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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Complex Compounds of Biogenic Metals, Aroxyacetic Acids, and Triethanolamine

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Abstract—A series of previously unknown promising biologically active compounds, complexes of biogenic metal salts, aroxyacetic acid salts, and triethanolamine, were prepared. The structure and acid–base properties of these compounds were studied by NMR and IR spectroscopy and by potentiometric titration.

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Organylheteroacetic acids and their salts with 2-hydroxyalkylamines exhibit high specific biological activity [1–6]. For example, triethanolammonium salts of *o*-methylphenoxy- and *o*-methyl-*p*-chlorophenoxyacetic acids of the general formula $RR^1C_6H_3OCH_2COO^-\cdot N^+H(CH_2CH_2OH)_3$, where R = *o*-$CH_3$, R^1 = H (**1**), R = *o*-CH_3, R = *p*-Cl (**2**) (cresacin, CR, and chlorocresacin, CCR, respectively) exhibit immunomodulatory and adaptogenic properties in immunity disorders and erythropoiesis dysfunctions and stimulate hemopoiesis [7]. With the aim to develop new biologically active compounds, we performed the reaction of CR and CCR with salts of biogenic metals (M) to obtain previously unknown complexes **3–10** (Table 1):

$$n[RR_1C_6H_3OCH_2COO^-\cdot N^+H(CH_2CH_2OH)_3] + MX_m \rightarrow n[RR_1C_6H_3OCH_2COO^-\cdot N^+H(CH_2CH_2OH)_3]\cdot MX_m$$

(**3**–**8**)

The melting points and yields of compounds **3–10** are given in Table 1.

Complex compounds **12** and **13** consisting of the same components as **3** and **4** but having a different structure were prepared by the reaction of zinc *o*-methoxyphenoxyacetate (MPA) (**11**) with triethanolamine (TEA):

$$(2\text{-}CH_3\text{-}C_6H_4OCH_2COO)_2Zn + n(HOCH_2CH_2)_3N$$
(**11**)

Table 1. Characteristics of the synthesized compounds

Compd. no.	*n*	*m*	R	R_1	M	X	Yield, %	T_m, °C
3	1	2	CH_3	H	Zn	Cl	98	115
4	1	2	CH_3	H	Zn	CH_3COO	89	103
5	2	2	CH_3	H	Mn	Cl	67	240
6	1	2	CH_3	H	Ni	Cl	71	242
7	2	2	CH_3	H	Ni	Cl	79	180,dec.
8	1	3	CH_3	Cl	Rh	Cl	70	165,dec.
9	1	2	CH_3	H	Co	Cl	72	240
10	1	2	CH_3	H	Cu	Cl	59	–

$\rightarrow (2\text{-}CH_3\text{-}C_6H_4OCH_2COO)_2Zn \cdot [(HOCH_2CH_2)_3N]_n$,

$n = 1$ (**12**); $n = 2$ (**13**).

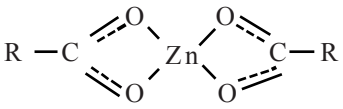
Compound **12** was also prepared by an exchange reaction of H(MPA) with a complex of zinc chloride with TEA:

$$2\ (2\text{-}CH_3\text{-}C_6H_4OCH_2COOH) + Cl_2Zn(HOCH_2CH_2)_3N \rightarrow (2\text{-}CH_3\text{-}C_6H_4OCH_2COO)_2Zn \cdot (HOCH_2CH_2)_3N + 2HCl \quad (\mathbf{12})$$

Compounds **3–13** are powders. Their structure was examined by IR spectroscopy and potentiometric titration. The IR spectrum of CR contains the vibration bands of the carboxylate ion at about 1590 [$\nu_s(COO^-)$] and 1403 cm^{-1}, and also absorption bands in the range 2700–2500 cm^{-1} [$\nu(N^+H)$]. The salt structure of CR is also preserved in its complexes with Mn (**5**) and Ni (**6, 7**). It is characterized by a broad $\nu(N^+H)$ band in the range 2700–2500 cm^{-1}.

