 10 ± 5 × 10^{-5} erg oersted^{-2} mole^{-1}. The error in analysis of ClO_4^- and in measuring the pressure can introduce an error in each value of $\Delta\chi$ of ±0.3 × 10^{-5} and ±1 × 10^{-5}, respectively. Taking account of the possible error in total cobalt, and the precision of the cobaltic analyses shows that the corresponding relative error in cobaltous can affect $\Delta\chi$ in each experiment by ±5 × 10^{-5}.

A second set of experiments using the iodide analytical method, and with Ga^{+++}aq. as the comparison cation, yielded as a result (χ_M of Co^{+++}aq. − χ_M of Ga^{+++}aq.) = 26 ± 14 × 10^{-5} erg oersted^{-2} mole^{-1}. The precision is lower because only two comparisons of susceptibility were made. Ga^{+++}aq. and Al^{+++}aq. were observed to have the same values of susceptibility within experimental error, hence the results of the two sets of experiments can be compared directly.

Discussion

A dependable conclusion which may be drawn from the data is that Co^{+++}aq. is, at most, only very slightly more paramagnetic than Al^{+++}aq. or Ga^{+++}aq. The ion therefore exists principally in the form of a penetration complex of the same electronic type as $Co(NH_3)_6^{+++}$. If Co^{+++} retained 4 unpaired electrons in the complex with water, χ_M would be expected to be greater than χ_M for Ga^{+++}aq. or Al^{+++}aq. by 1071 × 10^{-5} erg oersted^{-2} mole^{-1}. The observed excess is only *ca.* 10 × 10^{-5} erg oersted^{-2} mole^{-1}. Rosenbohm[8] has shown that when the data on the magnetic susceptibilities of a number of cobalt ammines are treated by subtracting from them the diamagnetic contribution of the non-metallic components, a magnetic susceptibility of 5–10 × 10^{-5} erg oersted^{-2} mole^{-1} is left as the contribution of cobalt. A similar effect has been noted in other cases. The slight paramagnetic excess observed for Co^{+++}aq. as compared to Ga^{+++}aq. or Al^{+++}aq. may be an effect of the same type.

The present work which establishes the electronic similarity of Co^{+++}aq. and $Co(NH_3)_6^{+++}$ presents Co^{+++}aq. as an exception to the general behavior[9] that penetration complexes are relatively non-labile. The observation that Co^{+++}aq. exchanges H_2O rapidly with the solvent is surprising whether the process involves direct substitution, or whether it is catalyzed by Co^{++}aq.[4] Even if it were catalyzed by Co^{++}, the question can be raised: why is electron exchange in the pair Co^{++}aq.–Co^{+++}aq. rapid, while in the electronically similar pair $Co(NH_3)_6^{++}$–$Co(NH_3)_6^{+++}$ it is very slow?[10] A possible explanation for the exceptional rate behavior of the Co^{+++}aq. is that the paramagnetic non-penetration form of the ion may be only a few kilocalories above the ground state in energy. A difference of energy between the two states of 4 kcal. would present a system in which *ca.* 99.9% of the ion would be in the ground diamagnetic state; 4 kcal. added to the activation energy for

(2) Data reviewed in "The Nature of the Chemical Bond."

(3) Bommer, *Z. anorg. Chem.*, **246**, 275 (1941).

(4) Friedman, Taube and Hunt, *J. Chem. Phys.*, **18**, 757 (1950).

(5) Treadwell and Hall, "Analytical Chemistry (Quantitative)," John Wiley and Sons, Inc., New York, N. Y., 1942.

(6) Willard, private communication.

(7) Kolthoff and Sandell, "Textbook of Quantitative Inorganic Analysis," The Macmillan Company, New York, N. Y., 1936.

(8) Rosenbohm, *Z. physik. Chem.*, **93**, 693 (1919).

(9) Hunt and Taube, *J. Chem. Phys.*, **19**, 602 (1951).

(10) Lewis, Office of Naval Research, NR-026-001 Technical Report No. 19, January 7, 1949.

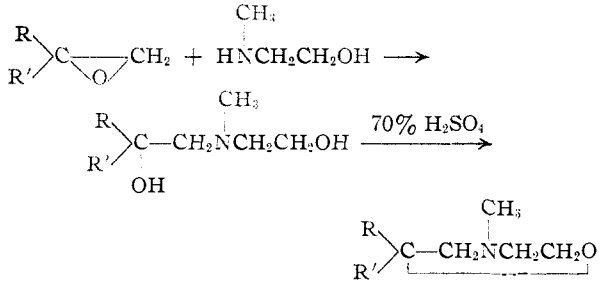
substitution of the non-penetration ion (or for electron transfer) might still result in a system which would be fairly labile with respect to change. In view of the fact that Co^{+++} associating with F^- forms a complex in which the paramagnetic state is the ground state, while with NH_3 the diamagnetic state is the ground state, it would not be surprising if with the ligand H_2O, which is intermediate in polarizability between F^- and NH_3, the two states have nearly the same energy.

