The humin molecule is thus shown to be not the simplest compound that can be formed from one molecular equivalent of indole plus two of aldehyde, but a complex of two to four times that size. It is very possible that this is simply an association in the solvents phenol and benzene, since it is a common occurrence for the more basic indolidene derivatives to polymerize the solvents. On the other hand, the inactivity of the humins and their behavior toward solvents are evidence of high molecular weight. For the present the humin from α-methylindole and o-tolylaldehyde can be represented by the formula $(C_{25}H_{21}N)_X$, where X is not greater than 4.

The synthesis and chemical properties of the humin from α-methylindole and o-tolylaldehyde can be represented by Fig. 2.

In short, compounds of similar inactivity and complexity to the humin resulting from the acid hydrolysis of proteins can be prepared from substituted indoles and aromatic or aliphatic aldehydes. All of the accumulated data point to the conclusion that such artificial humins are not simple molecular condensations but that it is possible to isolate at least two intermediate products. These intermediate products have been purified and analyzed, and their structures have been ascertained. These products belong to the rosindole and indolidene methane groups. The final humin results by the condensation of one molecule of aldehyde with the indolidene methane derivative, but during this condensation some rearrangement apparently takes place, for the resulting humin is extremely resistant to drastic chemical treatment such as alkaline fusion and permanganate oxidation. The data so far available do not permit us to decide as to the structural formulas.

St. Paul, Minnesota

THE DECOMPOSITION OF DIHYDROXYMALEIC ACID[1]

By Arthur Locke

Among the various theories which have been advanced to explain the photosynthesis of optically active sugars in nature, the one involving the condensation of glycolaldehyde deserves more careful scrutiny.[2] A prerequisite for such a study is more definite knowledge of the condensation of glycolaldehyde to tetroses and hexoses.[3] A symmetric orientation

[1] This paper embodies a portion of the work carried out at the suggestion of Dr. H. A. Spoehr while the author was a fellow of the Carnegie Institution of Washington at the Coastal Laboratory, Carmel-by-the-Sea, California.

[2] Reinke, *Ber.*, **14**, 2148 (1881). (b) Lippmann, *Ber.*, **24**, 3306 (1891). (c) Fincke, *Biochem. Z.*, **61**, 157 (1914). (d) Nef, *Ann.*, **376**, 7, 115 (1910).

[3] Fenton, (a) *J. Chem. Soc.*, **65**, 899 (1894); (b) **67**, 48, 774 (1895); (c) **69**, 546 (1896); (d) **71**, 375 (1897); (e) **73**, 71 (1898); (f) **81**, 426 (1902); (g) **87**, 817 (1905). (h) Fischer and Landsteiner, *Ber.*, **25**, 2549 (1892).

in this condensation was first attempted through the carboxyl group of dihydroxymaleic acid whose solutions decompose spontaneously at room temperature into glycolaldehyde and carbonic acid. The condensation of the glycolaldehyde to sugars occurs at a somewhat higher temperature. The rate of decomposition of the acid, however, so far exceeded the rate of condensation of the aldehyde that the orienting effect of the quinine and menthol used was lost before it could act.

Alkali was added to accelerate the condensation of the glycolaldehyde, when the unexpected observation was made that while dihydroxymaleic acid itself decomposes rapidly in its aqueous solutions, the sodium and potassium salts appear to be relatively stable. This required a preliminary examination into the mechanism of decomposition of dihydroxymaleic acid.

The earliest mechanism proposed restricted the decomposition to molecules of trihydroxysuccinic acid, produced by hydration of the dihydroxymaleic acid, and was based upon the observation that benzene and chloroform solutions of the acid are perfectly stable. It was later found that the addition of dry pyridine to these solutions would also incite a rapid decomposition and the alternative mechanism was postulated that only the dihydroxymaleate *ion* is capable of spontaneous decomposition.[4]

This hypothesis may be tested by an examination of the rates at which dihydroxymaleates decompose. Substitution of experimental values for the number of moles, x, decomposed in the time t in the monomolecular reaction velocity equation $1/t \log (A/(A - x)) = 0.4343 \, k$ should reveal whether A really represents the concentration of dihydroxymaleate ions through the presence or absence of a fluctuation in the values calculated for k.

