drate and 0.125 g. (0.311 mmole) of nickel tosylate in 21 ml. of ethylene glycol dimethyl ether and 21 ml. of water was allowed to stand for 40 hr. at room temperature. The reaction was worked up as in the corresponding hydrolysis of carbo-(8-quinoloxy)-glycinanilide to give 0.1612 g. (77%) of glycinebenzylamide tosylate, m.p. 259–260°.

Carbobenzoxyglycylglycinebenzylamide.—To a stirred suspension of 2.53 g. of N-ethyl-5-phenylisoxazolium 3′-sulfonate[7] in 45 ml. of acetonitrile was added 2.09 g. of carbobenzoxyglycine and 1.01 g. of triethylamine and the resulting mixture was stirred for 1 hour at 0°. To the reaction mixture was then added a suspension of 2-amino-N-benzylacetamide in 50 ml. of acetonitrile and stirring was continued at the same temperature overnight. The reaction mixture was filtered to give 3.20 g. of material, m.p. 173–175°. The filtrate was evaporated to dryness under reduced pressure. The residue was taken up in saturated sodium bicarbonate solution and the insoluble material collected by filtration, washed with water and air-dried to give 0.80 g., m.p. 156–160°. The combined precipitates were recrystallized from 95% ethanol to give 3.30 g. (89%) of product, m.p. 161–162°. Further recrystallization from the same solvent did not change the melting point.

Anal. Calcd. for $C_{19}H_{21}N_3O_4$: C, 64.21; H, 5.96; N, 11.83. Found: C, 64.33; H, 5.92; N, 12.20.

Glycylglycine Benzylamide Hydrobromide.—A mixture of 2.6 g. of carbobenzoxyglycylglycinebenzylamide and 9 ml. of a 4 *N* solution of hydrogen bromide in acetic acid was heated for 5 min. on a steam-bath. The reaction mixture was diluted with ether and the solid material collected by filtration. The solid was washed with much ether and air-dried to give 2.27 g. of material, m.p. 205–208°. This material was recrystallized from ethanol–ether to give 1.74 g. (79%) of glycylglycinebenzylamide hydrobromide, m.p. 222–223°. Further recrystallization from the same solvent gave no further change in the melting point.

Anal. Calcd. for $C_{11}H_{16}BrN_3O_2$: C, 43.72; H, 5.34; N, 13.91. Found: C, 44.09; H, 5.23; N, 14.18.

Carbo-(8-quinoloxy)-glycylglycinebenzylamide.—To a suspension of 0.318 g. (1.0 mmole) of glycylglycine benzylamide hydrobromide in 3 ml. of methanol was added 0.544 ml. (1.0 mmole) of a 1.84 *N* solution of sodium methoxide in methanol and the mixture was swirled until a clear solution was obtained. The methanol solution was evaporated to dryness under reduced pressure. The residue was taken up in 10 ml. of methylene chloride and the resulting suspension was filtered. To the filtrate was added 0.316 g. (1.0 mmole) of bis-(8-quinolyl) carbonate and the resulting solution was kept at 0° for 8 hr. The reaction mixture was evaporated to dryness under reduced pressure. The residue was triturated with several portions of ether and the solid material obtained was collected by filtration to give 0.360 g. (92%) of product, m.p. 130–132°. The analytical sample was recrystallized to constant melting point from 2-butanone–ether; m.p. 132–133°.

Anal. Calcd. for $C_{21}H_{20}N_4O_4$: C, 64.27; H, 5.14; N, 14.28. Found: C, 63.91; H, 4.97; N, 14.16.

Glycylglycinebenzylamide Tosylate.—A solution of 0.201 g. (0.512 mmole) of carbo-(8-quinoloxy)-glycylglycinebenzylamide and 0.104 g. (0.256 mmole) of cupric tosylate in 17 ml. of acetone and 17 ml. of water was allowed to stand at room temperature for 0.5 hr. The reaction was worked up as in the hydrolysis of carbo-(8-quinoloxy)-D,L-phenylalaninecyclohexylamide to give 0.139 g. (69%) of glycylglycinebenzylamide tosylate, m.p. 236–237°. The analytical sample was recrystallized to constant melting point from ethanol–ether; m.p. 238–239°.

Anal. Calcd. for $C_{18}H_{23}N_3O_5S$: C, 54.95; H, 5.89; N, 10.68. Found: C, 55.07; H, 5.74; N, 10.78.

