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Macro Chelate Rings. II.[*1] Syntheses and Properties of 2,7-Dimethyl-4,5-bis(salicylideneaminomethyl)xanthone as a Quadridentate Chelating Agent and Its Metal Complexes

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2,7-Dimethyl-4,5-bis(salicylideneaminomethyl)xanthone, a new quadridentate chelating agent, was synthesized by a sequence of steps and subsequently characterized. Some divalent metal complexes of the ligand were isolated, and their properties were characterized on the basis of infrared spectra. The non-coplanar structure of the complex derived from the ligand was suggested by the resolution of a cobalt(II) complex into optical isomers.

No detailed study has been reported on the metal chelate with a macro chelate ring, in spite of the great interest in the configuration of the complex. In a preceding paper[1] we studied the syntheses and properties of a quadridentate chelating agent, 2,7-dimethyl-4,5-bis(salicylideneaminomethyl)acridone, and its metal complexes. Neither the complexes nor the ligand, however, was sufficiently stable for our ultimate purpose to utilize it as a catalyst for an assymmetric synthesis. One reason for the unstability of the ligand may be the presence of the acridone nucleus in it; this problem could be overcome by the replacement of the acridone nucleus by another more stable one with a similar structure, such as the xanthone nucleus.

In this work, therefore, the syntheses and the properties of a new quadridentate chelating agent, 2,7-dimethyl-4,5-bis(salicylideneaminomethyl)xanthone (I) (abbreviated as H_2SAX), with the xanthone nucleus in place of the acridone nucleus, were investigated, as were those of its metal complexes.

Results and Discussion

The synthetic scheme of the ligand I is shown in Chart 1. Although there have been some reports upon the synthesis of 2,7-dimethylxanthone V, in which the most reactive sites of xanthone are blocked by methyl groups, all of them are impractical for preparation in large quantities. We newly synthesized 2,7-dimethylxanthone V as follows. Starting from 2-bromo-4,4′-dimethyldiphenyl ether II, which had been obtained from 4,4′-dimethyldiphenyl ether, 2-cyano-4,4′-dimethyldiphenyl ether III was made by means of a modification of the Rosenmund-von

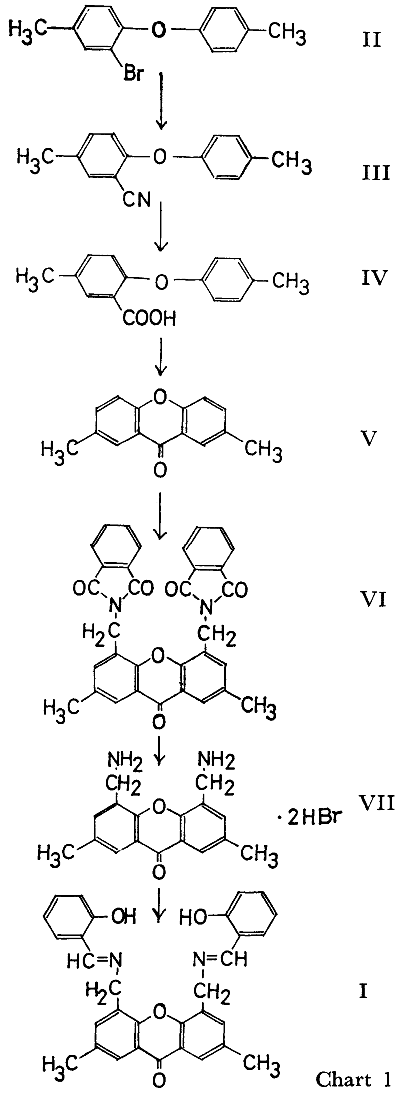

Chart 1

[*1] Part I: Ref. 1.

[1] H. Okawa and T. Yoshino, This Bulletin, **42**, 1934 (1969).

