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The Stability of Fused Rings in Metal Chelates. III. The Relative Stability of Copper(II) Complexes of Aldehyde- and Ketone-Schiff Bases[1]

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The relationship between the structure of fused-ring systems and the relative stability of copper(II) Schiff base chelates has been discussed, on the basis of the properties of six copper(II) complexes, in connection with the transamination reaction. As the conclusion it has been suggested that the transamination reaction in fused-ring systems containing copper(II)-glyoxylate- or -pyruvate-Schiff bases may be expected only in such appropriately unstable systems as have two five-membered rings and that it is generally accompanied by a stabilization of the system. The preparation and properties of the two new copper(II) chelates, glyoxylidene-β-alaninatoaquocopper(II) and pyruvidene-α-alaninatoaquocopper(II), have been described.

The previous effort in this laboratory has been directed toward the investigation of the properties of fused-ring systems in copper(II) complexes of Schiff bases derived from salicylaldehyde[2] or pyruvic acid[3] and amino acids or other amino compounds. In order to extend our previous interpretation concerning the relationship between the relative stability of metal chelates and the

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[1] A part of this work has already been published as a "Short Communication": Y. Nakao, K. Sakurai and A. Nakahara, This Bulletin, **38**, 687 (1965).

[2] A. Nakahara, H. Yamamoto, and H. Matsumoto, *Sci. Rep.* (*College of General Education, Osaka University*), **12**, 11 (1963).

[3] A. Nakahara, H. Yamamoto and H. Matsumoto, This Bulletin, **37**, 1137 (1964).

structure of fused-ring systems, we have recently undertaken the syntheses of some copper(II) chelates of Schiff bases derived from glyoxylic acid and amino acids.

In the meantime we have found that there is a delicate correlation between the structure of fused-ring systems and the transamination reaction. For example, the complex isolated in the crystalline state from the copper(II)-glyoxylate-alaninate system has been proved to be pyruvideneglycinatoaquocopper(II) instead of glyoxylidenealaninatoaquocopper(II). This finding is apparently related to a transamination reaction occurring in the fused-ring system of the metal complex. It seems noteworthy that only a chelate of glycine with pyruvate and copper(II), not of one alanine with glyoxylate and copper(II), is isolated. In such a way we can describe the relative stability of fused ring systems containing aldehyde- or ketone-Schiff bases in connection with the transamination reaction.

The preparation and some properties of two new complexes, glyoxylidene-β-alaninatoaquocopper(II) and pyruvidene-α-alaninatoaquocopper(II), will also be described.

The Transamination Reaction of the Copper(II)-glyoxylate-α-alaninate System.—We prepared a pair of copper(II) Schiff base complexes which could be discriminated from each other only through the relative location of the >C=N– double bond in the fused-ring system, as is indicated by the structures I and II. The two complexes isolated

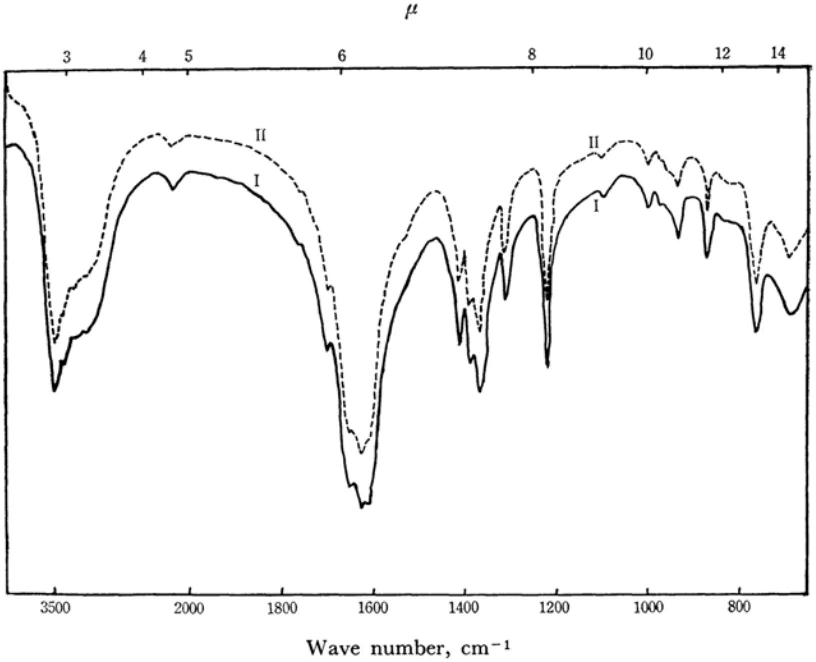


Fig. 1. Infrared spectra of [Cu pyv=gly(H_2O)]·$2H_2O$, I, and the complex derived from copper(II), α-alanine and glyoxylic acid, II.