[CONTRIBUTION FROM THE CONVERSE LABORATORY OF HARVARD UNIVERSITY, CAMBRIDGE 38, MASS.]

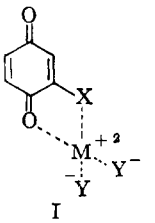
Acylation by a Metal-ion Salt–Quinone System

BY E. J. COREY AND HORST KÖNIG[1]

RECEIVED AUGUST 2, 1962

Metal-ion salts, *e.g.*, carboxylates, are converted to the corresponding anhydrides (or esters in the presence of an alcohol) by interaction with the coördinating quinone 6,7-dichloro-5,8-quinolinequinone (II, DQQ). The quinone is simultaneously transformed into the complexed 6-oxy-7-chloro-5,8-quinolinequinone anion. The properties of the metal salt–DQQ combination are detailed as is the evidence concerning chemical mechanisms.

Intensification of the electrophilic character of an organic grouping by coördination with a metal cation is fundamental to many cases of catalysis by such ions, including Friedel–Crafts syntheses, the Meerwein–Ponndorf–Oppenauer processes and certain hydrolytic reactions.[2–4] The electron-withdrawing capacity of metal ions also accounts for their function as catalysts through stabilization of negative charge.[5] Superimposed on the simple electron-withdrawing effect is the extremely favorable entropy factor in cases of stable chelate ring formation,[6–8] a matter of enormous importance in the area of biochemistry.[9] The present paper concerns an investigation of the effect of metal cation coördination on an already electron-deficient quinonoid system of the type I with X a coördinating



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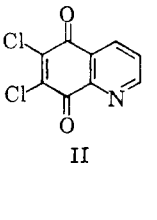


II

group in the quinone molecule, M a divalent chelating metal ion and Y^- an appropriate anion. At the outset it was anticipated that in a complex such as I the quinonoid moiety would be electron deficient relative to the uncoördinated condition with the result that its reactions with nucleophiles would be accelerated both at oxygen and at carbon. Such complexes might be potent hydride acceptors, for

(1) Research Associate under a grant (G-14473) from the National Science Foundation.

(2) H. Kroll, *J. Am. Chem. Soc.*, **74**, 2036 (1952).

(3) M. L. Bender and B. W. Turnquest, *ibid.*, **79**, 1889 (1957).

(4) M. L. Meriwether and F. H. Westheimer, *ibid.*, **78**, 5119 (1956).

(5) *Cf.* M. Sato, K. Okawa and S. Akabori, *Bull. Chem. Soc., Japan*, **30**, 937 (1957); M. Murakami and K. Takahashi, *ibid.*, **32**, 308 (1959).

(6) F. Basolo and R. G. Pearson, "Mechanisms of Inorganic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1958, Chapter 8.

(7) A. E. Martell and M. Calvin, "The Chemistry of Metal Chelate Compounds," Prentice–Hall, Inc., Englewood Cliffs, N. J., 1956, Chapter 8.

(8) M. Stiles and H. L. Finkbeiner, *J. Am. Chem. Soc.*, **81**, 505 (1959); M. Stiles, *ibid.*, **81**, 2598 (1959).

(9) See F. H. Westheimer in "The Enzymes," Academic Press, Inc., New York, N. Y., Second Edition, Chapter 6, 1959.

example. It also seemed possible that the combined effect of the electron-deficient quinone and the metal cation might promote a chemically significant electron withdrawal from Y^-. In the extreme the Y groups might even become electrophiles. The specific quinone chosen for the initial studies was 6,7-dichloro-5,8-quinolinequinone (II, herein abbreviated as DQQ), a strongly oxidizing quinone of structure analogous to the strong chelating agent 8-hydroxyquinoline.

One of the first observations made in this study was that the quinone DQQ exhibited remarkable reactivity toward metal salts. With copper salts in hydroxylic media, for example, a rapid reaction set in as evidenced by formation of deeply colored solutions and/or precipitates (purple to brown) from which the starting DQQ (pale yellow in color) could not be recovered.

It is noteworthy, however, that DQQ is stable under comparable conditions in the absence of metal ion. Thus, it may be recrystallized without appreciable decomposition from boiling *n*-butyl alcohol or hot acetic acid.

