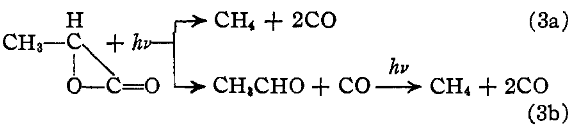
since no aldehyde was found.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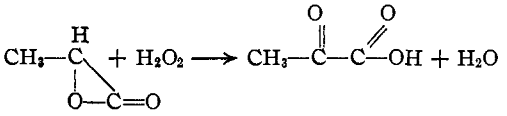
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[CONTRIBUTION FROM THE WEIZMANN INSTITUTE OF SCIENCE]

The Chemical Structure of Some Diamine Carbamates[1]

BY EPHRAIM KATCHALSKI, CHAJA BERLINER-KLIBANSKI AND ARIE BERGER

One mole of carbon dioxide reacts with one mole of ethylenediamine or hexamethylenediamine to yield the corresponding carbamate. These diamine carbamates give with diazomethane the N,N′-dicarbomethoxydiamines (V), the N-monocarbomethoxydiamines (IV) and the free diamines. This result is interpreted by the assumption that the carbamate of an aliphatic diamine consists of a mixture of an intramolecular salt of the N-monocarboxydiamine (II) and of an "intermolecular" salt of the diamine-N,N′-dicarboxylic acid (III) with the free diamine.

Whilst the formula I of the products resulting from the action of carbon dioxide on ammonia and primary aliphatic monoamines has been well established[1a,3]

$$2RNH_2 + CO_2 = \underset{\text{I}}{RNHCOO^-H_3N^+R}$$

little seems to be known on the structure of compounds derived from carbon dioxide and aliphatic diamines. The present investigation deals with the constitution of diamine carbamates, ethylenediamine and hexamethylenediamine carbamates serving as model compounds.

Crystalline products formed readily when dry carbon dioxide was passed through a cold alcoholic solution of the diamines. The products are very soluble in water, giving strongly alkaline solutions. By measuring the amount of combined carbon dioxide (Van Slyke[2]) liberated upon addition of mineral acids,[3] and by determination of the amino groups regenerated (Linderstrøm-Lang[4]), it could be shown that under the experimental conditions used, one mole of carbon dioxide reacted with one mole of the diamine.

In accordance with formula I, it can be assumed that in these *diamine carbamates*, the carbon dioxide is linked by covalent bonds to half of the original amino groups in the form of an N-carboxylic acid, which is neutralized by the other half of the amino-groups as ammonium ions. Indeed, formula (II, $n = 2$), which satisfied the analytical data, has been ascribed recently[5] to the compound between ethylenediamine and carbon dioxide described in 1900.[6] Obviously, however, (II, $n = 2$) is not the only structure in accord with the analytical findings. Also in the "bimolecular" diammonium salt of an N,N′-dicarboxydiamine (III, $n = 2$), half of the original amino groups appear in the form of N-carboxylic acids, while the other half neutralizes these groups; on treatment with mineral acids also (III) would give equimolar amounts of diamine and carbon dioxide. Obviously, the analysis would fit also any mixture of (II) and (III).[7] If one can assume that both amino-groups of a symmetric diamine molecule have an equal chance of being converted into $NHCOO^-$ or NH_3^+, the carbamate would contain equal weights of (II) and (III); if it be assumed, however, that the chance of the amino groups to form $NHCOO^-$ and NH_3^+ is different from the above but in accordance with the analytical data, other weight ratios of (II) to (III) can be calculated.

In order to investigate the presence and relative ratio of (II) and (III) in the carbamates of ethylenediamine and hexamethylenediamine, use was made of the reaction between diazomethane and ammonium salts of carboxylic acids[8]

$$RCOO^-H_3N^+R' + CH_2N_2 = RCOOCH_3 + R'NH_2 + N_2$$

which would convert (II) into the monocarbomethoxy derivative (IV), and (III) into an equimolar mixture of the dicarbomethoxy derivative (V) and the original free diamine.

In fact, both for ($n = 2$) and ($n = 6$), the compounds (IV), (V) and the free diamine were formed in the reaction between an ethereal diazomethane solution and the carbamates. For comparison, (V, $n = 2$) was prepared from ethylenediamine and methyl chloroformate, (IV, $n = 2$) by amination of N-carbomethoxybromoethylamine according to Délépine,[9] and (V, $n = 6$) from hexamethylenediamine and methyl chloroformate.

