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# Novel complexes of 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole with metal acetates and arylchalcogenylacetates

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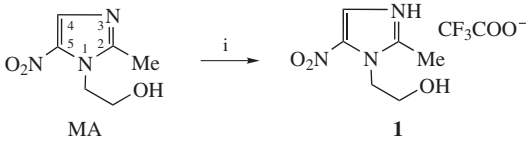
The reaction of 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (Metronidazole) with salts of biologically active arylchalcogenylacetic acids affords novel perspective physiologically active metal complexes.

Imidazoles are an important class of heterocyclic compounds that are abundant in structure of many natural and synthetic pharmacologically active substances.[1] Among them, 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (Metronidazole, MA) is a very important representative.[2] However, it is poorly soluble in water, possesses unstable efficacy against aerobic and anaerobic microflora, its period of pharmacological action is short, development of resistance to this drug is possible, and a number of toxic reactions of this compound can occur.[2]

Majority of drugs are used in the salt (ionic) form to increase their solubility. Recently, we have synthesized a series of promising physiologically active water-soluble salts and ionic liquids based on biologically active benzimidazoles and arylchalcogenylacetic acids $ArYCH_2COOH$ (Y = O, S, $SO_2$, Se).[3] The latter are active components of hydroxyalkylammonium salts and ionic liquids exerting high pharmacological, including immunomodulatory, anti-allergic and anti-cancer action.[4]

Therefore, the increase of solubility and expansion of pharmacological action of MA represent an urgent research challenge. In this work we have investigated the reaction of MA with arylchalcogenylacetic acids $ArYCH_2COOH$ (Y = O, S). However, unlike benzimidazoles, MA under the studied conditions (65 °C, 48–72 h) does not react with such relatively weak acids ($pK_a$ = = 3.05–3.13). Apparently, this is due to the decrease in basicity of the nitrogen atom $N^3$ because of the presence of such a strong electron-withdrawing substituent as the $NO_2$ moiety in MA heterocycle. MA can be protonated at the $N^3$ atom only with strong carboxylic acids such as $CF_3COOH$ ($pK_a$ = 0.23) to furnish a water-soluble salt (ionic liquid) **1** (Scheme 1).

Structure and composition of salt **1** was proved by IR, $^1H$, $^{13}C$, $^{15}N$ NMR spectroscopy and elemental analysis.† In the IR spectrum of **1**, a short-wave shift of the absorption bands of the heteroring is observed in the region 1300–1500 $cm^{-1}$ (Δ 15–20 $cm^{-1}$). Also, the spectrum shows a band at 1610 $cm^{-1}$ (ν, $COO^-$) and a broad band at 2600–3000 $cm^{-1}$ (ν, $N^+H$). Values of the bands at 1368 ($\nu_s$, $NO_2$), 1535 ($\nu_{as}$, $NO_2$), 3220 (ν, OH) $cm^{-1}$ indicate that these groups do not participate in the reaction. In the $^1H$ NMR spectra of salt **1**, the heterocycle proton signal is significantly shifted downfield as compared to the spectrum of the starting MA (7.9 ppm to 8.5 ppm). In the $^{13}C$ NMR spectrum of **1**, chemical shifts of the heterocycle signals do not essentially differ from those of the initial MA. In the $^{15}N$ NMR spectra, the values of $N^1$ signals for MA ($\delta_{^{15}N^1}$ –217.0 ppm) and adduct **1** ($\delta_{^{15}N^1}$ –217.1 ppm) remain virtually unchanged, while the $\delta_{^{15}N^3}$ signal of **1** (–177.6 ppm) is shifted upfield (Δδ 46.1 ppm) relative to MA ($\delta_{^{15}N^3}$ –131.5 ppm) that is indicative of the protonation of the nitrogen atom $N^3$. We failed to record the $\delta_{^{15}N}$ signal in 2D HMBC spectra of the exocyclic atom nitrogen ($NO_2$) under these conditions ($CD_3OD$, 20 °C).