In non-hydroxylic media the reaction between DQQ and copper salts appeared to be much slower and, consequently, solvents such as chloroform and dioxane were chosen for the study of the interaction of the metal salt–quinone combination with various substrates. In an experiment to test the possibility of metal-ion enhanced hydride removal by DQQ, a solution of DQQ and 4-methoxybenzhydrol in chloroform was treated with copper trifluoroacetate (chosen because of its moderate solubility in chloroform). A rapid reaction ensued. However, the product from the benzhydrol was not the corresponding benzophenone as expected for hydride transfer to quinone,[10] but 4-methoxybenzhydryl trifluoroacetate. A similar result was obtained using zinc or nickel trifluoroacetate. In all these reactions a colored precipitate formed which contained the quinoline residue in some modified form. The infrared and ultraviolet spectra of the precipitated material were drastically different from those of DQQ and indicated that the quinonoid system was altered in some way. With DQQ, copper trifluoroacetate and ethanol in chloroform, ethyl trifluoroacetate was produced and no acetaldehyde could be detected (by infrared analysis). Approximately two moles of ethyl ester was formed per mole of copper trifluoroacetate starting with a molar equivalent of DQQ. In addition, the reaction of copper acetate or magnesium acetate and ethanol with DQQ produced ethyl acetate and smaller amounts of acetic acid. It is clear that the metal ion is indispensable in this process since an experiment with tetramethylammonium acetate, ethanol and DQQ, under the same conditions, gave no visible reaction and neither ethyl acetate nor acetic acid could be detected by infrared assay. Furthermore, DQQ is necessary also since the cupric salts and ethanol alone do not react under the above conditions. In a similar reaction, treatment of the cupric salt of *o*-hydroxymethylbenzoic acid with DQQ produced phthalide in good yield.

(10) *Cf.* E. A. Braude, R. P. Linstead, P. W. D. Mitchell and K. R. H. Wooldridge, *J. Chem. Soc.*, 3595 (1954), and earlier papers in the series.

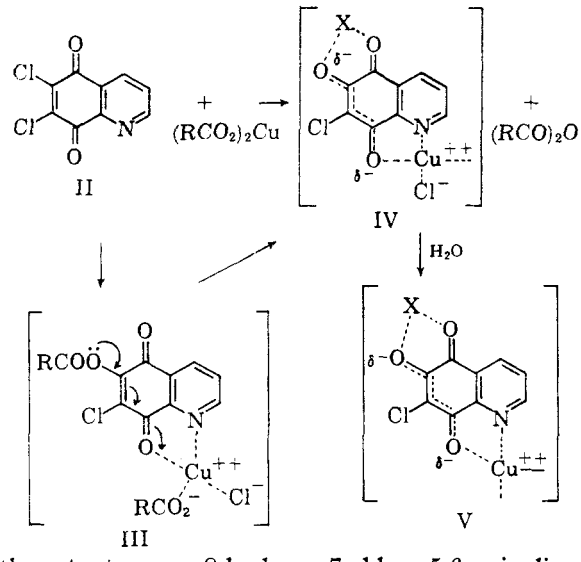
Even more striking evidence for the formation of reactive acylating agents was obtained from experiments on the interaction of DQQ and metal salts in the *absence* of alcohols. Thus, the reaction of DQQ with cupric acetate in alcohol-free chloroform at reflux affords acetic anhydride and acetic acid (in yields of 42% and 5%, respectively, based on the stoichiometry $1DQQ + 1Cu(OAc)_2 \rightarrow 1Ac_2O$ or 2HOAc). Again the quinone was transformed into a purple precipitate containing strongly complexed copper (not broken down by aqueous Versene). Also, it was shown that the coördinating metal ion is necessary for reaction. In a control experiment in which tetramethylammonium acetate was substituted for cupric acetate under the above conditions, no acetic anhydride or acid was formed and the DQQ was unchanged.

The purple solids obtained as a product of the above-described acylation reactions with DQQ and cupric ion salts appeared to be identical despite variation of the copper salt and the reaction conditions. The composition of this complex, which is clearly vital to the understanding of the acylation process, has been defined by the following experimental data. The complex was prepared by reaction of DQQ and cupric undecylenate (chosen because of its good solubility) in dioxane solution at room temperature. The initially blue-green solution gradually turned red-brown and deposited a purple precipitate which was collected by filtration, washed well with dioxane and dried. The dioxane soluble product was a mixture of undecylenic anhydride and undecylenic acid (the latter was probably formed as a result of the presence of traces of water in the reaction mixture). Treatment of the precipitate with cold distilled water resulted in a modified insoluble copper complex with the removal of one-half the original copper as *cupric chloride.* The water-insoluble part was treated with hydrogen sulfide which precipitated all the remaining copper and left a yellow solution containing an equivalent amount of 5,6,8-trihydroxy-7-chloroquinoline, isolated quantitatively as the triacetate derivative.[11] Thus it appears that during the acylation reaction the 6-substituted chlorine atom is displaced and consequently that the over-all reaction of DQQ with a cupric salt should be formulated as (in which. . . X represents coördination with other metal ions in the solid lattice).