The stretching vibration frequencies of the carbonyl group and the difference between the vibration frequencies of the carbonyl and carboxy groups $\Delta\nu = \nu(C{=}O) - \nu(C{-}O)$, which can be used for determining the structure of aroxyacetate complexes [8], are given in Table 2.

For compounds **5** and **6**, $\Delta\nu$ is large, 164 and 157 cm^{-1}, as for 1 (187 cm^{-1}), whereas for salt **11** $\Delta\nu$ is considerably smaller (75 cm^{-1}) than for **1**. Apparently, compound **11** is a bidentate chelate complex of the following structure:



Low values of $\Delta\nu$ (66 and 69 cm^{-1}) are also characteristic of compounds **12** and **13.** This fact suggests formation of coordination bonds between the metal atom and cresoxyacetate groups, as in **11**. Verkade et al. [9, 10], based on the results of X-ray structural analysis of the complexes $2TEA{\cdot}Cd(NO_3)_2$ and $2TEA{\cdot}Y(ClO_4)_3$, suggested the structure of *O*-hydrometallatranes containing HO → M and N → M coordination bonds. Apparently, compounds **12** and **13** also have an *O*-hydrometallatrane structure with one (**12**) or two (**13**) N→M coordination bonds. This also follows from the presence in the IR spectra of C–O stretching (1260, 1066 cm^{-1}) and C–H bending (916, 891 cm^{-1}) vibration bands of TEA and of the ν(OH) band at 3300 cm^{-1}, belonging to the hydroxy groups bound to M. At the same time, in the spectrum of 1 the ν(OH) band is located at 3170 cm^{-1}, which is characteristic of intermolecular hydrogen bonds.

Compounds **5**, **6**, **12**, and **13** and the starting compounds for their synthesis (TEA, H(MPA), CR) were studied by potentiometric titration. As titrants we used 0.1 N solutions of $HClO_4$ and KOH in MeOH. The concentration acidity and basicity constants calculated from the titration curves are given in Table 3.

The CR molecule containing TEA and MPA fragments is bipolar. This is indicated by the value of pK_a obtained by titration with $HClO_4$, which appeared to be lower than pK_a obtained in titration with KOH. Shielding with three CH_2CH_2OH groups of the H atom bound to the N atom increases the basicity of CR compared to TEA. Compounds **5** and **6**, which are complexes of CR with Mn and Ni chlorides, respectively, react with $HClO_4$ under the conditions of potentiometric titration with the formation of two (**5**) or one (**6**) equivalent of H(MPA). Titration with KOH results in exchange of the Cl atoms by the OH group, with preservation of the structure of compounds **5** and **6** as a whole. In titration with $HClO_4$ of compounds **10** and **11**, for which the *O*-hydrometallatrane structure

Table 2. Frequencies of bands in the IR spectra of the synthesized compounds

Compound	ν(C=O)	ν(C–O)	Δν
	cm^{-1}		
(1) CR	1590	1403	187
(5) $2CR \cdot MnCl_2$	1584	1420	164
(6) $CR \cdot NiCl_2$	1590	1415	175
(11) $Zn(MPA)_2$	1633	1558	75
(12) $TEA \cdot Zn(MPA)_2$	1626	1560	66
(13) $2TEA \cdot Zn(MPA)_2$	1640	1571	69

Table 3. Acidity and basicity constants of the synthesized compounds

Compound	$pK_{a\,BH^+}$	pK_a
	KOH/CH_3OH	$HClO_4$/CH_3OH
TEA	–	9.08
H(MPA)	8.40	–
CR	9.71	7.84
(5) $2CR \cdot MnCl_2$	9.81	7.29
(6) $CR \cdot NiCl_2$	7.57	5.64
(12) $TEA \cdot Zn(MPA)_2$	10.50	7.41
(13) $2TEA \cdot n(MPA)_2$	10.64	8.68

was suggested, 3 or 4 equivalents of the acid is consumed. Estimation of the pK_a values shows that two H(MPA) molecules are formed in each case, and one (**10**) or two (**11**) N atoms of atrane rings interact with $HClO_4$.