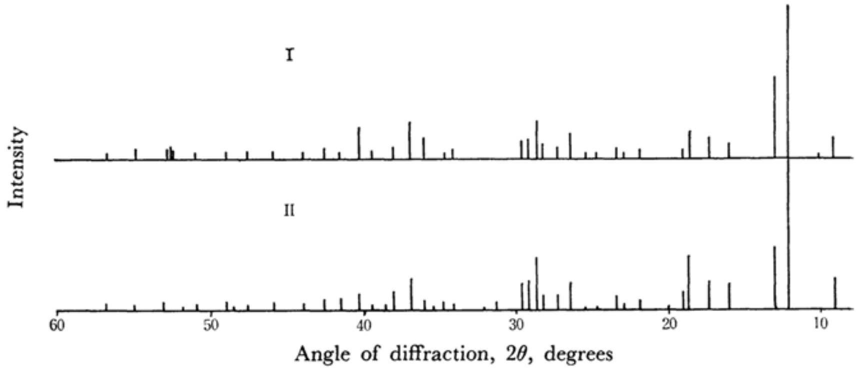
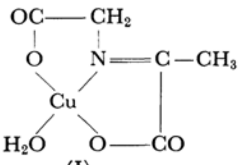
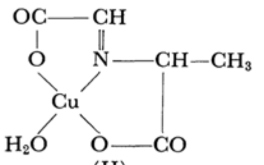


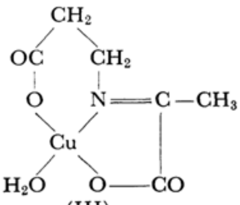
Fig. 2. X-Ray diffraction patterns of [Cu pyv=gly(H_2O)]·$2H_2O$, I, and the complex derived from copper(II), α-alanine and glyoxylic acid, II.

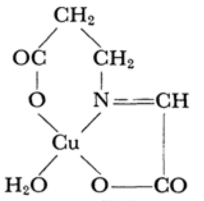
in the crystalline state, however, revealed that there was no difference in their colors, shapes and habits; both the compounds displayed the same decomposition temperature (192°C). No difference was observed either in their solubilities in water, ethanol and dimethylsulfoxide. The infrared study and the X-ray powder measurements of the two crystals also verified their identity, as is shown in Figs. 1 and 2 respectively, although there were some apparently meaningless small differences in relative intensity of the X-ray diffraction pattern. These differences can probably be supposed to be due to inevitable errors in the preparation of the powder. However, an additional decisive proof for the identity of the two compounds and the elimination of the possibility for the structure II was given by a cleavage reaction of the Schiff base >C=N– double bond of the respective complex. The two solutions obtained by precipitating copper(II) as cupric sulfide exhibited only one spot corresponding to glycine in the presence of pyruvic acid in their paper chromatographic examination. An amino acid analyzer was also employed to ascertain the above result. While the existence of glycine was confirmed for both the solutions, no sign for alanine was recorded in either case. If the real structure of the complex produced from the copper(II)-glyoxylate-alaninate system were II, α-alanine would have been detected instead of glycine.

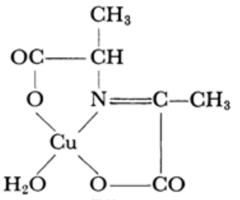
Although this kind transamination and of the glyoxylate-pyridoxamine system in the presence of metal ions have already been reported, the previous conclusions were drawn only from equilibrium studies of solutions[4]; the intermediate complexes were not isolated. Furthermore, it should be emphasized that the present transamination proceeds almost quantitatively. This may be one of the most clear-cut examples of an effective transamination catalyzed by a metal ion.