The effect of metal-ion coördination with DQQ is evidently to render the quinone susceptible to nucleophilic attack by carboxylate at C(6) giving, probably by way of intermediate III,[12] a polydentate complex of the 6-oxy-7-chloro-5,8-quinolinequinone anion with cupric ion as an insoluble product (IV). Treatment with water removes cupric chloride but leaves the polymeric complex V. In agreement with the formulation of the water-treated complex as V, it has been shown that an identical material is produced directly from 6-hydroxy-7-chloro-5,8-quinolinequinone[11] (possibly

(11) Prepared as described in the Experimental part from the known 6-hydroxy-7-chloro-5,8-quinolinequinone [D. W. Schellhammer and S. Petersen, *Ann.*, **624**, 108 (1959)].

(12) Alternatively it is possible that the addition of carboxylate ion to C(6) is followed by concerted elimination of acyl chloride with formation of the oxyquinone anion complex directly (*vide infra*).



the tautomer 8-hydroxy-7-chloro-5,6-quinolinequinone) and cupric ion in aqueous solution (as judged by infrared and ultraviolet absorption, physical properties and chemical behavior). The electron-withdrawing effect of the coördinated metal ion in the DQQ system can be expected to operate not only at C(6) but also on a 6-acyloxy substituent. As a consequence, the complex III clearly should be a very effective acylating agent. It should also be noted that the stability (and insolubility) of the chelate IV serves to increase the *extent* of anhydride formation or acylation.[13]

One view of the reaction of DQQ with metal-ion salts is that this represents a process in which part of the oxidation potential of the quinone is applied to power acylation by over-all transfer of electron deficiency to an otherwise unreactive anionic group. In this sense there is a formal connection with biochemical oxidative phosphorylation.[14] Because of this similarity we thought it of interest to investigate the possible formation of a pyrophosphate from the corresponding phosphate anion using DQQ under the usual (anhydrous) conditions. In this experimentation the salt of trimethylene phosphate monoanion was used for solubility reasons. Indeed, it was observed that interaction of DQQ with this cupric salt led to the formation of isolable quantities of bis-trimethylene pyrophosphate, characterized by m.p. and spectral comparison with an authentic sample. Although this result has only indirect biochemical significance, it is an unusual and interesting example of quinone-promoted phosphorylation.

The study of metal-catalyzed reactions of quinones beyond the special case of DQQ is obviously desirable and this is contemplated. At present we are in a position to report only a few additional data on other quinonoid systems. First it appears that most non-complexing quinones, *e.g.*, chloranil, generally do not show any special behavior in the presence of metal ions. Secondly, the combination of 1-aza-9,10-anthraquinone (VI) with various metal ions also does not exhibit unusual reactivity; neither acylation nor enhanced oxidation has been observed. This may be due to the intrinsic low electron deficiency of this particular quinone, a member of the relatively stable anthraquinone series. 1,10-Phenanthroline-5,6-quinone (VII) was also investigated as a possible oxidizing agent in the presence of cupric tosylate but again no reaction was obtained under mild conditions (*e.g.*, with benzhydrol in dimethyl sulfoxide at room temperature).

Experimental[15]

Preparation of Quinones.—6,7-Dichloro-5,8-quinolinequinone (II,DQQ) was synthesized according to Urbanski[16] and was obtained as stable yellow crystals, m.p. 218–220° from *n*-butyl alcohol. 1-Aza-9,10-anthraquinone[17] and 1,10-phenanthroline-5,6-quinone[18] were also obtained by procedures previously described.