The complexes obtained are water-soluble and low-toxic (LD_{50} = 1000–6000 mg kg^{-1}) donors of biogenic metals, precursors of metalloenzymes.

O-Hydrometallatranes $(CH_3COO)_2M[(HOCH_2CH_2)_3N]_m$ (M = Cu, Zn, Mn, Ni; m = 1–2) stimulate the cell growth in vegetable cultures [11].

EXPERIMENTAL

The IR spectra of the substances (mulls in mineral oil) were taken on a Varian 3100 FT-IR75 spectrophotometer, and the NMR spectra in D_2O, methanol-d_4, or acetone-d_6, on a DPX 400 spectrometer (400.13 MHz for ^{1}H, 101.62 MHz for ^{13}C) at 25°C. The acidity and basicity constants [pK_a, pK_a(BH$^+$)] were determined by potentiometric titration in methanol with an accuracy of ±0.03 unit [12]. Triethanolamine was purified by triple distillation, H(MPA) was recrystallized from isopropyl alcohol, and CR and CCR, from acetone. The metals, oxides, and salts used were of analytically pure grade.

CR·ZnCl$_2$ (3). A methanol solution of 0.34 g (0.002 mol) of $ZnCl_2·1.5H_2O$ was added dropwise to a solution of 0.66 g (0.002 mol) of CR in 10 ml of methanol. The mixture was stirred for 12 h at 25°C. The solvent was distilled off in a vacuum. The solid residue was repeatedly washed with ether and dried in a vacuum desiccator over P_2O_5. A colorless powder readily soluble in water and organic solvents was obtained. ^{1}H NMR spectrum, δ, ppm (D_2O): 7.05–6.62 (m, 4H, C_6H_4O), 4.32 (s, 2H, CH_2COO), 3.76 (s, 6H, 3OCH_2), 3.28 (s, 6H, 3NCH_2), 2.07 (s, 3H, C_6H_4–CH_3). ^{13}C NMR spectrum, δ_C, ppm (D_2O): 176.99 (C=O), 155.81 (C_6H_4O), 130.78–111.55 (C_6H_4), 66.89 (*C*H_2COO), 55.09 (OCH_2), 54.83 (NCH_2), 15.28 (C_6H_4–*C*H_3). IR spectrum, ν, cm^{-1}: 1560 (C=O), 3300 (OH). Found, %: C 41.09; H 5.05; N 2.78; Zn 15.21; Cl 14.99. $C_{15}H_{25}O_6NZnCl_2$. Calculated, %: C 39.85; H 5.53; N 3.1; Zn 14.47; Cl 15.69.

CR·Zn(CH$_3$COO)$_2$ (4) was prepared similarly to 3 from CR and $Zn(OAc)_2$ (1 : 1). ^{1}H NMR spectrum, δ, ppm (acetone-d_6): 7.06–6.76 (m, 4H, C_6H_4O), 4.46 (s, 2H, CH_2COO), 3.67 (s, 6H, 3OCH_2), 2.78 (s, 6H, 3NCH_2), 2.20 (s, 3H, C_6H_4–CH_3), 1.88 (s, 6H, 2CH_3COO). ^{13}C NMR spectrum, δ_C, ppm (acetone-d_6): 177.00 (CS=O), 156.56 (C_6H_4O), 129.85–110.81(C_6H_4),78.00 (*C*H_2COO), 57.12 (OCH_2), 54.87 (NCH_2), 28.27 (CH_3COO), 15.22 (C_6H_4–*C*H_3). IR spectrum, ν, cm^{-1}: 1565 (C=O), 1620 (C=O), 3290 (OH). Found, %: C 46.24; H 5.90; N 2.01; Zn 14.15. $C_{19}H_{31}O_{10}NZn$. Calculated, %: C 45.74; H 6.22; N 2.80; Zn 13.30.