Further evidence was obtained for the presence of (III) in the diamine carbamates by the isolation of the calcium salts of N,N′-dicarboxyethylene-

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[1] This paper is part of the dissertation presented by Chaja Berliner-Klibanski to the Hebrew University, Jerusalem, in partial fulfillment of the degree of Ph.D.

[1a] *Cf.* V. Meyer and P. Jacobson, "Lehrbuch der organischen Chemie," Vol. I, Part 2, Leipzig, 1913, p. 1370; F. Fichter and B. Becker, *Ber.*, **44**, 3481 (1911); C. Faurholt, *J. chim. phys.*, **22**, 1 (1925).

[2] D. D. Van Slyke and J. M. Neill, *J. Biol. Chem.*, **61**, 523 (1924); J. P. Peters and D. D. Van Slyke, "Quantitative Clinical Chemistry," Vol. II, 1932, p. 283.

[3] M. Frankel and E. Katchalski, THIS JOURNAL, **65**, 1670 (1943).

[4] K. Linderstrøm-Lang, *Z. physiol. Chem.*, **173**, 32 (1928).

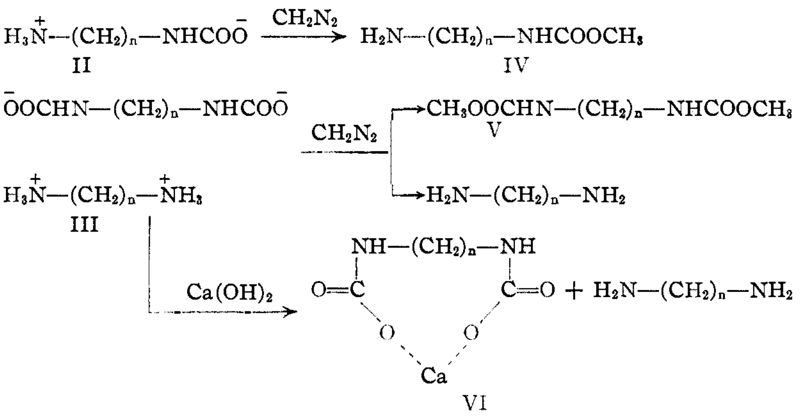
[5] J. F. Mulvaney and R. L. Evans, *Ind. Eng. Chem.*, **40**, 393 (1948).

[6] E. Schering, German Patent 123,138 (1900); *Chem. Zentr.*, **72**, II, 519 (1901).

[7] W. Siefken, *Ann.*, **562**, 6 (1948), suggested the presence of structures (II) and (III) in order to explain the reaction between the carbamates of aliphatic diamines and phosgene.

[8] M. Frankel and E. Katchalski, THIS JOURNAL, **66**, 763 (1944).

[9] M. Délépine, *Compt. rend.*, **120**, 501 (1895); **124**, 292 (1897); *Bull. soc. chim.*, [3] **17**, 290 (1897); [4] **31**, 108 (1922); *cf.* A. Galat and G. Elion, THIS JOURNAL, **61**, 3585 (1939).



diamine (VI, $n = 2$) and N,N′-dicarboxyhexamethylenediamine (VI, $n = 6$) upon treatment of the carbamates with calcium hydroxide. The yields of the salts were in good agreement with the amounts of (V, $n = 2, 6$) in both cases isolated.

From the yields of IV, V, VI and free diamine ($n = 2$, $n = 6$) (*cf.* Tables I and II) the weight ratio of II to III in the diamine carbamates could be estimated. It was found to be approximately 1:1.

For the study of carbamates of unsymmetrical aliphatic diamines, the carbamate of lysine methyl ester was selected, which is easily formed from equal moles of lysine methyl ester and carbon dioxide. Its esterification with diazomethane, however, gave only N,N′-dicarbomethoxylysine methyl ester and all attempts to isolate from the reaction mixture the free methyl ester and α- or ε-N-monocarbomethoxylysine methyl ester were unsuccessful. As the hydrochloride fraction expected to contain the hydrochlorides of lysine methyl ester and the N-monocarbomethoxy derivatives contained methoxy groups and chloride ion in excess over amino-nitrogen, it is possible that lysine derivatives containing free amino groups undergo other reactions (N-methylation) with diazomethane.[10]

The conclusions drawn concerning the structure of the carbamates of aliphatic diamines can easily be extended to *poly*-amines. This application may be of interest in the study of biological systems in which carbamates of proteins containing free amino-groups are present.[11]