Reaction of Trifluoroacetate and Acetate Salts with DQQ and Alcohols.—Copper, magnesium and nickel trifluoroacetates were prepared by reaction of excess anhydrous trifluoroacetic acid with the carbonates, evaporation of the excess acid and drying at 100° *in vacuo*. Analysis was performed by passing a solution of a weighed sample of salt through a column of protonated Amberlite-IR-100 ion-exchange resin and titrating the liberated acid. The esterification reactions were generally performed at room temperature (or at reflux for shorter times) with DQQ, the alcohol and the metal salt in dry chloroform or dioxane. The precipitate was removed by filtration and the filtrate analyzed for products. The precipitates formed with cupric ion (IV) and with nickel were purple, those with zinc and magnesium were red. In the case of the reactions of ethanol, the volatile products were determined by quantitative infrared analysis and gas chromatography; 4-methoxybenzhydryl trifluoroacetate was identified by the characteristic carbonyl absorption at 5.60 μ and the lack of hydroxyl absorption. The reactions of the copper and nickel salts were generally faster than those of magnesium or zinc, as expected on the basis of coördinating ability. With an excess of ethanol and equivalent amounts of salt and quinone the yields of ester (moles) per mole of salt were approximately: trifluoroacetate 1.9, acetate 1.7. Control experiments in which the acid and ethanol were heated under appropriate conditions showed that part (but not all) of the yield of ester could have been formed by an esterification of free acid and ethanol under the reaction conditions. Identical experiments using cupric trifluoroacetate or acetate and ethanol *without* DQQ gave no ester and a similar result was obtained with DQQ and tetramethylammonium salts as mentioned below.

Reaction of DQQ with Cupric Acetate.—A mixture of 1 mmole of DQQ and 2 mmoles of cupric acetate in 8 ml. of dry alcohol-free chloroform was heated at reflux for 16 hours under anhydrous conditions. The volatile materials were distilled into a Dry Ice trap at 1 mm. and the distillate was subjected to quantitative infrared analysis which showed the presence of a total of 0.42 mmole of acetic anhydride and 0.10 mmole of acetic acid. The non-distillable residue was a purple solid identical with that identified below from DQQ and cupric undecylenate.

(13) Proton donors appear to be relatively ineffective in promoting acylation. For example, it was observed that treatment of DQQ with excess acetic acid alone at 115° for 30 minutes neither produced acetic anhydride nor consumed DQQ. Infrared analysis of the recovered DQQ showed the absence of 6-acetoxy-7-chloro-5,8-quinolinequinone (lack of characteristic strong absorption at 5.59 μ).

(14) See, D. E. Green, *Adv. in Enzymol.*, **21**, 73 (1959); G. E. W. Wolstenholme and C. M. O'Connor, Editors, "Ciba Foundation Symposium on Quinones in Electron Transport," Little-Brown Co., Boston, Mass., 1961.

(15) Analyses by the Scandinavian Microanalytical Laboratory, Copenhagen, Denmark. Vapor phase chromatography was performed with a commercial (F and M) apparatus using authentic reference compounds and infrared comparison. The infrared analyses were carried out with Perkin–Elmer model 21 and Infracord instruments.

(16) T. Urbanski and St. Kryzanowski, *Roczn. Chem.*, **27**, 390 (1953); *C. A.*, **49**, 1041b (1955).

(17) M. Yokote, Y. Shimizu and T. Tanimoto, *J. Chem. Soc. Japan, (Ind. Chem. Sect.)*, **54**, 219 (1951).

(18) G. F. Smith and F. W. Cagle, Jr., *J. Org. Chem.*, **12**, 781 (1947); J. Druey and P. Schmidt, *Helv. Chim. Acta*, **33**, 1080 (1950).

Control Experiments with DQQ and Tetramethylammonium Acetate or Acetic Acid. A.—In order to prove the hypothesis that the complexing of a cation with DQQ was necessary to effect acylation of an alcohol, tetramethylammonium acetate was substituted for cupric and magnesium acetates under conditions which were known to lead to ethyl acetate. Thus, 1 mmole of DQQ, 0.5 mmole of tetramethylammonium acetate and 5 mmoles of ethanol in chloroform were heated at reflux for 12 hours. Removal of the volatile material and infrared analysis showed the absence of ethyl acetate or acetic acid in the distillate. The residue contained the DQQ unchanged.

B.—A mixture of 1 mmole of DQQ and 2 mmoles of tetramethylammonium acetate in 10 ml. of dry alcohol-free chloroform was heated at reflux for 36 hours and then distilled under reduced pressure into a Dry Ice trap. The volatile fraction contained only chloroform (infrared analysis) and the residue only DQQ and the starting acetate salt. The lack of absorption at 5.59μ in the recovered DQQ indicated the absence of any appreciable amount of 6-acetoxy-7-chloro-5,8-quinolinequinone.[11]

C.—One mmole of DQQ and 500 mg. of glacial acetic acid were heated at 115° for 30 minutes. The volatile part which was distilled into a cold trap (−78°) at 100 mm. was shown to be acetic acid, free of acetic anhydride, by infrared analysis. The yellow solid residue was unchanged DQQ, m.p. 220–222°, free of 6-acetoxy-7-chloro-5,8-quinolinequinone[11] as determined by the lack of infrared absorption at 5.59 μ.