The rate of decomposition of dihydroxymaleic acid[5] and that of its disodium salt at 25°, were determined by taking advantage of the great precedence of the rates of solution over the rate of decomposition. Suspensions of the acid were maintained by vigorous stirring. Suspensions of the salt were maintained by the bubbling of hydrogen, a departure necessitated by the susceptibility of solutions of the salt to atmospheric oxidation.[6] As

---

[4] Compare Ref. 3 g. An additional incompatibility of the earlier hypothesis is that trihydroxysuccinic acid would decompose, not into glycolaldehyde and carbonic acid, but into trihydroxypropionic acid and carbonic acid. Ref. 2 d.

[5] The preparation of the dihydroxymaleic acid was in accordance with the directions of Nef [*Ann.*, **357**, 291 (1907)]. It was found that Nef's yields could be realized when directions were followed with exactness. (Compare, however, Neuberg and Schwenk, *Biochem. Z.*, **71**, 112 (1915).) Crystallization of dihydroxymaleic acid from the reaction mixture ensues without the addition of sulfuric acid but is greatly accelerated thereby. The stability of the solution is also increased by such addition.

[6] Disodium dihydroxymaleate was prepared according to the method of Fenton, Ref. 3 a, pp. 906, 910. Its aqueous solutions are practically neutral (P_H approx. 6.4). The marked susceptibility to atmospheric oxidation, in contrast to the behavior of the free acid, is worthy of further investigation.

decomposition proceeded, the depletion in concentration of the decomposing substance was counterbalanced by solution from the excess of suspended solid so that constant concentration was maintained. The progress of the decomposition was followed by measurement of the increase in reducing capacity of the solution. Samples were withdrawn at consecutive intervals, filtered from suspended solid, acidified in the case of the salt samples, warmed for complete decomposition to glycolaldehyde and diluted to such a volume that the concentration of glycolaldehyde in all solutions analyzed was approximately the same. A fresh Benedict solution was then standardized against a solution of glycolaldehyde prepared by decomposition of a weighed amount of pure dihydroxymaleic acid and corresponding in concentration to the sample to be analyzed.[7]
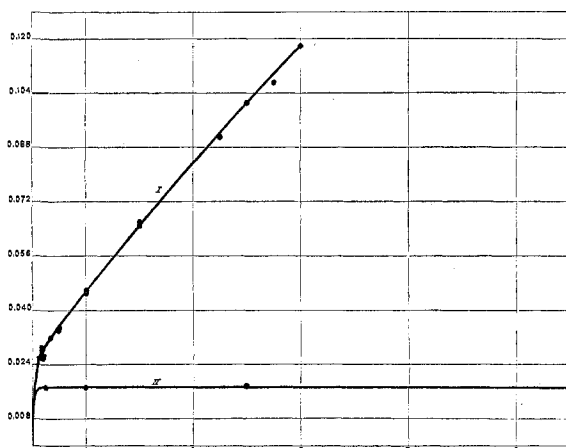

Fig. 1.—The rate of decomposition of dihydroxymaleic acid (Curve I) and of its disodium salt (Curve II). The ordinates represent the sum of the molar concentrations of dihydroxymaleate and glycolaldehyde in the decomposing solution. The abscissas represent the time in hours.