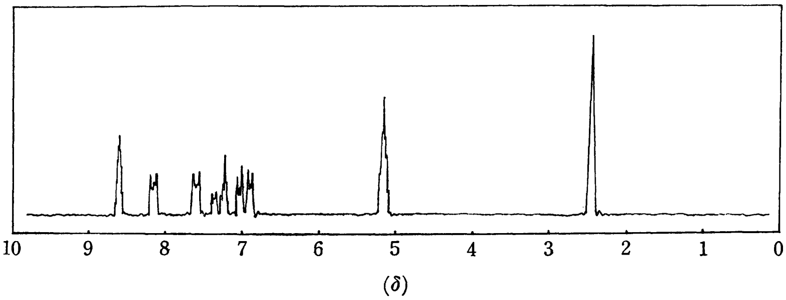

Chart 2. NMR spectrum of H_2SAX.

Braun reaction;[2] the bromide II and cuprous cyanide were treated in *N*,*N*-dimethylformamide, and then with a ferric chloride solution. The cyanide III thus separated was hydrolyzed with sodium ethoxide to give 4,4′-dimethyldiphenyl ether-2-carboxylic acid (IV), which was then converted to 2,7-dimethylxanthone V by treatment in hot sulfuric acid.

Like 2,7-dimethylacridone,[1] 2,7-dimethylxanthone could also be converted to 2,7-dimethyl-bis-(phthalimidomethyl)xanthone (VI) by treatment with *N*-hydroxymethylphthalimide; the compound VI was hydrolyzed in a mixture of hydrobromic acid and acetic acid to give 2,7-dimethyl-di(aminomethyl)xanthone dihydrobromide (VII). The di-(aminomethyl)derivative VII seemed stable only in its salt form, and the attempt to isolate the free diamine was unsuccessful. Because of the instability of the free diamine of VII, in addition to the insolubility of the compound VI, in most organic solvents, the positions of the substitution were tentatively assigned to 4 and 5 positions from a consideration of the meta-directing action of the carbonyl group in xanthone. The appropriateness of the assignment, however, was supported by the NMR spectrum of the compound I, which could be prepared from the diamine dihydrobromide VII and salicylaldehyde in the presence of an alkali.

The NMR spectrum of the ligand is given in Chart 2. The signal at $\delta=8.18$ can be attributed to protons at the 1 and 8 positions; both are strongly shielded by the carbonyl group in xanthone. On the other hand, the signal at $\delta=7.60$ is to be ascribed to the protons at the 3 and 6 positions, because the coupling constants of the peaks at $\delta=8.18$ and 7.60 are at least 1.7 Hz; this is consistent with the result given by Mathis and Goldstein.[3] The coupling constant, J_{13}, in xanthone itself is 1.78 Hz, while J_{14} is only 0.50 Hz. In this connection, two salicylideneaminomethyl groups must be at the 4 and 5 positions. The protons on the benzene rings are in the range of $\delta=6.95$—7.40. The protons of the methyl and methylene groups are at $\delta=2.45$ and 5.13 respectively, while the protons on the two azomethin groups appear at $\delta=8.61$, strongly shielded both by the phenyl group and by the C=N group.

The structure of the compound I was further confirmed by elementary analysis and by a study of the infrared spectrum, which indicated the existence of the chelated azomethin group at 1636 cm^{-1}. The C=O stretching vibration was observed at 1650 cm^{-1}.

Some stable divalent metal complexes have been derived from the ligand. They are listed in Table 1. Metal acetates were successfully used as a metal source, while metal chlorides and metal sulfates caused the decomposition of the ligand into salicylaldehyde and the diamine salt. The complex XIII was derived from XII by heating it under reduced pressure. Furthermore, we obtained two additional mixed complexes, XIV and XV, starting from XIII. The structures of the complexes thus obtained were confirmed by elementary analyses and by a study of the infrared spectra, which indicated a shift of the C=N stretching vibration from 1636 cm^{-1} in the ligand to near 1600 cm^{-1} and the appearance of a new absorption band in the range of 1535—1540 cm^{-1}; we could not assign the latter phenomenon, but it was useful for detecting a complex formation.