Analysis and Constitution of the Complex from DQQ and Cupric Salts.—The purple complexes obtained from copper salts and DQQ in the various experiments were essentially indistinguishable by the various tests described below and spectroscopically, and so these are considered to be identical. Though almost insoluble in water, the complex dissolves in strong base or acid giving red or yellow solutions, respectively. The complex is easily reduced and is dissolved to give yellow solutions by the reducing agents: sodium borohydride, stannous chloride–hydrochloric acid and sulfur dioxide. Essentially colorless solutions are formed after oxidation with bromine water or permanganate–aqueous pyridine.

The purple solid as precipitated from chloroform or dioxane exhibits characteristic infrared absorption at 5.82, 6.2 and 6.55 μ (the last a very strong band); these bands persist after washing with water which serves to remove ionic chlorine and that part of the cupric ion which is weakly bound. The water-washed insoluble complex is not broken down by treatment with aqueous solutions of: 8-hydroxyquinoline, ethylenediaminetetraacetic acid, triethylenetetramine and 1,10-phenanthroline. On the other hand these substances (and also cyanide ion) appear to increase the solubility of this material in water.

No chromatographic data were obtained on the cupric complex because of its insolubility. However, the analogous magnesium complex, which is more soluble, appeared to be homogeneous by paper chromatography in aqueous solution or column chromatography on alumina or protonated Dowex-50 in aqueous solution.

A sample of the purple complex was prepared for structural studies from 10 mmoles of DQQ and 10 mmoles of cupric undecylenate in 400 ml. of purified dioxane kept at room temperature until no further change could be seen. After collection of the precipitate, washing with dioxane and drying, 3.69 g. of purple solid was obtained. A 584-mg. portion of this material (15.8% of the entire complex) was washed with demineralized water and the extract (400 ml.) was treated with nitric acid and silver nitrate to precipitate chloride. A total of 215.3 mg. of silver chloride (1.53 mmoles) was isolated. This corresponds to *ca.* 10 mmoles of chloride for the total precipitate or one chloride ion for each molecule of DQQ involved in the reaction. Another portion of the precipitate was washed with water and treated with hydrogen sulfide to give a precipitate of cupric sulfide. This was dissolved in aqua regia, evaporated to dryness with sulfuric acid, diluted with water and titrated for cupric ion using standard ethylenediaminetetraacetic acid solution with murexide indicator. In this way it was calculated that *ca.* 4 mmoles of cupric ion was removable from the original precipitate by washing with water. Thus the water wash removes essentially one mole of cupric chloride per mole of quinone.

An aliquot of the water-washed insoluble complex was treated with hydrogen sulfide in dilute hydrochloric acid. The insoluble cupric sulfide was filtered and subjected to copper analysis as described above. This showed that 5.16 meq. of copper remained in the precipitate as calculated for the entire run after water washing. The aqueous solution from precipitation of cupric sulfide was treated with sodium acetate and a large excess of acetic anhydride under nitrogen for 48 hours at room temperature. Concentration of the aqueous solution under reduced pressure and extraction with benzene gave, after removal of solvent, 5,6,8-triacetoxy-7-chloroquinoline. This was sublimed *in vacuo* to give pure triacetate, m.p. 179–180°, in amount corresponding to 10 mmoles for the entire run (quantitative yield based on the starting DQQ). This product was identical with an authentic sample (prepared as described below) by infrared and n.m.r. spectra and mixed m.p.

The analytical procedure thus accounts for all the DQQ as complexed in the form of a 6-oxy-derivative, all the displaced 6-chloro atoms as ionic chlorine in the complex and essentially all the copper. The dioxane solution from the formation of this complex afforded mainly undecylenic anhydride and some undecylenic acid.

Finally a sample of complex V was prepared directly from 6-hydroxy-7-chloro-5,8-quinolinequinone[11] and cupric ion in aqueous solution. It was obtained as a purple precipitate which had chemical properties and infrared spectrum identical with the water-insoluble complex from the DQQ–metal salt reactions.