Ten cc. of the glycolaldehyde solution to be analyzed was then added, drop-wise, to 15 cc. of the boiling Benedict solution contained in a 100cc. Erlenmeyer flask. One g. of sodium carbonate was previously added to the Benedict solution in the salt series to compensate for the earlier acidification of these salt solutions. The addition, together with a subsequent cooling, covered a period of five minutes. The contents of the flask were quickly transferred to a 40cc. centrifuge. Analysis was completed by the method of Spoehr.[8]

[7] Glycolaldehyde is oxidized quantitatively to glycolic acid by the Benedict solution but concomitant condensation of the glycolaldehyde to tetroses and hexoses which have a lower reducing power necessitates the strict observance of the procedure outlined.

[8] Spoehr, *Carnegie Inst. Pub.*, **287**, 31, 36 (1919).

The results of these analyses are shown in Tables I and II and further illustrated in the accompanying curves. Extrapolation of the curve to zero time gives in each case the solubility of the substance. Since the solubility defines the concentration of decomposing substance in the solution at any instant, the difference between this value and the value obtained from the total reducing capacity of the solution represents the glycolaldehyde content of the solution in moles of substance decomposed. The quotient of this glycolaldehyde content by the duration of the period of decomposition (dx/dt) represents the rate of decomposition. This is seen to diminish very slightly with time due, in the case of the acid, to diminished solubility with increasing concentration of glycolaldehyde and, in the case of the salt, to unavoidable oxidation.

TABLE I

THE DECOMPOSITION OF A SATURATED SOLUTION OF DIHYDROXYMALEIC ACID AT 25°

Time in hours	0	0.17	0.50	1.00	2.00	4.00	5.00
Molal concn. of glycolaldehyde + dihydroxymaleic acid...............	0	0.28	0.35	0.045	0.065	0.101	0.118
Increase in molal concn. of glycolaldehyde per min. $\times 10^{-4}$...............	0	..	3.5	3.3	3.3	3.0	2.8

TABLE II

THE DECOMPOSITION OF A SATURATED SOLUTION OF DISODIUM DIHYDROXYMALEATE AT 25°

Time in hours	0	0.25	1.00	4.00	46.5
Molal concn. of glycolaldehyde + disodium dihydroxymaleate.....................	0	0.0174±2	0.0174±2	0.0174±2	0.0170±2
Increase in molal concn. of glycolaldehyde per minute....	0	.....	0	0	-1.6×10^{-7}

It will be observed that the rate of decomposition of the acid is apparently infinitely greater than that of the disodium salt.

The concentration of dihydroxymaleate ions in solutions of dihydroxymaleic acid and of its disodium salt was calculated from conductivity measurements. The results of these measurements are incorporated in Tables III and IV. It is necessary to allow for the instability of the dihydroxymaleic acid solution by projection of the measurement over an interval of time and extrapolation to the instant of solution. The values obtained for the molecular conductance of dihydroxymaleic acid solution at 25° for the concentrations $M/64$ and $M/128$ correspond closely to those reported by Skinner.[9] The molecular conductance of the disodium salt at infinite dilution is taken as 215 ± 7 ohms^{-1}, a value obtained by extrapolation to zero concentration of the values recorded in the table. Since the conductance of Na$^+$ at infinite dilution is 50.6 ohms^{-1} at 25°, the conductance of dihydroxymaleate ion ($^{1}/_2$ C$_4$O$_6$H$_2^{--}$)

⁹ Skinner, *J. Chem. Soc.*, **73**, 483 (1898).

at infinite dilution is $^1/_2$ 215 ± 7 − 50.6 or 57 ± 4 ohms⁻¹. The molal conductance of dihydroxymaleic acid (primary ionization) at infinite dilution becomes therefore[10] 57 ± 4 plus 347, the conductance of the hydrogen ion at infinite dilution, or 404 ± 4 ohms⁻¹.