In the comparison of the infrared spectra of the ligand and the complexes, a recognizable blue shift of the C=O stretching vibration was observed in each case, demonstrating some interaction between a central metal atom and the ether oxygen atom. The bonding between them, however, was neglected because the infrared absorption peaks due to the ether bonding in the xanthone nucleus given by Kimoto[4] did not recognizably shift upon the complex formation, as would be expected from the very weak coordinating ability of the oxygen atom in diphenyl ether (Table 1). Thus, the ligand I acts as a quadridentate (Chart 3a) rather than as a quinquedentate chelating agent (Chart 3b). The blue shift (about 5 cm^{-1}) in the complexes XI, XIV and XV, which were characterized by their insolu-

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[2] L. Friedmann and H. Schechter, *J. Org. Chem.*, **26**, 2522 (1961).

[3] C. T. Mathis and J. H. Goldstein, *Spectrochim. Acta*, **20**, 871 (1964).

[4] S. Kimoto, *Yakugaku Zasshi*, **75**, 763 (1955).

TABLE 1. IR ABSORPTION PEAKS OF COMPLEXES

	Complex	C=O	C=N[a]	New band	Bands due to C–O–C				
I	H_2SAX	1650	1636		—[b]	1240	1213	1173	1150
VIII	CuSAX	1660	(1600)	1538	1315	1247	1215	1170	1153
IX	NiSAX	1659	(1600)	1540	1315	1247	1215	1170	1153
X	ZnSAX	1660	(1600)	1538	1315	1246	1215	1170	1152
XI	$MnSAX \cdot 2H_2O$	1656	(1600)	1537	1316	1249	1215	1175	1153
XII	$CoSAX \cdot H_2O \cdot 2Py$	1660	1597	1534	1318	1265	1217	1175	1153
XIII	$CoSAX \cdot \frac{1}{2}H_2O$	1660	(1600)	1536	1318	1270	1212	1174	1153
XIV	$CoSAX \cdot phen \cdot 2H_2O$	1655	(1600)	1535	1317	1265	1212	1173	1152
XV	$CoSAX \cdot bipy \cdot H_2O$	1655	(1600)	1535	1320	1265	1212	1175	1150

a) The absorption parenthesized could be detected as a shoulder on a strong C=C vibration peak.
b) The peak could not be detected by a strong absorption of phenolic oxygen.

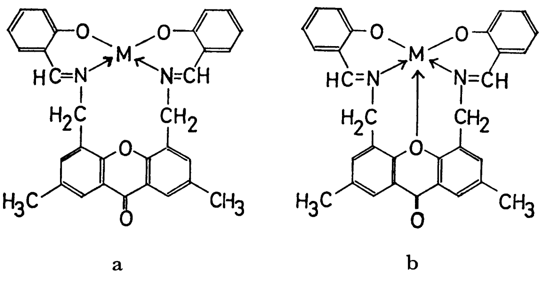

Chart 3

bility in most organic solvents and which were expected to possess an octahedral configuration, was smaller than that (about 10 cm^{-1}) in other, supposedly tetrahedral-configurational complexes (Table 1). The blue shift of the C=O stretching vibration upon a complex formation can be interpreted as the inhibition of the mesomery as a result of interaction between a metal cation and the positively-charged oxygen atom in a canonical form of the xanthone nucleus (Chart 4), while the larger blue shift in a tetrahedral complex than in an octahedral complex can be explained by the shorter distance between a metal and the ether oxygen in the former than in the latter. That is, the interatomic distance, which was roughly estimated from the model, beween a metal and the ether oxygen in an octahedral complex was about 3.5 Å, while that in a tetrahedral complex was about 2.8 Å.