Anal. Calcd. for $C_{18}H_6O_6N_2Cl_2Cu \cdot H_2O$: C, 43.3; H, 1.6; Cl, 14.2. Found: C, 42.5; H, 1.7; Cl, 14.8.

5,6,8-Triacetoxy-7-chloroquinoline.—A solution of "6-hydroxy-7-chloro-5,8-quinolinequinone" (possibly the tautomer 8-hydroxy-7-chloro-5,6-quinolinequinone)[11] in aqueous hydrochloric acid was reduced with sulfur dioxide and evaporated under reduced pressure. Acetylation of the residue with acetic anhydride, evaporation and extraction with benzene gave solid triacetate which was purified by sublimation at 120° (0.005 mm.); colorless needles, m.p. 180°.

Anal. Calcd. for $C_{15}H_{12}ClNO_6$: C, 53.35; H, 3.58; N, 4.15; Cl, 10.50. Found: C, 53.30; H, 3.61; N, 4.37; Cl, 10.79.

Reaction of DQQ with Cupric *o*-Hydroxymethylbenzoate.—The cupric salt was precipitated from a concentrated aqueous solution of the barium salt (from phthalide and barium hydroxide) with concentrated cupric chloride and was dried at 110° *in vacuo* before use. Reaction of 1 mmole of DQQ with 1 mmole of the cupric salt in chloroform at reflux for 40 hours gave the usual purple precipitate and a colorless solution from which 1.54 mmoles of pure phthalide was obtained.

Reaction of DQQ with Cupric Trimethylene Phosphate.—A mixture of 1 mmole of cupric trimethylene phosphate and 0.5 mmole of DQQ in 100 ml. of dry alcohol-free chloroform was heated at reflux for 110 hours. The purple solid was separated by filtration, the filtrate was concentrated and the residue was recrystallized several times from acetonitrile–ether using Norite to give colorless needles of bistrimethylene pyrophosphate, m.p. 134–136°, identical mixed m.p. and infrared spectrum with an authentic sample.[19]

The starting cupric salt was prepared from the cylic monohydrogen phosphate of propane-1,3-dial-(trimethylene phosphoric acid),[19] m.p. 89°, neut. equiv. 142 (calcd. 138), using excess basic cupric carbonate in water. Filtration of the reaction mixture, evaporation and drying (at 140°) *in vacuo* gave blue crystals, slightly soluble in chloroform or dimethylformamide, more soluble in dimethyl sulfoxide.

Attempted Reactions of Other Quinone–Metal Ion Systems. A. Chloranil.—A mixture of 1 mmole of chloranil, 1 mmole of cupric acetate, 4 mmoles of ethanol and 8 ml. of chloroform was heated to reflux for 90 hours. Collection of volatile materials in a cold trap and infrared analysis of the distillate showed the complete absence of carbonyl compounds. Thus formation of acetaldehyde, ethyl acetate or acetic acid can be excluded.

(19) H. G. Khorana, G. M. Tener, R. S. Wright and J. G. Moffatt, *J. Am. Chem. Soc.*, **79**, 430 (1957).

B. **Aza-9,10-anthraquinone.**—An experiment similar to that described above with equimolar amounts of quinone and copper salt and excess ethanol gave neither acetaldehyde nor ethyl ester after 100 hours at reflux. Another experiment with the quinone, cupric tosylate and benzhydrol in dimethyl sulfoxide solution gave no benzophenone (infrared analysis) after 5 days at room temperature; benzhydrol was recovered nearly quantitatively.

C. **1,10-Phenanthroline-5,6-quinone** in experiments identical to those described under B was completely ineffective in causing oxidation or acylation, although a green cupric complex is readily formed.

[CONTRIBUTION FROM THE JAMES BRYANT CONANT LABORATORY OF HARVARD UNIVERSITY, CAMBRIDGE, MASS., AND THE DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY, EVANSTON, ILL.]

Imidazole Catalysis of the Hydrolysis of δ-Thiovalerolactone

BY F. H. WESTHEIMER AND MYRON L. BENDER

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Bruice and Bruno recently published a study of the hydrolysis of δ-thiovalerolactone, catalyzed by imidazole. They reported a maximum in the *p*H–rate profile, determined two apparent *pK* values, which can account for the maximum, and proposed a mechanism for the reaction. They derived equations directed toward showing how one of the apparent *pK*'s can be represented as a complex kinetic quantity, rather than as the *pK* of any particular group present in the reactants or intermediates. However, their kinetic analysis is here shown to be inconsistent with the principles of dynamic equilibrium. An alternative mechanism, consistent with their data, is proposed.

