CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY,
MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE, MASSACHUSETTS 02139

Reactions of Coordinated Ligands. Some Studies on Bis-Salicylideneamine Chelates of Copper and Nickel

BY G. A. AULD AND A. DAVISON

Received July 12, 1967

Transesterification studies on bis[N-(alkoxycarbonylalkyl)salicylideneaminato]metal complexes, particularly those where alkoxy = *t*-butoxy, indicate that a dissociative mechanism with subsequent activation of the carbonyl group of the coordinated ligand is the preferred mechanism for the rapid ester exchange. A new reaction for coordinated ligands in this general class is reported, namely, the rapid transesterification of bis[N-(alkoxyglycylcarbonylmethyl)salicylideneaminato]-metal(II) complexes. Support for the proposed mechanism comes from the isolation of the tetradentate complexes ammonium N-(glycylatocarbonylmethyl)salicylideneaminatometalate(II) (M = Ni and Cu). Deuterium-exchange studies have shown that the rapid racemization of bis[N-(alkoxycarbonylalkyl)salicylideneaminato]metal(II) complexes is due to a unique proton exchange at the α position *via* a short-lived carbanion intermediate.

Schiff base complexes of amino acids have been the subject of considerable research since their discovery by Pfeiffer. He observed[1] a number of interesting reactions of coordinated amino acid esters. His proposed mechanism for the racemization of these complexes, which involves a tautomeric equilibrium between a salicylideneaminato chelate and an *o*-hydroxybenzyliminato chelate, has been frequently quoted.[2-5]

We present evidence which substantiates a suggested alternative mechanism[4,5] involving the collapse of a carbanion intermediate similar to those proposed for other azomethine reactions.[6] We also show that the proton exchange, which leads to racemization, is independent of the facile transesterification reactions of these chelates. Further, studies on the transesterification reactions show that the peptide linkage in glycylglycine ester complexes is stable to hydrolysis while the terminal ester group undergoes transesterification.

Experimental Section

Infrared spectra were measured for Nujol mulls on a Perkin-Elmer 237B spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer. Amino acids and esters were obtained from Mann Research Laboratories or Eastman Organic Chemicals. All melting points are uncorrected.

Preparation of Compounds.—The bis-salicylideneaminato chelates listed in Table I were prepared by Pfeiffer's methods[1] of condensation or ester exchange. The condensation procedure involves the refluxing of a mixture of the bis-salicylaldehydato chelate, the appropriate amino acid ester hydrochloride, and sodium acetate in alcohol solution. Ester exchange is effected by refluxing a product of the preceding reaction with a large excess of the appropriate alcohol.

Glycine *t*-butyl ester was prepared by the method of Moore and Rydon.[7] The *t*-butoxy chelates (Table I) are best prepared by the condensation of the free ester with the bis-salicylaldehydato chelate in benzene.

Ammonium N-(Glycylatocarbonylmethyl)salicylideneaminatocuprate(II).—A mixture of 1.0 g (0.0033 mol) of bis(salicylaldehydato)copper(II), 0.5 g (0.0038 mol) of glycylglycine, and 0.5 g (0.006 mol) of ammonium acetate was refluxed for 30 min in 50 ml of methanol. The violet solution was cooled and the product separated as flocculent plates. These were removed and washed first with cold methanol and then with diethyl ether. Recrystallization from 25 ml of ethanol and drying *in vacuo* at 80° for 12 hr gave 0.9 g (65%) of the product as violet plates which did not melt below 300°. *Anal.* Calcd for $C_{11}H_{13}CuN_3O_4$: C, 41.82; H, 4.46; N, 13.36. Found: C, 42.45; H, 4.34; N, 13.16.

Ammonium N-(Glycylatocarbonylmethyl)salicylideneaminatonickelate(II).—The complex was prepared in 70% yield, as orange plates, from bis(salicylaldehydato)nickel(II) dihydrate in a manner similar to that described above. *Anal.* Calcd for $C_{11}H_{13}NiN_3O_4$: C, 42.45; H, 4.53; N, 13.59. Found: C, 42.29; H, 4.35; N, 13.47.