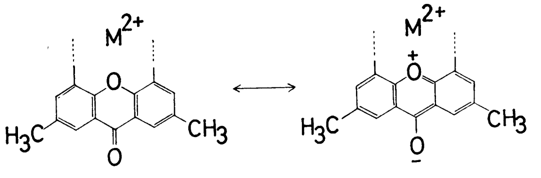

Chart 4

We have already suggested a non-coplanar structure for the complex derived from the ligand similar to I.[1] The visible spectrum of the copper complex, VIII, measured in chloroform had an absorption band centered around 720 mμ; this band was located at a longer wavelength than that at 580 mμ in a typical square planar copper(II) complex, bis-(salicylaldehyde)ethylenediimine-copper(II). This indicated that the copper complex VIII was nearly tetrahedral, but not planar. Another experimental fact regarding a non-coplanar structure was obtained by resolving the complex derived from I into optical isomers. Krebs *et al.*[5] observed that there was no separation unless the compound was soluble in water or an aqueous organic solvent, and that separation was better, in general, in water than in a solvent mixture when starch was used as an adsorbent. However, it seemed possible to resolve a complex using benzene as the eluent when D-glucose was utilized as an adsorbent. The only available complex for the separation was the complex XIII, which easily soluble in benzene and which could be recovered without any change in the complex. The eluate was separated into fifty fractions using a fraction collector. The combined first five fractions showed dextro-rotatory ($[\alpha]^{15}_{D}$ $+0.32°$), while the combined last ten fractions indicated levo-rotatory ($[\alpha]^{15}_{D}-0.98°$).

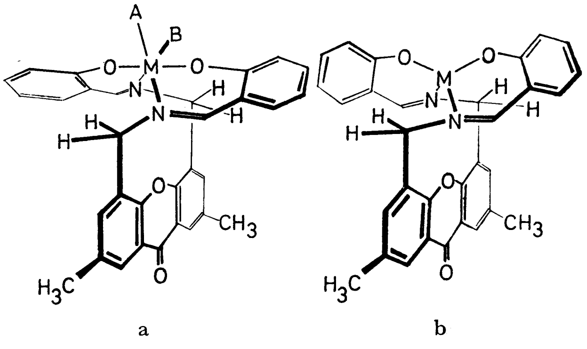

Chart 5. Probable structures for an octahedral complex (a) and a tetrahedral complex (b).

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[5] H. Krebs, J. Diewald and J. A. Wagner, *Angew. Chem.*, **67**, 705 (1958).

The appropriateness of a non-coplanar structure of a metal and four donor atoms in a complex was, therefore, assured by the partial resolution of the compound XIII into optical isomers. The supposed, most probable structures for an octahedral and a tetrahedral complex are given in Chart 5.

Experimental

Apparatus. The NMR spectrum was recorded on a Varian Associates A-60 model, using tetramethylsilane as the internal standard and $CDCl_3$ as the solvent. A Hitachi infrared spectrometer EPI-S2 was used for the measurement of the infrared absorption spectra in the 4000—650 cm^{-1} region. The visible spectra were measured on a Hitachi EPS-3T spectrophotometer. The specific rotations were measured using a Yanagimoto OR-20 polarimeter.

Syntheses. All melting points and boiling points are uncorrected.

2-Bromo-4,4′-dimethyldiphenyl Ether (II). To a solution of 4,4′-dimethyldiphenyl ether (99 g, 0.5 mol) in acetic acid (300 m*l*) containing iodine (0.1 g), we added bromine (81.6 g, 0.51 mol) at 80°C over a period of two hours. After the reaction mixture had then been heated on a boiling bath for one hour, it was poured into water. The bromide was extracted with benzene and distilled at 155—165°C/7 mmHg. The yield was 113 g.

Found: C, 60.39; H, 4.88%. Calcd for $C_{14}H_{13}OBr$: C, 60.67; H, 4.73%.

2-Cyano-4,4′-dimethyldiphenyl Ether (III). A mixture of the bromide II (110.8 g, 0.40 mol) and cuprous cyanide (45 g, 0.5 mol) in *N*,*N*-dimethylformamide (200 m*l*) was refluxed on an oil bath for five hours. The reaction mixture was then filtered out and poured into a solution of ferric chloride ($FeCl_3 \cdot 6H_2O$ 180 g, concd. HCl 30 m*l*, water 300 m*l*); after which the mixture was heated on a water bath for half an hour. The nitrile III thus separated was extracted with benzene and purified by distillation at 163—170°C/6 mmHg to give a colorless liquid (57 g), which soon solidified.

Found: N, 5.87%. Calcd for $C_{15}H_{13}NO$: N, 6.27%.