In a recent issue, Bruice and Bruno[1] published a kinetic study of the hydrolysis of δ-thiovalerolactone, catalyzed by imidazole. They reported a *p*H–rate maximum near 7.8, and analyzed the *p*H–rate profile according to eq. 1 in terms of two ionization constants: that of imidazole, K_1, and an apparent constant, $\bar{K}$, to which they assigned the value 4.78×10^{-9}. They proposed the mechanistic scheme shown in Chart I, and derived kinetic equations which were intended to account for $\bar{K}$. Unfortunately, their kinetic analysis is unsound. An alternative mechanism, presented in Chart II, is in agreement with their data.

$$k_{obs} = \frac{k}{[(\bar{K}/(H^+)) + 1][((H^+)/K_1) + 1]} \quad (1)$$

The published study[1] shows two pathways by which an intermediate is formed from imidazole and thiolactone (Chart I). The various rate and equilibrium constants along these two pathways leading to IH″ are necessarily related, since the same thermodynamic equilibrium for the intermediate must be achieved without regard to path. The required relationship (see Appendix) is expressed by eq. 2.

$$k_1k_4K_3K_4 = k_2k_5K_2 \quad (2)$$

The approximations essential to Bruice and Bruno's argument are in direct conflict with this equation. From the scheme of Chart I, Bruice and Bruno derive eq. 3 (their eq. 5) for the disappearance of thiolactone L.

$$-d(L)/dt = \frac{k_3[k_1(H^+) + k_5K_2]}{(H^+)\left(k_3 + \frac{k_2}{K_3}\right) + k_4K_4}(L)(ImH) \quad (3)$$

Then they assume that "k_5K_2 may be ignored," *i.e.*, that in eq. 3

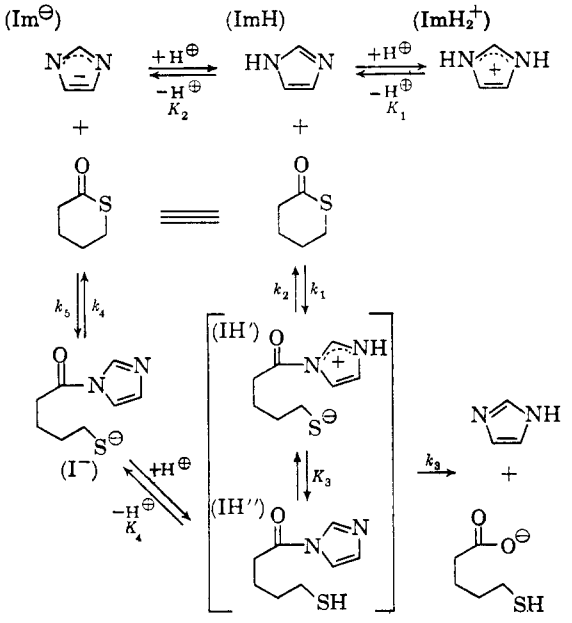
$$k_5K_2 << k_1(H^+) \quad (4)$$

But if the inequality of eq. 4 is assumed, then, from eq. 2

$$k_4K_4 << (k_2/K_3)(H^+) \quad (5)$$

This comparison appears in the denominator of eq. 3. If k_5K_2 in the numerator of eq. 3 is neglected, then, k_4K_4 in the denominator of eq. 3 *must* also be neglected. This algebraic requirement is equivalent to the statement that if the forward reaction to the intermediate *via* k_5 is negligible, then the reverse reaction *via* k_4 is likewise negligible. The presentation may be considered an example of the principle of microscopic reversibility; the violation of this principle is shown even without this algebraic demonstration by eq. 9 of Bruice and Bruno.[1]

CHART I



The inclusion of the product-forming step with rate constant k_3 in the kinetic eq. 3 does not in any way change these conclusions. The value of k_3 will not affect the free energy of any of the reactants, or the equilibrium constant for the formation of the intermediate which would obtain if k_3 were zero; therefore k_3 cannot affect the validity of eq. 2. Further, inspection of eq. 3 shows that the introduction of k_3 can only further reduce the importance of the product k_4K_4. If this term must be neglected

(1) T. C. Bruice and J. J. Bruno, *J. Am. Chem. Soc.*, **84**, 2128 (1962).