Bis(salicylaldehydato)diamminecopper(II).—Dry ammonia gas was passed through a solution of 1 g (0.0033 mol) of bis(salicylaldehydato)copper(II) in 50 ml of dichloromethane for 10 min. The product separated immediately and was removed by filtration. It was washed with dichloromethane and air dried to give 1.0 g (89%) of the product as a pale green powder. *Anal.* Calcd for $C_{14}H_{16}CuN_2O_4$: C, 49.48; H, 4.75; N, 8.24. Found: C, 49.90; H, 4.56; N, 7.87.

When this material was refluxed in benzene for 30 min it was completely converted to bis(salicylaldehydato)copper(II). However, heating in ethanol with an equal weight of sodium acetate for 30 min resulted in complete conversion to bis(salicylideneaminato)copper(II).

Bis(salicylaldehydato)diamminenickel(II).—The yellow-green complex was prepared in 50% yield from bis(salicylaldehydato)-dipyridinenickel(II)[8] by the procedure described above. *Anal.* Calcd for $C_{14}H_{16}NiN_2O_4$: C, 50.19; H, 4.82; N, 8.36. Found: C, 50.30; H, 4.74; N, 7.98.

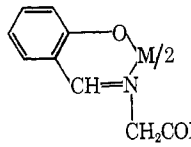
Bis(salicylaldehydato)nickel(II).—Drying the diammine *in vacuo* at 110° for 60 hr produced the pale green product. *Anal.* Calcd for $C_{14}H_{10}NiO_4$: C, 55.87; H, 3.35. Found: C, 55.26; H, 3.55.

Magnetic Measurements.—Measurements were made by the Gouy method. Mercury tetrathiocyanatocobalt(II) was used as a standard. Susceptibilities were determined at four different field strengths for three samples of each compound measured. The following average magnetic moments were found: bis(salicylaldehydato)diamminenickel(II), $10^6\chi^M_{cor}$ = 4410, μ_{eff} =

(1) P. Pfeiffer, W. Offerman, and H. Werner, *J. Prakt. Chem.*, **159**, 139 (1942).
(2) A. E. Martell and M. Calvin, "Chemistry of the Metal Chelate Compounds," Prentice-Hall, Inc., New York, N. Y., 1952.
(3) S. Chaberek and A. E. Martell, "Organic Sequestering Agents," John Wiley and Sons, Inc., New York, N. Y., 1959.
(4) F. P. Dwyer in "Chelating Agents and Metal Chelates," F. P. Dwyer and D. P. Mellor, Ed., Academic Press Inc., New York, N. Y., 1964, p 355.
(5) R. H. Holm, G. W. Everett, and A. Chakravorty, *Progr. Inorg. Chem.*, **7**, 83 (1966).
(6) D. J. Cram and R. D. Guthrie, *J. Am. Chem. Soc.*, **87**, 397 (1965).
(7) A. T. Moore and H. N. Rydon, *Org. Syn.*, **45**, 47 (1965).
(8) F. Basolo and W. R. Matoush, *J. Am. Chem. Soc.*, **75**, 5665 (1953).

TABLE I

BIS-SALICYLIDENEAMINATO CHELATES



			Analyses, %					
			Calcd			Found		
R	M	Mp, °C	C	H	N	C	H	N
O(*i*-C_3H_7)[a]	Cu	189–190	57.30	5.60	5.56	56.99	5.77	5.47
O(*sec*-C_4H_9)[a]	Cu	174–175	58.69	6.06	5.27	58.72	6.03	5.34
O(*t*-C_4H_9)[b]	Cu	194–195	58.69	6.06	5.27	59.08	6.20	5.24
O(*t*-C_4H_9)[b]	Ni	199–200	59.23	6.12	5.31	59.47	6.13	5.29
$NHCH_2CO_2C_2H_5$[b]	Cu	228–229	52.92	5.13	9.49	53.18	5.48	9.29
$NHCH_2CO_2C_2H_5$[b]	Ni	269–270	53.36	5.17	9.57	53.03	5.14	9.13
$NHCH_2CO_2CH_3$[c]	Cu	224–225	51.29	4.66	9.97	51.41	4.77	9.80

[a] Prepared by ester exchange from bis[N-(ethoxycarbonylmethyl)salicylideneaminato]copper(II). [b] Prepared by condensation. [c] Prepared by ester exchange from bis[N-(ethoxyglycylcarbonylmethyl)salicylideneaminato]copper(II).