4,4′-Dimethyldiphenyl Ether-2-carboxylic Acid (IV). The nitrile III (57 g) was placed in an alcoholic sodium hydroxide solution (300 m*l*) and heated on an oil bath while being stirred. After forty hours a white mass of sodium salt of 4,4′-dimethyldiphenyl ether-2-carboxylic acid IV separated. It was collected and neutralized with hydrochloric acid; the free acid thus obtained was crystallized from alcohol to give colorless needles with a mp of 112—113°C. The yield was almost theoretical.

Found: C, 74.04; H, 5.84%. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82%.

2,7-Dimethylxanthone (V). Crude 4,4′-dimethyldiphenyl ether-2-carboxylic acid IV (50 g) was dissolved in concentrated sulfuric acid (150 m*l*), and then the mixture was heated on a boiling bath for two hours. After it had cooled, the reaction mixture was poured onto ice water to give a white precipitate. This precipitate was collected, washed with a 10% sodium bicarbonate solution and then with water, and crystallized from alcohol as colorless needles with a mp of 144°C. The yield was almost quantitative.

The compound, V, made by this new method was identified by the coincidence of our description with that of Kimoto *et al.*[6]

2,7-Dimethyl-4,5-bis(phthalimidomethyl)xanthone (VI). 2,7-Dimethylxanthone (15 g) and *N*-hydroxymethylphthalimide (25 g) were dissolved in chilled concentrated sulfuric acid (200 m*l*), after which the mixture was left standing at room temperature for a week. Then the reaction mixture was poured onto ice water to give a white precipitate, which was collected and washed with a 10% sodium bicarbonate solution and then with water. A portion was crystallized from acetic acid or dioxane for analysis. It formed colorless prisms with a mp of 262—265°C. The yield was 80—90%.

Found: C, 72.98; H, 4.17; N, 5.09%. Calcd for $C_{33}H_{22}N_2O_6$: C, 73.06; H, 4.09; N, 5.16%.

2,7-Dimethyl-4,5-di(aminomethyl)xanthone Dihydrobromide (VII). The compound VI (10 g) was suspended in a mixture of acetic acid (100 m*l*) and 40% hydrobromic acid (100 m*l*), and then the mixture was heated on an oil bath for eighty hours under stirring. The hot reaction mixture was filtered and cooled to give white needles, which were collected and recrystallized from water as colorless needles. The yield was about 2.5 g.

Found: C, 42.27; H, 5.25; N, 5.96%. Calcd for $C_{17}H_{10}N_2O_2Br_2$: C, 42.52; H, 5.04; N, 5.83%.

2,7-Dimethyl-4,5-bis(salicylideneaminomethyl-xanthone (I). The diamine dihydrobromide VII (2.0 g) and salicylaldehyde (1.5 g) were dissolved in a hot dilute ethanol (50%, 50 m*l*). To it was added a dilute aqueous sodium bicarbonate solution until neutralization; pale yellow needles (1.7 g) were thus obtained. These needles were recrystallized from dioxane as pale yellow needles with a mp of 225—226°C.

Found: C, 75.94; H, 5.58; N, 5.71%. Calcd for $C_{31}H_{26}N_2O_4$: C, 75.90; H, 5.34; N, 5.71%.

CuSAX (VIII). A solution of the ligand I (50 mg) in dioxane (15 m*l*) was added to a solution of copper acetate monohydrate (25 mg) in ethanol (10 m*l*). The mixture was heated on a water bath for one and a half hours. The greenish-brown precipitate which separated was collected and washed with ethanol.

Found: C, 67.48; H, 4.65; N, 5.19; Cu, 11.18%. Calcd for $C_{31}H_{24}N_2O_4Cu$: C, 67.44; H, 4.38; N, 5.09; Cu, 11.51%.

NiSAX (IX). This was obtained from the ligand (50 mg) and nickel acetate tetrahydrate (30 mg) as a green precipitate, which was collected and washed with ethanol.

Found: C, 67.85; H, 4.37; N, 5.30%. Calcd for $C_{31}H_{24}N_2O_4Ni$: C, 68.04; H, 4.05; N, 5.13%.