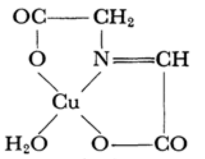

(I)
[Cu pyv=gly(H_2O)]


(II)
[Cu glyox=α-ala(H_2O)]


(III)
[Cu pyv=β-ala(H_2O)]


(IV)
[Cu glyox=β-ala(H_2O)]


(V)
[Cu pyv=α-ala(H_2O)]


(VI)
[Cu glyox=gly(H_2O)]

Thus it can be concluded that the complex I is more stable than the complex II (I>II).

Copper(II) Complexes of Schiff Bases with β-Alaninate.—The copper(II) complex of the Schiff base derived from β-alanine and pyruvic acid, III, was introduced in a previous paper.[3] In order to obtain knowledge concerning the delicate difference between aldehyde- and ketone-Schiff base complexes, the copper(II) complex of the Schiff base derived from glyoxylic acid and β-alanine, IV, has now been prepared.

First of all, no transamination reaction was observed in the cases of III and IV. This was recognized by means of the paper chromatographic examination of the solutions obtained from III and IV using the same procedure as was used for I and II. The decisive factor was the failure to find the spot for α-alanine or for glycine; only β-alanine was detected for both the solutions. It seems, however, rather reasonable that the transamination reaction in the β-alaninate-Schiff base complexes does not occur, since the electronic arrangement in the transaminated structure is supposed to be quite unfavorable for the stabilization of the fused-ring system. Apart from the transamination reaction, one may conclude, on the basis of the experimental data indicated in Table I, that the complex III is probably more stable than the complex IV. An inspection of Table I reveals that the decomposition temperature of the complex III is distinctly higher than that of IV, and that the polarographic half-wave potential for the reduction of copper(II) is more negative in III than in IV. In addition to those numerical data, their behavior in an aqueous solution shows that the complex III is more stable than IV. For instance, it is considerably difficult to recover the complex IV from its aqueous solution without decompsotion, while it is not so difficult to recover the complex III.

Although it is not the authentic way of discussing the stability of complexes, the above described view may aid in the consideration of the qualitative relative stabilities of the two compounds. Hence, we may conclude that pyruvidene-β-alaninatoaquocopper(II), III, is more stable than glyoxylidene-β-alaninatoaquocopper(II), IV (III>IV).

Copper(II) Complexes of Schiff Bases with α-Alaninate.—The complex produced from copper(II), α-alanine and glyoxylic acid has already

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[4] D. E. Metzler, J. Olivard and E. E. Snell, *J. Am. Chem. Soc.*, **76**, 644 (1954); H. Mix, *Z. physiol. Chem.*, **325**, 106 (1961).

TABLE I. PROPERTIES OF COPPER(II) SCHIFF BASE COMPLEXES

	Schiff base (ligand)	Decomp. temp. °C	Absorp. max. (ν_{max} in 10^{13} sec^{-1} and log ε_{max})	Half-wave potential vs. SCE at 25°C	Transamination reaction
I	Pyruvic acid and glycine	192—206	ν, 40.5 log ε, 1.85	$E_{1/2}^{(1)}$ −0.09 V. $E_{1/2}^{(2)}$ −0.42 V.	No
II	Glyoxylic acid and α-alanine	—	—	—	↑ Yes
III	Pyruvic acid and β-alanine	205—215	ν, 42.9 log ε, 1.82	$E_{1/2}^{(1)}$ −0.15 V. $E_{1/2}^{(2)}$ −0.28 V.	No
IV	Glyoxylic acid and β-alanine	188—193	ν, 42.9 log ε, 1.84	$E_{1/2}^{(1)}$ −0.05 V. $E_{1/2}^{(2)}$ −0.28 V.	No
V	Pyruvic acid and α-alanine	181—190	ν, 42.9* log ε, 1.62*	$E_{1/2}^{(1)}$ −0.09 V. $E_{1/2}^{(2)}$ −0.27 V.	No
VI	Glyoxylic acid and glycine	—	—	—	Probably yes

* These values for ν_{max} and log ε_{max} are considered as inappropriate to be the data for a fused ring system having two five-membered rings compared with those of other same type chelates.[3] This is perhaps because of a coexistence of a small amount of bis(alaninato)-copper(II) on which we described in the section of the Experimental.

TABLE II. SPECIFIC ROTATION OF A STANDARD AND THE RECOVERED L-α-ALANINE
Solvent: 1 N HCl, Cell: 5 cm.