**Scheme 1** *Reagents and conditions*: i, $CF_3COOH$, MeOH, 65 °C, 15 min.

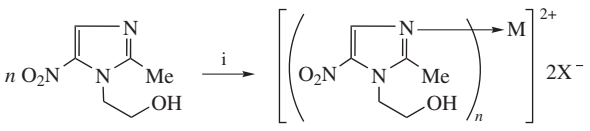
Complex compounds of microelements containing drug substances as ligands (including imidazole derivatives) are known to be highly efficient and low toxic.[5] For instance, medicines Acizole and Cobazole have been designed on the basis of zinc and cobalt salts and *N*-vinylimidazole.[6] Complexes of zinc, nickel and copper sulfates with MA exhibit a higher bacteriostatic and bactericidal activity as compared to the pure MA. In addition, these complexes possess fungicidal properties.[7]

† *General procedure for the synthesis of protic compounds* **2–9**. A mixture of MA (0.01 mol) and the corresponding salt (in 1:1, 2:1, 4:1 ratios) in absolute methanol (30–70 ml) was stirred at 20–40 °C for 10–20 min. The solvent was distilled off, and the residue was repeatedly washed with diethyl ether and dried (24 h) at 0.03 Torr to obtain colourless or coloured powders.

For **2**: yield 99%, colourless powder, mp 124–126 °C. IR (KBr, ν/$cm^{-1}$): 1368 ($NO_2$), 1535 ($NO_2$), 1618 (C=O), 3220 (OH). $^1H$ NMR ($CD_3OD$) δ: 7.90 (s, 1H, $C^4H$), 4.49 (t, 2H, $NCH_2$), 3.84 (t, 2H, $OCH_2$), 2.58 (s, 3H, Me), 1.99 (s, 6H, AcO). $^{13}C$ NMR ($CD_3OD$) δ: 181.75 (C=O), 153.62 ($C^5$), 139.87 ($C^2$), 132.27 ($C^4$), 61.52 ($OCH_2$), 50.15 ($NCH_2$), 21.93 (*Me*COO), 14.31 (Me). $^{15}N$ NMR ($CD_3OD$) δ: –144.6 ($N^3$), –217.8 ($N^1$). Found (%): C, 30.19; H, 3.82; N, 10.30; Cd, 28.27. Calc. for $C_{10}H_{15}N_3O_7Cd$ (%): C, 29.90; H, 3.76; N, 10.46; Cd, 27.98.

For **5**: yield 99 %, colourless powder, mp 145–146 °C. IR (KBr, ν/$cm^{-1}$): 1368 ($NO_2$), 1535 ($NO_2$), 1620 (C=O), 3220 (OH). $^1H$ NMR ($CD_3OD$) δ: 7.97 (s, 1H, $C^4H$), 7.09–6.70 (m, 8H, $C_6H_4$), 4.56 (s, 4H, $OOCCH_2$), 4.45 (t, 2H, $NCH_2$), 3.84 (t, 2H, $OCH_2$), 2.51 (s, 3H, Me), 2.25 (s, 6H, *Me*$C_6H_4$). $^{13}C$ NMR ($CD_3OD$) δ: 177.85 (C=O), 153.43 ($C^5$), 147.17 ($C_6H_4$), 139.76 ($C^2$), 131.71 ($C^4$), 131.61–112.66 ($C_6H_4$), 67.88 ($OOCCH_2$), 61.36 ($OCH_2$), 50.00 ($NCH_2$), 16.48 (*Me*$C_6H_4$), 14.01 (Me). $^{15}N$ NMR ($CD_3OD$) δ: –152.7 ($N^3$), –217.0 ($N^1$). Found (%): C, 51.15; H, 4.56; N, 7.30; Zn, 11.81. Calc. for $C_{24}H_{27}N_3O_9Zn$ (%): C, 50.85; H, 4.80; N, 7.41; Zn, 11.53.

For characteristics of compounds MA, **1**, **3**, **4**, **6–9**, see Online Supplementary Materials.