Experimental

Preparation of "Ethylenediamine Carbamate."—At about −10°, a stream of dry carbon dioxide was passed through a solution of anhydrous ethylenediamine (2 g.) in absolute methanol (10 ml.) over a period of four hours, moisture being rigorously excluded. The stream of gas was then continued at room temperature until all the methanol had evaporated from the reaction mixture. The semi-solid residue was triturated with anhydrous ether under a carbon dioxide atmosphere; the ether was decanted and the colorless powder (3 g.) dried over sulfuric acid, m.p. 170° (sealed capillary). "Ethylenediamine carbamate" is sparingly soluble in methanol and ethanol, insoluble in ether, chloroform, benzene, acetone and carbon tetrachloride. It is readily soluble in water with a strong alkaline reaction. On acidification, carbon dioxide is evolved.

Anal. Calcd. for $C_3H_8N_2O_2$: C, 34.6; H, 7.8; N, 26.9; amino-N, 26.9; CO_2, 42.3. Found: C, 35.0; H, 8.0; N, 27.2; amino-N, 26.6[4]; CO_2, 42.0.[2,3]

Action of Diazomethane on "Ethylenediamine Carbamate."—"Ethylenediamine carbamate" (1.66 g.) was treated with diazomethane (3 g.) in ether (450 ml.) at room temperature. With liberation of nitrogen, the solid gradually disappeared. From the filtered ethereal solution, which showed a strong alkaline reaction, N,N′-dicarbomethoxyethylenediamine (V, $n = 2$), N-monocarbomethoxyethylenediamine (IV, $n = 2$) and ethylenediamine were isolated as follows: the ethereal solution was acidified (congo red) with 2 *N* methanolic hydrogen chloride. The oil, which separated, solidified at low temperature (1.91 g.). The supernatant liquid was decanted and the residue **A** washed with ether. From the combined solution the ether was removed through a 16-plate column. A crystalline, colorless residue **B** (0.48 g.) was thus obtained which was recrystallized twice from dibutyl ether, m.p. 131–132°. The melting point was not depressed upon admixture of an authentic sample of N,N′-dicarbomethoxyethylenediamine (V, $n = 2$) (see below).

Anal. Calcd. for $C_6H_{12}N_2O_4$: C, 40.9; H, 6.9; N, 15.9; CH_3O, 35.2. Found: C, 41.4; H, 7.2; N, 15.8; CH_3O, 35.6.

To an ice-cold solution of **A** (1.91 g.) in water (15 ml.), sodium bicarbonate (1.9 g.) was added in four portions. After each addition the solution was extracted with chloroform. The combined extracts were dried over anhydrous sodium sulfate and the chloroform removed at atmospheric pressure. The dark, oily, strongly alkaline residue (0.8 g.) was distilled at 108° (8 mm.); the distillate readily dissolved in alcohol, chloroform and acetone and to a lesser extent in benzene and water. Its picrolonate prepared in chloroform solution melted at 202–203° and proved identical with that of authentic **N-carbomethoxyethylenediamine** (IV, $n = 2'$) (see below).

Anal. Calcd. for $C_{14}H_{18}N_6O_7$: C, 44.0; H, 4.7; N, 22.0; CH_3O, 8.1. Found: C, 44.1; H, 4.7; N, 21.7; CH_3O, 8.3.

The aqueous bicarbonate solution contained, after the extraction with chloroform, 0.128 g. of nitrogen (Kjeldahl), equivalent to 0.274 g. of ethylenediamine. The latter was isolated by distillation of the aqueous solution to dryness, acidification of distillate and renewed evaporation. The resulting dihydrochloride of **ethylenediamine** was reprecipitated from water with absolute alcohol and converted into the **dipicrate**; m.p. and mixed m.p. 232–233° (dec.).

Anal. Calcd. for $C_{14}H_{14}N_8O_{14}$: N, 21.6. Found: N, 21.3.

Isolation of the Calcium Salt (VI, $n = 2$) of N,N′-Dicarboxyethylenediamine from "Ethylenediamine Carbamate."—An ice-cold thick aqueous suspension of calcium hydroxide (3 ml.) was added to an ice-cold solution of "ethylenediamine carbamate" (0.315 g.) in water (5 ml.). The reaction mixture was left at 0° for 30 minutes, the excess of calcium hydroxide filtered off and an equal volume of absolute ethanol added to the clear filtrate. The colorless precipitate was washed with a small volume of cold water, then with alcohol and ether, and dried *in vacuo;* yield 0.130 g.