3.27 BM; bis(salicylaldehydato)nickel(II), $10^6\chi_{cor}^M$ = 4665, μ_{eff} = 3.36 BM. Measurements were made at 26°.

Deuterium-Exchange Studies.—O-Deuterioethanol was prepared in 80% yield by refluxing equimolar quantities of diethyl sulfite and deuterium oxide with a trace of hydrochloric acid for 12 hr. The product was distilled four times with alternate freezing under vacuum to remove the remaining sulfur dioxide. O-Deuterio-*t*-butyl alcohol was prepared in 60% yield by refluxing an excess of potassium *t*-butoxide with deuterium oxide in diethyl ether for 24 hr. The product was dried over calcium oxide and separated by fractional distillation in apparatus previously washed with dilute base.

A solution of 1.2 g (0.0025 mol) of bis[N-(ethoxycarbonylmethyl)salicylideneaminato]copper(II) in 20 ml of C_2H_5OD was refluxed for 1 hr. The solution was cooled and filtered to yield 1.0 g (88%) of the deuterated product. Copper was removed from the chelate with a large excess of disodium ethylenediaminetetraacetate by the method of Houghton and Pointer[9] to give the phenol as a yellow solid. The nmr spectrum of the ligand dissolved in carbon tetrachloride showed (Figure 1): τ 2.1 (0.95), azomethine proton; τ 3.00 (3.9), AA'BB' pattern, aromatic protons; τ 6.0 (2.7), a singlet (τ 5.9), α-methylene protons superimposed on a quartet ($J_{CH_3-CH_2}$ = 6.5 cps) from methylene protons of the C_2H_5 group; τ 8.9 (3.0) ($J_{CH_2-CH_3}$ = 6.5 cps), methyl protons. The undeuterated material gave a similar spectrum (Figure 1) with τ 2.1 (0.95), 3.9 (4), 6.0 (4), and 8.9 (3).

A sample of bis[N-(ethoxycarbonylmethyl)salicylideneaminato]copper(II) was prepared from stoichiometric amounts of glycine ethyl ester and salicylaldehyde in C_2H_5OD and copper acetate and sodium acetate in D_2O. The nmr spectrum of the ligand removed from this complex was similar to that in Figure 1a, with τ 2.1 (0.95), 3.9 (4.0), 6.0 (3.1), and 8.9 (3).

Identical spectra were obtained from samples isolated by extraction with EDTA in H_2O and EDTA in D_2O.

A sample of 0.1 g of bis[N-(*t*-butoxycarbonylmethyl)salicylideneaminato]copper(II) was refluxed in 10 ml of *t*-C_4H_9OD for 1 hr. The solution as cooled and filtered to give the deuterated product. The ligand was removed by the usual procedure and the nmr spectrum of the yellow solid was taken in carbon tetrachloride solution: τ 2.1 (1.0), azomethine proton; τ 3.9 (4.0), aromatic protons; τ 6.2 (1.2), a singlet, methylene protons; τ 9.0 (9.0), a singlet, methyl protons. The nmr spectrum of the undeuterated material gave the following values: τ 2.1 (1.0), 3.9 (4.0), 6.2 (2), 9.0 (9.0).