Sample	$[\alpha]_D^{15}$	$[\alpha]_{500}^{15}$	$[\alpha]_{450}^{15}$	$[\alpha]_{400}^{15}$
L-α-Alanine (standard)	+14.3°	+20.9°	+27.8°	+40.4°
α-Alanine (recovered from the complex V)	+13.0°	+19.5°	+26.2°	+37.6°

been described above. The complex II is not isolated as crystals since it spontaneously transforms itself into the I structure. On the other hand, the complex derived from copper(II), α-alanine and pyruvic acid, V, is comparatively easy to prepare. In this particular case, however, the paper chromatographic test is not suitable for investigating the transamination reaction in the fused-ring system, since the solution obtained from V is always expected to give the spot for α-alanine, regardless of the transamination reaction, as may be understood from the V structure. We have, therefore, measured the loss of the optical rotatory power of the L-α-alanine recovered from the complex V. If the transamination reaction occurs freely in the fused-ring system, the alaninate moiety will transform into pyruvate, and, conversely, the original pyruvate moiety will transform into alaninate. In the course of that intramolecular rearrangement, L-α-alanine will entirely be racemized. However, we have observed just a slight loss of the rotatory power for the recovered alanine, even after the complex had been allowed to stand in water for more than three days at 30 to 40°C. It may, therefore, be concluded that no remarkable transamination reaction proceeds in the copper(II)-α-alaninate-pyruvate system. However, this finding doees not eliminate all possibility of transamination in the complex V, since our experiment has been confined to the neutral region.

As a matter of course, it can be asserted that the complex V is more stable than the complex II (V>II). This is because the complex II undergoes the transamination, while the complex V does not.

Attempts to Isolate the Copper(II) Complex of the Schiff Base Derived from Glyoxylic Acid and Glycine.—It has been disclosed above that the copper(II) complexes of glyoxylate-Schiff bases are always less stable than the corresponding complexes of pyruvate-Schiff bases. If this conclusion is valid, the fused-ring in the copper(II)-glyoxylate-glycinate system may be expected to be quite unstable, since the complex is obliged to have a glyoxylate moiety regardless of the transamination reaction, as may be understood from the VI structure. Indeed, all our efforts to isolate the complex VI have been in vain, though we could observe, for several minutes, a bluish green color which was probably due to the formation of the complex VI. It may be speculated that the instability of this particular complex originates from the violent transamination reaction occurring to-and-fro in the fused-ring system. Though we do not have a proper way of verifying this, an investigation using ^{18}O is now under way.

At all events, the complex VI is apparently less stable than the complex I or V (I>VI; V>VI).

The Structure of Fused-rings and the Transamination Reaction.—On the basis of the properties of the six copper(II) complexes, we have discussed the relationship between the structure of fused-rings and the relative stability of copper(II) Schiff base chelates in connection with the transamination reaction. All the findings concerning the relative stability of copper(II) complexes of aldehyde- and ketone-Schiff bases may be summarized as follows:

$$I > II; \; III > IV; \; V > II; \; V > VI; \; I > IV.$$

All these relations indicate that the fused-rings of aldehyde-Schiff bases are generally less stable than those of ketone-Schiff bases. Therefore, the transamination from the aldehyde- to the ketone-type structure corresponding to a stabilization of the fused-ring system in the metal chelate. On the other hand, it has already been pointed out that the copper(II) complexes of Schiff bases with β-alaninate do not undergo transamination, even in the case of the less stable aldehyde-type structure. This was elucidated in terms of the unfavorable electronic arrangement of the fused-ring system in the transaminated structure. However, it may also be supposed to be important to take into account that the β-alaninate Schiff base chelates are too stable to undergo transamination.

This is because of the previous conclusion that the fused-ring system with one five- and one six-membered ring is more stable than that with two five-membered rings.

By combining all this knowledge, we may suggest that *the non-enzymatic transamination reaction of the present kind can be expected only in such appropriately unstable fused-ring system as one with two five-membered rings and that it is generally accompanied by a stabilization of the system.* A different catalytic effect may be expected for a different metal ion; investigations of this are now in progress in this laboratory.