TABLE I

YIELDS OF IV, V, VI ($n = 2$), AND ETHYLENEDIAMINE FROM 100 MG. OF "ETHYLENEDIAMINE CARBAMATE" (CONTAINING 26.9 MG. N)

Product	Yield, mg.	Yield, mg. N	Total N, %
Free ethylenediamine	16.5[a]	7.7	28.6
IV	48.2[b]	11.4	42.5
V	28.9[c]	4.6	(17.1)
VI	41.2	6.2	23.0

[a] Calculated from nitrogen content of aqueous solution. [b] Weight of material before distillation. [c] Weight of material before crystallization; these figures are only semiquantitative.

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(10) *Cf.* R. Kuhn and W. Brydówna, *Ber.*, **70B**, 1333 (1937).

(11) F. J. W. Roughton, *Physiol. Rev.*, **15**, 241 (1935).

Anal. Calcd. for $C_4H_6N_2O_4Ca$: N, 15.0; Ca, 21.5. Found: N, 15.0; Ca, 21.0.

Table I summarizes the result of the experiments described above.

N,N'-Dicarbomethoxyethylenediamine (V, *n* = 2).—To a solution of ethylenediamine (5.8 g.) in water (25 ml.) there was added at 0° 4 *N* sodium hydroxide (75 ml.) and methyl chloroformate (18.9 g.) during 20 minutes with vigorous shaking. The mixture was acidified (congo red) and the crystalline product filtered, washed with cold water (yield 80%) and recrystallized from dibutyl ether; m.p. 131–132°.[12]

Anal. Calcd. for $C_6H_{10}N_2O_4$: C, 40.9; H, 6.9; N, 15.9. Found: C, 41.2; H, 7.1; N, 15.8.

Preparation of N-Carbomethoxyethylenediamine (IV, *n* = 2).—A cold saturated chloroform solution of hexamethylenetetramine (5.5 g.) was added to N-carbomethoxy-β-bromoethylamine (6.7 g.),[13] and the mixture kept at room temperature for seven days. The precipitate (6.9 g.) $Br^-(CH_2)_6N_4^+(CH_2)_2NHCOOCH_3$ was filtered and washed with chloroform.

Anal. Calcd. for $C_{10}H_{20}N_5O_2Br$: N, 21.7; Br, 24.8. Found: N, 21.6; Br, 24.6.

A mixture of the salt (2.9 g.) and 10% methanolic hydrogen chloride (10 ml.) was refluxed for 30 minutes, the methanol evaporated and the residue washed with ether, dissolved in water (5 ml.) and treated with sodium bicarbonate (5 g.) at 0°. The monoamine was extracted from the aqueous solution with chloroform; it boiled at 108° (8 mm.); yield of crude product, 0.9 g., soluble in water, chloroform, ether and acetone, sparingly soluble in benzene. Its **picrolonate**, prepared in chloroform, melted at 202–203°.

Anal. Calcd. for $C_{14}H_{18}N_6O_7$: C, 44.0; H, 4.7; N, 22.0; CH_3O, 8.1. Found: C, 44.3; H, 5.0; N, 22.2; CH_3O, 8.0.

The **chloroaurate**, a golden-yellow crystalline product, was recrystallized from dilute hydrochloric acid, obtained as monohydrate.

Anal. Calcd. for $C_4H_{13}N_2O_3Cl_4Au$: N, 5.9; Au, 41.4. Found: N, 6.2; Au, 41.3.

"Hexamethylenediamine carbamate" was prepared in the same manner as the ethylenediamine derivative; yield 2.49 g. from 2 g. of the diamine; m.p. 150°.

Anal. Calcd. for $C_7H_{16}N_2O_2$: C, 52.5; H, 10.1; N, 17.5; amino-N, 17.5; CO_2, 27.5. Found: C, 52.7; H, 10.3; N, 17.3; amino-N, 17.6[1]; CO_2, 27.7.[2,3]

TABLE II

YIELDS OF IV, V, VI, (*n* = 6) AND FREE HEXAMETHYLENEDIAMINE, DERIVED FROM 100 MG. OF "HEXAMETHYLENEDIAMINE CARBAMATE" (CONTAINING 17.5 MG. N)

Product		Yield, mg.	Yield, mg. N	Total N, %
Free diamine	R = $(CH_2)_6$	18.3[a]	4.4	25.1
IV	R = $(CH_2)_6$	52.1[b]	8.4	48.0
V	R = $(CH_2)_6$	27.6[c]	3.3	(18.9)
VII	R = $(CH_2)_6$	39.6	4.6	26.2

[a] Calculated from nitrogen content of aqueous solution. [b] Weight of material before distillation. [c] Weight of material before crystallization; these figures are only semiquantitative.