Results and Discussion

Pfeiffer's initial observations[1] that transesterification of bis[N-(alkoxycarbonylmethyl)salicylideneaminato]

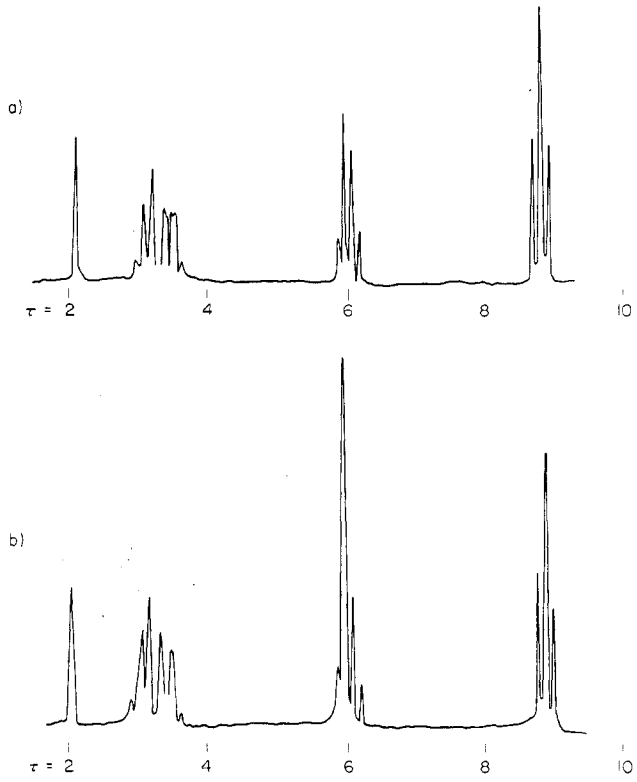


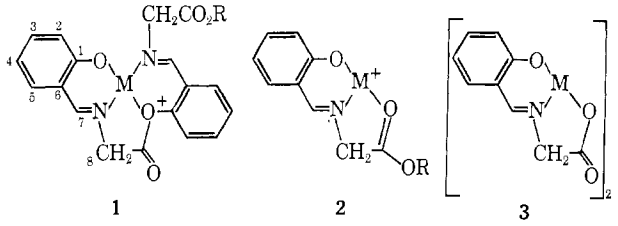
Figure 1. Nmr spectra of N-(ethoxycarbonylmethyl)salicylideneamine: (a) deuterated, (b) normal.

complexes of copper and nickel occurred rapidly by refluxing the complexes in primary alcohols have been confirmed and extended in two recent reports, both of which suggested mechanisms for the reaction. The first by Verter and Frost[10] called attention to the apparent specificity of this reaction to a *trans* arrangement in the bis chelate. The proposed mechanism involved the formation of an internal lactone-ring system utilizing attack by the *trans* oxygen of the salicylaldehyde fragment followed by elimination of an alkoxide ion from the ester group. Attack by the solvent alcohol opened the lactone ring in the intermediate **1** to give the new ester. The second mechanism proposed by

(9) R. P. Houghton and D. J. Pointer, *J. Chem. Soc.*, 3302 (1964).

(10) H. S. Verter and S. E. Frost, *J. Am. Chem. Soc.*, **82**, 85 (1960).

Houghton and Pointer[9] involves initial dissociation of one of the N-(alkoxycarbonylmethyl)salicylideneaminato ligands. The carbonyl group of the ester in the resulting cation is activated by the metal ion to give an intermediate such as **2** which is attacked by solvent alcohol to generate the new ester grouping. Support for this mechanism came in part from transesterification reactions performed in aqueous alcoholic media which gave in addition to the transesterified product substantial amounts of the N-acetatosalicylideneaminatometal complex (**3**). In this mechanism,