Experimental

Pyruvideneglycinatoaquocopper(II), I, [Cu pyv=gly(H_2O)].—The compound was prepared by the reaction of cupric acetate with a mixture of pyruvic acid and glycine according to the directions presented in a previous paper.[3)]

The Copper(II) Complex of the Schiff Base Derived from Glyoxylic Acid and α-Alanine.—To a mixture of 7.1 g. of D, L-α-alanine and 9.1 g. of sodium glyoxylate monohydrate in 25 ml. of aqueous ethanol (two-to-one by volume mixture) was added 4.8 g. of glacial acetic acid. Into this was added 16 g. of copper(II) acetate monohydrate with constant stirring at room temperature. The reaction was completed within one hour to give a dark blue solution, with the precipitation of pale blue microscopic crystals. After it had been filtered, the solution yielded more of the same product. The precipitate was recrystallized from a small amount of water. The final pure product appears as thin pale blue plates which begin to decompose at 192°C. The compound is soluble in water and dimethylsulfoxide and slightly soluble in ethanol, but it is insoluble in acetone and chloroform.

Found: C, 23.03; H, 4.27; N, 5.29; H_2O, 20.31. Calcd. for dihydrate of I or II: C, 23.00; H. 4.27; N, 5.36; H_2O, 20.65%.

All the experiment to discriminate the present complex from I were in vain. In other words, the complex was proved to be pyruvideneglycinatoaquocopper(II), I, and not glyoxylidene-α-alaninatoaquocopper(II), II.

Pyruvidene-β-alaninatoaquocopper(II), III, [Cu pyv=β-ala(H_2O)].—Although the method of preparing this compound has already been reported in a previous paper,[3)] the procedure used here was a little simplified by using cupric acetate and aqueous ethanol instead of freshly preciptated cupric oxide and water respectively.

Glyoxylidene-β-alaninatoaquocopper(II), IV, [Cu glyox=β-ala(H_2O)].—To a mixture of 5.1 g. of β-alanine and 6.5 g. of sodium glyoxylate monohydrate in 20 ml. of aqueous ethanol (two-to-one by volume mixture) 3.4 g. of glacial acetic acid was added. Into this 11.4 g. of copper(II) acetate monohydrate was added with constant stirring at room temperature. The reaction was completed within one hour, giving a dark blue solution. After it had been fiiltered, the solution was cooled at about 5°C. To this ethanol was added until the solution became turbid.

The reaction mixture was then allowed to stand for a few hours in a refrigerator. Hereupon a sky blue crystalline product was deposited.

The product was filtered and recrystallized from a small amount of water. M. p. 188—193°C(decomp.).

Found: C, 23.09; H, 4.20; N, 5.35. Calcd. for dihydrate of IV: C, 23.00; H, 4.21; N, 5.36%.

Pyruvidene-α-alaninatoaquocopper(II), V, [Cu pyv=α-ala(H_2O)].—Into a solution of 8.9 g. of D, L-α-alanine and 9 g. of pyruvic acid in 30 ml. of water 20 g. of copper(II) acetate monohydrate was added at 40°C with constant by stirring. The reaction was completed within one hour to give a dark blue solution. After it had been filtered, the solution was cooled at about 5°C. To this a large amount of ethanol was then added. Hereupon a large amount of a precipitate was obtained. This was recrystallized repeatedly from water by adding a large amount of ethanol. Finally the crystalline powder was washed by acetone and dried over silica gel. M. p. 181—189°C (decomp.). Found: C, 29.00; H, 4.55; N, 6.37; Cu, 25.5; H_2O, 10.2. Calcd. for hemihydrate of V: C, 29.03; H, 4.03; N, 5.65; Cu, 25.6; H_2O, 10.9%. As is clear from these values, the experimental values for nitrogen and hydrogen did not agree well with the corresponding calculated values on account of the difficulty in purifying the complex. However, this was not so serious as to negate the proposed structure, V, since there had to be taken into consideration the possibility of the co-precipitation of bis(alaninato)-copper(II) in such a recrystallization process as has been described above. The properties of the complex V are listed in Table I.

The Copper(II) Complex of the Schiff Base Derived from Glyoxylic Acid and Glycine.—Although the same method of preparation as was used for V was employed, only a dark brown solid, which was believed to be a decomposition product, was obtained. By the use of a nitrogen atmosphere, the reaction was improved to some extent, but no complex was isolated. In the midst of the reaction, however, a greenish blue solution, probably based on the formation of the complex VI, could be observed for a few minutes.