2CR·MnCl$_2$ (5) was prepared similarly from CR and $MnCl_2·4H_2O$ (2 : 1). ^{1}H NMR spectrum, δ, ppm (D_2O): 6.83–6.52 (m, 8H, 2C_6H_4O), 3.53 (s, 12H, 6OCH_2), 3.05 (s, 12H, 6NCH_2), 1.85 (s, 6H, 2C_6H_4–CH_3). IR spectrum, ν, cm^{-1}: 1584 (C=O), 3300 (OH). Found, %: C 48.17; H 6.32; N 3.34; Cl 8.88; Mn 7.77. $C_{30}H_{50}O_{12}N_2MnCl_2$. Calculated, %: C 47.60; H 6.60; N 3.70; Cl 9.38; Mn 7.27.

CR·NiCl$_2$ (6) was prepared similarly to 3 from CR and $NiCl_2·6H_2O$ (1 : 1). ^{1}H NMR spectrum, δ, ppm (D_2O): 9.33–9.03 (m, 4H, C_6H_4O), 6.06 (s, 6H, 3OCH_2), 5.58 (s, 6H, 3NCH_2), 4.40 (s, 3H, C_6H_4–CH_3). ^{13}C NMR spectrum, δ_C, ppm (D_2O): 178.91 (C=O), 157.00 (C_6H_4O), 124.12–114.80 (C_6H_4), 72.50 (*C*H_2COO), 57.09 (OCH_2), 56.84 (NCH_2), 17.50 (C_6H_4–*C*H_3). IR spectrum, ν, cm^{-1}: 1590 (C=O), 3300 (OH). Found, %: C 39.98; H 6.00; N 3.00; Cl 15.86; Ni 13.51. $C_{15}H_{25}O_6NCl_2Ni$. Calculated, %: C 40.40; H 5.62; N 3.15; Cl 15.94; Ni 13.20.

2CR·NiCl$_2$ (7) was prepared similarly to 6 (2 : 1). ^{1}H NMR spectrum, δ, ppm (D_2O): 7.06–6.68 (m, 8H, 2C_6H_4O), 3.79 (s, 12H, 6OCH_2), 3.31 (s, 12H, 6NCH_2), 2.12 (s, 6H, 2C_6H_4–CH_3). ^{13}C NMR spectrum, δ_C, ppm (D_2O): 178.17 (C=O), 156.17 (C_6H_4O), 131.00–111.74 (C_6H_4), 69.90 (*C*H_2COO), 55.31 (OCH_2), 55.02 (NCH_2), 15.58 (C_6H_4–*C*H_3). IR spectrum, ν, cm^{-1}: 1605 (C=O), 3160, 3310 (OH). Found, %: C47.36; H6.81; N3.83; Cl 9.21; Ni 7.69. $C_{30}H_{50}O_{12}N_2Cl_2Ni$. Calculated, %: C 47.30; H 6.51; N 3.68; Cl 9.33; Ni 7.62.

CCR·RhCl$_3$ (8) was prepared similarly to 3 from CCR and $RhCl_3·4H_2O$. Found, %: C 33.90; H 3.91; Rh 19.50. $C_{15}H_{24}O_6NCl_4Rh$. Calculated, %: C 32.19; H 4.29; Rh 18.40.

CR·CoCl$_2$ (9) was prepared similarly to 3 from CR and cobalt chloride (1 : 1). Yield 72%. Blue powder, mp 240°C. IR spectrum, ν, cm^{-1}: 1590 (C=O), 3300 (OH).