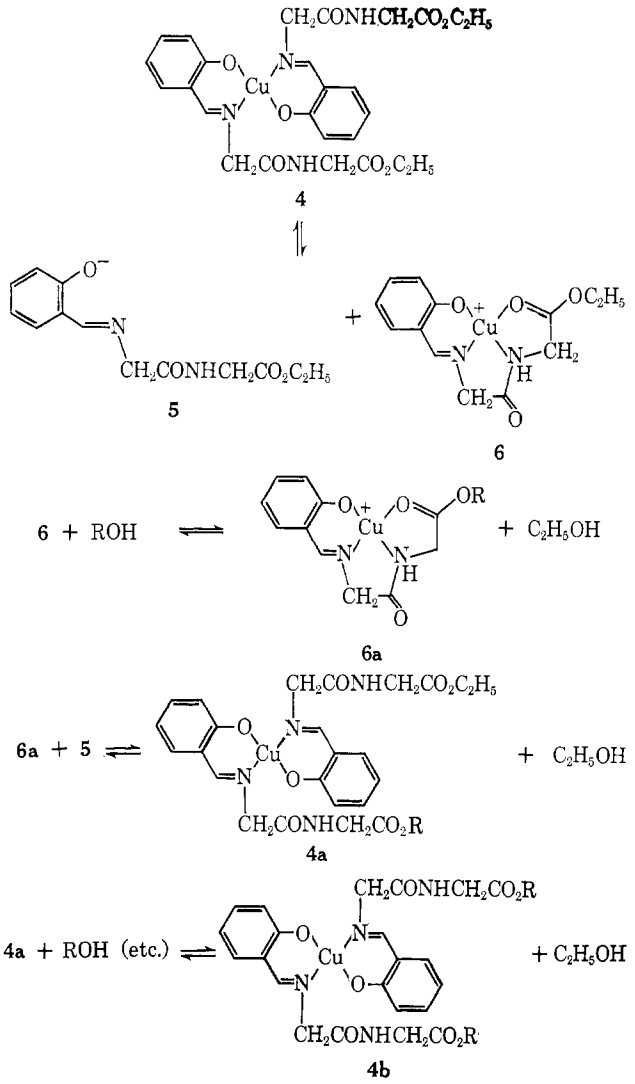


1 **2** **3**

unlike the previous one, the metal ion is an acid catalyst[11] for the transesterification reaction.

We have found that while transesterification proceeds rapidly for secondary alcohols, it does not occur with tertiary alcohols such as *t*-butyl alcohol even when refluxed for 60 hr. Significantly, however, bis[N-(*t*-butoxycarbonylmethyl)salicylideneaminato]copper(II), prepared from glycine *t*-butyl ester and bis(salicylaldehydato)copper(II), undergoes transesterification reactions fairly rapidly; *e.g.*, in methanol the reaction is complete within 20 min. This observation seems more in accord with the dissociative mechanism than that proposed by Verter and Frost which embodies nucleophilic attack at the sterically hindered *t*-butoxycarbonyl group.

Our failure to achieve a peptide coupling reaction on the bis[N-(alkoxycarbonylmethyl)salicylideneaminato]copper(II) complexes with excess glycine *t*-butyl ester, utilizing the potential reactivity of the ester group by the coordinated amino acid, led us to investigate the stability of the peptide linkage in bis[N-(ethoxyglycylcarbonylmethyl)salicylideneaminato]copper(II) (**4**) prepared by condensation of glycylglycine ethyl ester, under conditions which lead to either rapid transesterification or hydrolysis of the amino acid ester complexes. This complex was quite stable in refluxing ethanol or aqueous ethanol and could be recovered unchanged. However, it underwent complete conversion to the methyl ester bis[N-(methoxyglycylcarbonylmethyl)salicylideneaminato]copper(II) (**4b**, R = CH_3) when refluxed in methanol for 4–6 hr. It seemed likely that the mechanism for this new reaction of a coordinated Schiff base ligand occurred *via* a dissociative process in which the intermediate positively charged species (**6**) activated the ester carbonyl group in a manner similar to that proposed for the amino acid ester exchanges.



4

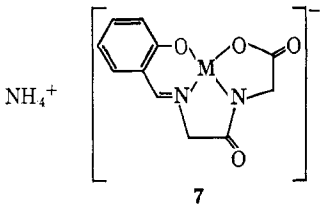
5 **6**

6a

4a

4b

Tetradentate N-(glycylatocarbonylmethyl)salicylideneaminatocuprate(II) complexes (**7**, M = Cu) simi-



7

lar in structure to that proposed for the intermediate **6** have been isolated from the reaction of glyclyglycine, copper acetate, and salicylaldehyde[12] or, more conveniently, by the addition of glycylglycine to a solution of bis(salicylaldehydato)copper(II) in the presence of ammonium acetate.