Other Chemicals Used.—Sodium glyoxylate was prepared from tartaric acid according to the method in the literature.[5] Unless otherwise specified, all the chemicals used in the measurements were of analytical reagent grade.

Transamination Study.—The following procedure was employed to estimate the transamination reactions in the fused-ring systems of chelates.

Through an aqueous solution of the chelate concerned, the hydrogen sulfide was bubbled until the bluish color characteristic of copper(II) complexes vanished. To this an appropriate amount of charcoal was added for the convenience of rapid filtration. After it had been filtered, the brown solution was concentrated to a small volume in vacuo at 30 to 40°C. The intact solution was used as a sample solution for the paper chromatographic test, which employed the solvent system of *n*-butanol : acetic acid : water (4 : 2 : 1) and Toyo filter paper No. 50. The same solution had to be appropriately diluted as a sample solution for an amino-acid analyzer. A Hitachi Amino-Acid Analyzer Model KLA-3 was used.

Optical Rotation Study.—The purpose of the experiment was to determine the loss of the optical rotatory power of L-α-alanine by the formation of the Schiff base chelate. Therefore, the specific rotation of a standard L-α-alanine was compared with that of a recovered α-alanine using several wave-lengths. The results are tabulated in Table II. In order to recover α-alanine from the pyruvidene-α-alaninatoaquocopper(II), V, principally the same procedure as that described above (Transamination Study) was employed. In this particular case, however, the complex solution had been allowed to stand at 30 to 40°C for about 75 hr. before the hydrogen sulfide was bubbled in; the solution which had been separated from cupric sulfide was evaporated to dryness in vacuo at about 50°C in order to remove the pyruvic acid. The white crystalline residue was dissolved in water and freed centrifugally from the insoluble residue. The solution was then concentrated again to a small volume. To this an appropriate amount of ethanol was added until the solution became turbid. When the solution was allowed to stand in a refrigerator, white crystals of α-alanine were deposited. These were used for the optical rotation study. The measurements were made by the use of a Yanagimoto Spectropolarimeter OR-100 at 15°C. The concentrations of α-alanine used were 4.77 and 4.79% in 1 N hydrochloric acid for the standard L-α-alanine and the recovered α-alanine respectively. The details are shown in Table II.

X-Ray Powder Measurements.—The X-ray powder patterns were recorded by the use of a Toshiba ADX-103 X-ray diffractometer at room temperature, with the Cu-$K\alpha$ line filtered through nickel. The diffraction patterns are depicted diagrammatically in Fig. 2.

Spectroscopic Measurements.—The visible and ultraviolet absorption spectra were determined with a Shimadzu Spectrophotometer QR-50 at room temperature. The solvent used in this work was water in all cases, while the concentration of the solutions varied from 10^{-2} to 10^{-3} M. Only the numerical data for the absorption band in the visible region are listed in Table I. The infrared spectra were recorded by the use of a Hitachi EPI-2 Infrared spectrophotometer. The measurements were made at room temperature using the pressed potassium bromide disk technique in the wave number range from 700 to 4000 cm^{-1} and using a rock salt prism.

The spectra obtained are shown in Fig. 1.

Polarographic Measurements. — The measurements were made with a Yanagimoto Recording Polarograph PA-102. An "H" cell was used, the reference electrode being a saturated calomel electrode and the whole cell being thermostated at 25±0.5°C. Pure distilled mercury was used throughout. Tank nitrogen was, without any further purification, bubbled through the sample to remove the dissolved oxygen. The concentration of the copper(II) chelates varied from 10^{-4} to 10^{-3} M. The supporting electrolyte used was 0.1 M potassium nitrate in all cases. The plot of log $i/(i_d - i)$ against the voltage revealed that the reduction wave for copper(II) was irreversible in all cases except in the complex I and the complex III. In addition, the half-wave potentials determined in this work for the complex I and the complex III did not agree well with the corresponding values reported previously.[3] This was, however, clarified as being due to the different concentration of the maximum suppressor, methyl red. As far as the present work was concerned, a constant concentration of methyl red was used throughout (0.03%).

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[5] D. E. Metzler, J. Olivard and E. E. Snell, *J. Am. Chem. Soc.*, **76**, 647 (1954).