TABLE III

THE DISSOCIATION OF DISODIUM DIHYDROXYMALEATE

Molal concn.	M/64	M/128	M/256	M/512	M/1024	M/∞
Molal conductance, ohms⁻¹	183±1	192±3	202±4	207±5	211±7	215±7
Degree of dissocn	0.85±2	0.89±1	0.94±1	0.960±5	0.980±5	1.00
Concn. $^1/_2$ (C₄O₆H₂)⁻⁻, N	0.027	0.014	0.073	0.038	0.019	0

TABLE IV

THE DISSOCIATION OF DIHYDROXYMALEIC ACID

Molal concn.	M/64	M/128	M/256	M/512	M/1024	M/2048	M/∞
Molal conductance, ohms⁻¹	292±3	329±6	373±9	426±12	477±15	533±18	404±4
Degree of dissoc.	0.72	0.810±5	0.920±15	1.05±2[a]	1.18±3[a]	1.32±3[a]	2.00[a]
Concn., $^1/_2$ (C₄O₆H₂)⁻⁻, N	0.011	0.0063	0.0036	0.0021	0.0011	0.0006	0

[a] Manifestation of secondary dissociation.

The relative concentration of dihydroxymaleate ions is seen to be practically twice as great in the salt solutions. Were Fenton's hypothesis tenable that the dihydroxymaleate ion is the decomposing unit, the salt should decompose twice as rapidly as the acid in the concentrations compared. As a matter of fact, we have seen that the salt decomposes at a rate infinitely less than that of the free acid.

Table V collects the values necessary for an exact calculation of the value of k in the monomolecular velocity equation upon the basis (k) that the rate of decomposition is proportional to the total concentration of carboxyl groups present, (k_1) that the rate is proportional to the concentration of non-ionized carboxyl groups, and (k_2) that the rate is proportional to the concentration of ionized carboxyl groups. The value of x in the first two steps was obtained as the difference between the succeeding values for the total concentration of carboxyl groups, which were in turn found as the quotient of the specific conductance observed, by the molal conductance as calculated from Table IV. The last value for x was taken from Table I. It will be observed that k_1 more nearly approaches constancy than k_2, that is, the decomposition is more nearly proportional to the concentration of *non-ionized* carboxyl groups.

[10] The deviation of this value from the value 356 used by Skinner and calculated from the Ostwald dilution equation is due to the partial secondary dissociation which, uncorrected for, vitiates the latter relation.

It is, however, not possible that the non-ionized carboxyl group, *per se*, is the decomposing unit, for solutions of the undissociated dihydroxy-

TABLE V

THE RATE OF DECOMPOSITION OF DIHYDROXYMALEIC ACID

Time, min.	0	61	0	60	0	1
Sp. conductance; mhos $\times$ 100.	0.4570	0.2712	0.2574	0.1590	See	
Molal conductance...........	292	328	329	368	Table I	
Molal concn.................	0.0156	0.0082	0.0078	0.00432	0.025	...
Degree of dissocn.............	.72	.81	.81	.91	.64	...
Total concn.................	.0312	.0164	.0156	.00864	.050	...
Concn. of non-ionized COOH..	.0200	.0098	.0093	.00471	.034	...
Concn. of ionized COOH......	.0112	.0066	.0063	.00393	.016	...
x..........................	...	.0148	...	.00696	..	0.00067
k..........................	...	.011	...	.010	..	.013
k_1.........................	...	.022	...	.023	..	.020
k_2.........................	...	.021	...	.019	..	.042

maleic acid in benzene and chloroform are perfectly stable. Since the addition of water, pyridine, and related substances renders these solutions unstable, and since the rate of decomposition in aqueous solutions is already proportional to some fraction of the total number of non-ionized carboxyl groups present, the further hypothesis is now put forward that the *solvated*, non-ionized carboxyl group is the decomposing unit. The composition of dihydroxymaleic acid represents a rearrangement of the type of the Hofmann and Curtius rearrangements. Rearrangements are equilibrations of strain. The extent of the strain depends upon the excess of driving force over resistance. In the dihydroxymaleic acid molecule this driving force is the affinity for combination of C^- and H^+. The resistance is due to the affinity of C^- for C^+. Solvation, by creating a drain of residual valence, reduces the resistance to dissociation at the C—C bond, increasing strain and decomposition. The affinity of combination of C^- for H^+ or other cations may be roughly gaged by the position of these latter in the solution tension (EM) series,[11] and the great stability of the disodium salt may be inferred from the minimal affinity of C^- for Na^+. Corroboration may be found in the rearrangement of disodium dihydroxymaleate to disodium tartronate which Lachman[12] has shown to pivot upon the instability of a $C—[C(OH)_3]$ linkage and the stability of a $C—[C{<}^O_{ONa}]$ arrangement. Among the diazonium salts, analogous decomposition into benzene derivatives and nitrogen is chiefly restricted to the non-dissociated salt and is proportional to a function of the oxidizing and reducing tension of the potential cation and anion.