GEORGE HERBERT JONES LABORATORIES
UNIVERSITY OF CHICAGO
CHICAGO 37, ILL. RECEIVED JANUARY 13, 1951

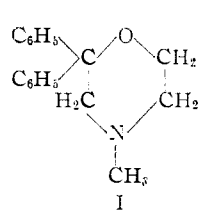
Some 2-Substituted-4-methylmorpholines

BY HENRY GILMAN AND CALVIN C. WANSER

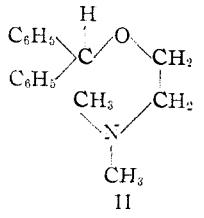
In connection with the extensive search for compounds possessing antihistaminic activity, it appeared desirable to synthesize a number of 2-substituted-4-methylmorpholines where the substituents were aryl groups. These morpholines were prepared by the dehydration of the corresponding dialkanolamines, which were obtained in good yields by the addition of methylethanolamine to the appropriate olefin oxide. Of particular



interest was the synthesis of 2,2-diphenyl-4-methylmorpholine (I), a cyclic structure differing from Benadryl[1] (II) only by the removal of two hydrogen



I



II

atoms. The antihistaminic activity of (II) is well known and a comparison of the activity of (I) with its linear analog is being made.

A new method of synthesis for one of the intermediates, 2-chloro-1,1-diphenylethanol, was investigated and found to work quite smoothly. Klages and Kessler[2] first prepared the compound by the reaction of phenylmagnesium bromide with ethyl chloroacetate but no yield was reported. During the course of this study, we found that the compound could be conveniently prepared in good yield by the addition of phenyllithium to phenacyl chloride at −70°.

An attempt was made to prepare 1,1-diphenylethylene oxide by the epoxidation of 1,1-diphenylethylene with monoperphthalic acid. The reaction yielded a small amount of product, m. p. 54–55°. A mixed melting point of this compound with 1,1-diphenylethylene oxide, prepared by the dehydrohalogenation of 2-chloro-1,1-diphenylethanol with sodium ethoxide and melting at 56–57°, showed a depression. Newbold and Spring[3] studied the reaction of perbenzoic acid with 1,1-diphenylethylene and obtained none of the expected epoxide.

Cottle and co-workers[4] synthesized a number of C-alkylmorpholines by the dehydration of the corresponding dialkanolamines with 95% sulfuric acid at elevated temperatures. The C-arylmorpholines described here were prepared by a modification of that procedure. Cyclization was effected with 70% sulfuric acid at temperatures ranging from 100–150°.

Experimental

The following experiments are typical of those given in Tables I and II. All melting points and boiling points are uncorrected.

2-Chloro-1,1-diphenylethanol.—To a stirred solution of 15.5 g. (0.1 mole) of phenacyl chloride in 150 ml. of anhydrous ether cooled to −70° was added dropwise 0.19 mole of phenyllithium in ether under an atmosphere of nitrogen. The phenyllithium was added until a positive Color Test I[5] was obtained. The reaction mixture was allowed to warm to −20° and then hydrolyzed with ammonium chloride solution. The ether layer was separated and the aqueous layer was extracted with ether. The combined extracts were washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was distilled under reduced pressure to yield 18.1 g. (78%) of colorless liquid, b.p. 139–140° (0.1 mm.), which solidified to a white crystalline mass, m.p. 61–63°. The product, after several recrystallizations from petroleum ether (b.p. 60–70°), melted at 64–65°. The reported[2] boiling point and melting point are 150–180° (11 mm.) and 66°, respectively. Treatment of 2-chloro-1,1-diphenylethanol with diethylamine by the method of Klages and Kessler[2] yielded 2-diethylamino-1,1-diphenylethanol, m.p. 47–48°. The reported[2] melting point of this compound is 49°.

1,1-Diphenylethylene Oxide.—The 1,1-diphenylethylene oxide was prepared from 2-chloro-1,1-diphenylethanol by the method of Klages and Kessler[2] in yields ranging from 66–70%, m.p. 56–57°.

Reaction of 1,1-Diphenylethylene with Monoperphthalic Acid.—The reaction was patterned after the procedure of Böhme[6] for the oxidation of ethylenic double bonds. Eighteen grams (0.1 mole) of 1,1-diphenylethylene,[7] in 20 ml. of ether was added dropwise with stirring to 0.14 mole of an ether solution of monoperphthalic acid[8] at −10°. The reaction mixture was kept at approximately 10° after the addition. After seventy-two hours the theoretical amount of peracid was consumed. The ether solution was extracted with 10% sodium bicarbonate, washed with water and dried over anhydrous sodium sulfate. The solvent was removed and the residue dissolved in absolute ethanol. Two grams

(1) For general references to Benadryl and related types see: G. Rieveschl, Jr., U. S. Patent 2,421,714 (1947) [*C. A.*, **41**, 5550 (1947)]; G. Rieveschl, Jr., and O. M. Gruhzit, *Federation Proc.*, **4**, 150 (1945); E. R. Loew, *et al.*, *J. Pharmacol.*, **83**, 120 (1945); and E. R. Loew, *Physiol. Revs.*, **27**, 542 (1947). In certain other antihistaminic types, K. B. Hamlin, *et al.*, THIS JOURNAL, **71**, 2731 (1949), the introduction of a *p*-chlorophenyl group was found to enhance the activity. In this regard, the synthesis of 2-phenyl-2-*p*-chlorophenyl-4-methylmorpholine is in progress.

(2) A. Klages and J. Kessler, *Ber.*, **39**, 1753 (1906).

(3) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 247 (1945).

(4) D. L. Cottle, *et al.*, *J. Org. Chem.*, **11**, 286 (1946).

(5) H. Gilman and F. Schulze, THIS JOURNAL, **47**, 2002 (1925).

(6) H. Böhme, *Ber.*, **70**, 379 (1937).

(7) Prepared by the procedure of C. F. H. Allen and S. Converse, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 226.

(8) Obtained by the method of H. Böhme, *Org. Syntheses*, **20**, 70 (1940), and the modifications of G. B. Bachman and D. E. Cooper, *J. Org. Chem.*, **9**, 302 (1944).