CR·CuCl$_2$ (10) was prepared similarly to 3 from CR and $CuCl_2·2H_2O$. Yield 59.54%. Brown powder without definite melting point. ^{1}H NMR spectrum, δ, ppm (D_2O): 7.10–6.60 (m, 4H, 2C_6H_4O), 3.78 (s, 6H, 6OCH_2), 3.31 (s, 6H, 6NCH_2), 2.12 (s, 3H, 2C_6H_4–CH_3). ^{13}C NMR spectrum, δ_C, ppm (D_2O): 177.85 (C=O), 154.74 (C_6H_4O), 132.10–110.00 (C_6H_4), 75.25 (*C*H_2COO), 54.52 (OCH_2), 54.52 (NCH_2), 18.30 (C_6H_4–*C*H_3). IR spectrum, ν,

cm^{-1}: 1610 (C=O), 3320 (OH). Found, %: C33.90; H 3.91; Rh 19.50. $C_{15}H_{24}O_6NCl_4Rh$. Calculated, %: C 32.19; H 4.29; Rh 18.40.

TEA·Zn(MPA)$_2$ (12). Equimolar amounts of TEA and $Zn(MPA)_2$ in 15 mol of methanol were refluxed for 5 h. The solvent was distilled off in a vacuum. The residue was repeatedly washed with ether and vacuum-dried. ^{1}H NMR spectrum, δ, ppm (acetone-d_6): 7.06–6.75 (m, 8H, C_6H_4O), 4.45 (s, 4H, $2CH_2COO$), 3.66 (s, 6H, OCH_2), 2.77 (s, 6H, NCH_2), 2.20 (s, 6H, $2C_6H_4$–CH_3). ^{13}C NMR spectrum, δ_C, ppm (acetone-d_6): 176.01 (C=O), 157.80 (C_6H_4O), 131.11–112.11 (C_6H_4), 67.43 (CH_2COO), 58.06 (OCH_2), 56.05 (NCH_2), 16.49 (C_6H_4–CH_3). IR spectrum, ν, cm^{-1}: 1626 (C=O), 3300 (OH). Found, %: C 52.56; H 6.17; N 3.00; Zn 12.05. $C_{24}H_{33}O_9NZn$. Calculated, %: C 52.89; H 6.11; N 2.57; Zn 12.00.

2TEA·Zn(MPA)$_2$ (13) was prepared similarly to 10 from $Zn(MPA)_2$ and TEA (1 : 2). ^{1}H NMR spectrum, δ, ppm (CD_3OD): 7.08–6.72 (m, 8H, $2C_6H_4O$), 4.46 (s, 4H, $2CH_2COO$), 3.64 (s, 12H, $6OCH_2$), 2.74 (s, 12H, NCH_2), 2.23 (s, 6H, $2C_6H_4$–CH_3). ^{13}C NMR spectrum, δ_C, ppm (CD_3OD): 175.80 (C=O), 156.67 (C_6H_4O), 130.13–110.78 (C_6H_4), 66.68 (CH_2COO), 57.55 (OCH_2), 55.18 (NCH_2), 15.13 (C_6H_4–CH_3). IR spectrum, ν, cm^{-1}: 1640 (C=O), 3350 (OH). Found, %: C 51.58; H 7.10; N 3.70; Zn 10.05. $C_{30}H_{48}O_{12}N_2Zn$. Calculated, %: C 51.90; H 9.8; N 4.03; Zn 9.42.

CONCLUSIONS

(1) Procedures were developed for preparing complex compounds of biogenic metals, aroxyacetic acids, and triethanolamine by reactions of triethylammonium salts of *o*-methyl- and *o*-methyl-*p*-chlorophenoxyacetic acids with chlorides or acetates of Mn, Fe, Co, Ni, Zn, Rh; by reaction pf zinc *o*-methylphenoxyacetate with triethanolamine; and by the exchange reaction of *o*-methylphenoxyacetic acid with the complex of zinc chloride with triethanolamine.

(2) The structures of the complexes obtained were studied by IR spectroscopy and potentiometric titration.

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