ZnSAX (X). This was prepared from the ligand (50 mg) and zinc acetate dihydrate (30 mg) as a yellow precipitate.

Found: C, 67.76; H, 4.51; N, 4.71%. Calcd for $C_{31}H_{24}N_2O_4Zn$: C, 67.22; H, 4.37; N, 5.06%.

MnSAX·2H₂O (XI). To a solution of I (50 mg) in pyridine (15 m*l*) there was added a solution of manganese acetate tetrahydrate (25 mg) in pyridine (15 m*l*); the mixture was then heated on a water bath for two hours

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[6] S. Kimoto, S. Sakai and K. Ohkuma, *Yakugaku Zasshi*, **69**, 155 (1949).

to give a whitish-brown precipitate, which was subsequently collected and washed with ethanol.

Found: C, 63.87; H, 4.67; N, 4.80; Mn, 9.89%. Calcd for $C_{31}H_{24}N_2O_4Mn \cdot 2H_2O$: C, 64.25; H, 4.87; N, 4.83; Mn, 9.48%.

CoSAX·H_2O·2Py (XII). A solution of I (100 mg) in pyridine (30 m*l*) was added to a solution of cobalt acetate tetrahydrate (60 mg) in pyridine (30 m*l*), and then the mixture was heated on a water bath for half an hour. After the reaction mixture had been concentrated to 10 m*l* and left standing over night, yellow prisms separated. These prisms were collected, recrystallized from pyridine, and air-dried at room temperature.

Found: C, 68.03; H, 5.11; N, 7.87; Co, 8.31%. Calcd for $C_{31}H_{24}N_2O_4Co \cdot H_2O \cdot 2Py$: C, 68.05; H, 5.01; N, 7.76; Co, 8.14%.

CoSAX·1/2H_2O (XIII). The compound XII was heated at 110°C/30 mmHg for five hours to give a brown powder which could subsequently be crystallized from dry benzene as orange needles.

Found: C, 67.02; H, 4.59; N, 5.20; Co, 10.69%; mol wt, 561(Chf). Calcd for $C_{31}H_{24}N_2O_4Co \cdot \frac{1}{2}H_2O$: C, 66.91; H, 4.59; N, 5.03; Co, 10.59%; mol wt, 556.49.

CoSAX·phen·2H_2O (XIV). The compound XIII (20 mg) and an excess of 1,10-phenanthroline were dissolved in ethanol (20 m*l*), and then the mixture was heated on a water bath for two hours. The orange precipitate which separated was collected and washed with ethanol. It was characterized by its insolubility in most organic solvents.

Found: C, 68.03; H, 4.58; N, 7.15%. Calcd for $C_{43}H_{32}N_4O_4Co \cdot 2H_2O$: C, 67.63; H, 4.75; N, 7.34%.

CoSAX·dipy·H_2O (XV). This was also prepared from the compound XIII (20 mg) and 2,2′-dipyridyl (excess) as a reddish-brown precipitate. It was also insoluble in most organic solvents.

Found: C, 68.33; H, 4.47; N, 4.55%. Calcd for $C_{41}H_{32}N_4O_4Co \cdot H_2O$: C, 68.24; H, 4.47; N, 4.76%.

Resolution of the Complex XIII. The conditions for the separation of the complex XIII were:

Adsorbent: anhydrous D-glucose (guaranteed reagent)
Diameter of column: 1.8 cm
Height of bed: 150 cm
Sample: Complex XIII, 70 mg
Eluent: benzene
Flow rate: about 6 m*l*/min.

The eluate was separated into fifty fractions by the use of a fraction-collector apparatus, Toyo Fraction Collector SF-200A. The first five fractions were combined, and the solvent was evaporated. A solution of the complex (1.25 mg) in chloroform (1.0 m*l*) showed a specific rotation of $[\alpha]_D^{15}$ +0.32°. The last ten fractions were combined, and the benzene was evaporated. A solution of the complex (0.90 mg) in chloroform (1.0 m*l*) showed a levo-rotation of $[\alpha]_D^{15}$ −0.98°.