[11] Locke, *Dissertation*, University of Chicago, **1922**.

[12] Lachman, THIS JOURNAL, **43**, 2091 (1921).

Summary

Asymmetric condensation of glycolaldehyde to optically active sugars, through the decomposition of active salts of dihydroxymaleic acid to glycolaldehyde and carbonates, was not obtained on account of the precedence of the rate of decomposition over the rate of subsequent condensation. Choice of a condensation catalyst disclosed an unexpected stability in disodium dihydroxymaleate and necessitated the study of the decomposition mechanism. It is concluded from a consideration of reaction rates that the rate of decomposition of dihydroxymaleates is proportional: (1) to the concentration of non-ionized dihydroxymaleate molecules present, (2) to the degree of solvation of these molecules, and (3) to the oxidizing tension of the cations produced by dissociation of the dihydroxymaleate.
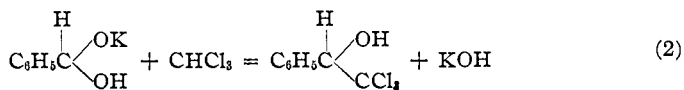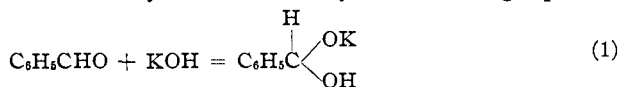
CARMEL-BY-THE-SEA, CALIFORNIA

THE ADDITION PRODUCTS OF METHYLETHYL KETONE WITH CHLOROFORM, BROMOFORM AND IODOFORM

BY JOHN B. EKELEY AND CARL J. KLEMME

The course of the reaction between methylethyl ketone and chloroform, bromoform or iodoform in the presence of powdered potassium hydroxide may be inferred from the experiments of Willgerodt[1] and of Guedras.[2] When these investigators allowed acetone to react with the same reagents, trihalogen-*tertiary*-butyl alcohols were produced, $(CH_3)_2C(OH)CX_3$. The chlorine and bromine derivatives possess some therapeutic value; during the world war, the British Government used the chlorine compound mixed with desiccated antitetanic serum as an anodyne and as a mild antiseptic to dust wounds.

Jocicz[3] studied the behavior of benzaldehyde under similar conditions; he claims that the reaction may be described by the following equations.

$$C_6H_5CHO + KOH = C_6H_5C\overset{\displaystyle H}{\underset{\diagdown OH}{\diagup OK}} \tag{1}$$

$$C_6H_5C\overset{\displaystyle H}{\underset{\diagdown OH}{\diagup OK}} + CHCl_3 = C_6H_5C\overset{\displaystyle H}{\underset{\diagdown CCl_3}{\diagup OH}} + KOH \tag{2}$$

It is evident that potassium hydroxide will react with chloroform simultaneously to produce potassium chloride and potassium formate; the solid residue gave tests for both of these compounds.

[1] Willgerodt, *Ber.*, **14**, 2451 (1881); **15**, 2305 (1882); **16**, 1585 (1883).

[2] Guedras, *Compt. rend.*, **133**, 1011 (1901).

[3] Jocicz, *Chem. Centr.*, [5] **1**, 1013 (1897).