Action of Diazomethane on "Hexamethylenediamine Carbamate."—The reaction of the carbamate with diazomethane was investigated by the methods described for the case of the parent substance. The results are summarized in Table II, expressed for 100 mg. of the starting material.

N,N'-Dicarbomethoxyhexamethylenediamine (V, *n* = 6), boiled at 110° (15 mm.) and melted at 113° (from water).

Anal. Calcd. for $C_{10}H_{20}N_2O_4$: C, 51.8; H, 8.7; N, 12.1; amino-N, 0; CH_3O, 26.7. Found: C, 52.0; H, 8.6; N, 12.2; amino-N, 0; CH_3O, 26.9.

For comparison, it was prepared in 80% yield from hexamethylenediamine (1.5 g.) in water (15 ml.) with 2 *N* sodium hydroxide (13 ml.) and methyl chloroformate (2.4 g.) at 0°. The crystalline product was filtered, washed with ice-cold water and recrystallized from water; m.p. 113°.

N-Carbomethoxyhexamethylenediamine (IV, *n* = 6), boiled at 195° (15 mm.), 150–160° (0.01 mm.).

Anal. Calcd. for $C_8H_{18}N_2O_2$: N, 16.1; amino-N, 8.0; CH_3O, 17.8. Found: N, 16.3; amino-N, 7.9[4]; CH_3O, 17.3.

The **picrolonate**, prepared in chloroform, had m.p. 158°.

Anal. Calcd. for $C_{18}H_{26}N_6O_7$: C, 49.3; H, 6.0; N, 19.2; CH_3O, 7.1. Found: C, 49.6; H, 6.1; N, 18.7; CH_3O, 7.5.

The **free hexamethylenediamine**, resulting from the action of diazomethane on its "carbamate," was identified as picrate, m.p. 216° (dec.) (from water)[14] and hydrochloride, m.p. 246–248° (from alcohol–ether).[15]

The **calcium salt** (VI, *n* = 6) was also prepared in the manner indicated for the corresponding ethylenediamine derivative.

Anal. Calcd. for $C_8H_{14}N_2O_4Ca$: N, 11.6; Ca, 16.5. Found: N, 11.9; Ca, 16.1.

The **"carbamate of lysine methyl ester"** was prepared from lysine methyl ester[16] in anhydrous ether at −10°. The colorless crystalline product was washed with ether and dried *in vacuo;* m.p. 87–90°; yield quantitative.

Anal. Calcd. for $C_8H_{16}N_2O_4$: C, 47.1; H, 7.9; N, 13.7; amino-N, 13.7; CO_2, 21.5. Found: C, 46.9; H, 8.3; N, 13.6; amino-N, 13.7[4]; CO_2, 21.7.[2,3]

The "carbamate" is insoluble in ether, benzene and acetone, sparingly soluble in ethanol, readily soluble in water.

Reaction with Diazomethane.—The "carbamate" (4.5 g.) was treated with diazomethane (25 g.) in ether (400 ml.) at room temperature. When the solid had disappeared, the free bases in the ethereal solution were precipitated as hydrochlorides (3.5 g.) and the oily residue of the supernatant liquid (1.5 g.) purified by fractionation; b.p. 210–215° (5 mm.): N,N'-dicarbomethoxylysine methyl ester.

Anal. Calcd. for $C_{11}H_{20}N_2O_6$: N, 10.1; CH_3O, 33.7. Found: N, 9.8; CH_3O, 33.6.

The hygroscopic hydrochloride fraction was carefully dried and analyzed (Cl (Volhard), 19.2; N, 11.3; amino-N, 7.0; CH_3O, 18.0). Although the data indicated the presence of amino and ester groups in the product, all attempts to isolate lysine methyl ester and α- or ε-monocarbomethoxylysine methyl ester failed.

REHOVOTH, ISRAEL RECEIVED NOVEMBER 24, 1950

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