Another important feature of the bis[N-(alkoxycarbonylalkyl)salicylideneaminato]metal complexes is that rapid racemization prevents isolation of optically active products when resolved amino acid esters are used in their synthesis. We have carried out a number of exchange reactions on bis[N-(alkoxycarbonylmethyl)salicylideneaminato]copper(II) complexes in deuterio alcohols in order to determine whether the

(11) See ref 4, Chapter 8

(12) A. Nakahara, *Bull. Chem. Soc. Japan*, **32**, 1195 (1959).

racemization and exchange involve a tautomeric equilibrium between the salicylideneamine chelate and an *o*-hydroxybenzylimine chelate or the collapse of a carbanion intermediate. The former mechanism would produce deuterium labeling at both the azomethine position 7 and the α-methyl position 8 but the latter mechanism only at position 8. The complex bis[N-(ethoxycarbonylmethyl)salicylideneaminato]copper(II) underwent rapid exchange of only the methylene protons at position 8 either by refluxing the complex in deuterioethanol, in which it is sparingly soluble, or during the preparation of the complex by condensation of bis(salicylaldehydato)copper(II) and glycine ethyl ester in deuterio ethanol. The extent and position of the deuterium labeling could be readily determined from the nuclear magnetic resonance spectrum of the free ligand. The ligand was obtained when the complex, in chloroform solution, was extracted with an aqueous solution of disodium ethylenediaminetetraacetate to remove the copper. The spectra of the deuterated and undeuterated Schiff base are shown in Figure 1. The azomethine proton (7), τ 2.1, the aromatic protons (2, 3, 4, and 5), τ = 3.3, and the methyl protons, τ 8.9, of the ethoxy group are clearly the same relative intensity in both spectra; the only change is the marked decrease in intensity of the methylene protons (8) at τ 5.9 in the deuterium-labeled species. Similarly, deuterium-exchange reactions utilizing deuterio-*t*-butyl alcohol showed that exchange was rapid at position 8 in this solvent. This study rules out the unlikely intervention of a common ketene intermediate for both the transesterification and proton-exchange reactions, since *t*-butyl esters cannot be prepared by the transesterification reaction.

The formation of Schiff base chelates by the condensation of amino compounds with the bis(salicylaldehydato)metal complexes is thought to proceed *via* a coordinated aminocarbinol.[13] We have shown that the unstable complexes which result from the addition of ammonia are not four-coordinate aminocarbinol complexes but are rather six-coordinate, presumably tetragonal, bis(salicylaldehydato)diamminenickel(II) or -copper(II) complexes. The reaction of anhydrous ammonia with bis(salicylaldehydato)copper(II) in dichloromethane solution gives a pale green precipitate of the unstable diammine complex. This complex loses ammonia on heating *in vacuo* or when refluxed in benzene or toluene to give complete conversion to bis(salicylaldehydato)copper(II). The analogous diammine complex of nickel was readily prepared from bis(salicylaldehydato)dipyridinenickel(II) by treatment with anhydrous ammonia in dichloromethane solution. Its magnetic moment, μ_{eff} = 3.27 BM, indicates that it is a six-coordinate complex of nickel. It could be readily converted into anhydrous bis(salicylaldehydato)nickel(II) by heating *in vacuo* and represents the most convenient synthesis of the anhydrous bis chelate. However, heating these complexes in ethanol solution with sodium acetate converts them to the bis(salicylideneaminato)metal(II) complexes. We were unable to obtain bis adducts with free amino acid esters and the bis(salicylaldehydato)metal complexes under similar conditions. Instead very smooth conversion to bis[N-(alkoxycarbonylalkyl)salicylideneaminato]-metal(II) complexes occurred.

Acknowledgment.—Financial support by the National Science Foundation (Grants GP 3468 and GP 6672) is gratefully acknowledged.

(13) See ref 4, p 352.