**2** $n$ = 1, M = Cd, X = AcO
**3** $n$ = 2, M = Zn, X = AcO
**4** $n$ = 1, M = Ni, X = AcO
**5** $n$ = 1, M = Zn, X = 2-$MeC_6H_4OCH_2COO$
**6** $n$ = 1, M = Zn, X = 4-$ClC_6H_4SCH_2COO$
**7** $n$ = 2, M = Ca, X = 2-$MeC_6H_4OCH_2COO$
**8** $n$ = 2, M = Mn, X = 2-$HOC_6H_4OCH_2COO$
**9** $n$ = 4, M = Zn, X = 2-$MeC_6H_4OCH_2COO$

**Scheme 2** *Reagents and conditions*: i, $MX_2$, MeOH, 20 °C, 10–20 min.

To obtain novel water-soluble perspective pharmacologically active metal-complex compounds, we have investigated the interaction of MA with metal acetates and arylchalcogenylacetates $MX_2$ (M = Zn, Ca, Ni, Mn, Cd; X = AcO, $ArYCH_2COO$; Y = = O, S). Under conditions studied and at various reagent ratios MA : $MX_2$, metal complexes **2**–**9** have been isolated in high yields (Scheme 2).

Compounds **2**–**9** are soluble in water and aqueous alcohol powders. Their composition and structure have been confirmed by IR, NMR techniques and elemental analysis.†

In the IR spectra of compounds **2**–**9**, the absorption bands typical of the initial metal salts appear at 1599–1624 $cm^{-1}$ (ν, $COO^-$), thus indicating the incorporation of these salts in structure of the complexes. Complexation of MA with metal salts does not lead to a shift of the heteroring stretching vibration bands. The $NO_2$ and OH groups of the ligand do not take part in the complexation since the absorption bands at 1368 ($\nu_s$, $NO_2$), 1535 ($\nu_{as}$, $NO_2$) and 3220 (ν, OH) $cm^{-1}$ are retained.

The $^1H$ and $^{13}C$ NMR spectra of compounds **2**, **3**, **5**–**7**, **9** show no significant shifts of the heterocycle signals as compared to the starting MA. In the $^{15}N$ NMR spectra, the signals of $N^1$ atom are shifted negligibly (217.1 ppm), while those of $N^3$ atom are shifted upfield ($\Delta\delta_{^{15}N}$ 8–21 ppm), that evidences the donor-acceptor interaction $N^3 \rightarrow M$. The values $\Delta\delta_{^{15}N}$ reflect a degree of $N^3 \rightarrow M$ interaction, which depends upon both metal nature and number of ligands. For compound **2** (M = Cd, $n$ = 1) $\Delta\delta_{^{15}N}$ is 13 ppm, for compound **3** (M = Zn, $n$ = 2) $\Delta\delta_{^{15}N}$ is 17.5 ppm, whereas for complex **5** (M = Zn, $n$ = 1) $\Delta\delta_{^{15}N}$ is maximum (21 ppm). For compound **9** (M = Zn, $n$ = 4), $\Delta\delta_{^{15}N}$ is 8 ppm.

In the case of compound **2**, the complexation is strongly evidenced by a downfield shift (42 ppm) of the resonance line observed in the $^{111}Cd$ NMR spectrum [relative to $Cd(OAc)_2$].

The $^1H$ NMR spectra of compounds **4** and **8** are significantly broadened and are detected at 1–40 ppm that is typical of paramagnetic complexes.[8] That is why we failed to record the $^{13}C$ and $^{15}N$ spectra of these compounds.

The principal difference of complexes **5**–**9** from hitherto known metal-containing congeners of Metronidazole[7] is that their molecules combine not two ('dual action' in the terminology[9]), but three physiologically active components, cations of MA medicine containing essential metals and anions of bioactive arylchalcogenylacetic acids, which makes them promising pharmaceutical precursors 'triple action'.

Earlier we have shown[10] that $[N(CH_2CH_2OH)_3Zn]^{2+} \cdot 2[2\text{-}MeC_6H_4OCH_2COO^-]$ (Crezoxyzincatrane) containing three active components enhances activity of triptophanyl-tRNA-synthetase enzyme (antisclerosis action) by 50% higher than $[N(CH_2CH_2OH)_3H]^+ \cdot [2\text{-}MeC_6H_4OCH_2COO^-]$ (Crezacine drug) which is comprised of two active components.

*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2014.09.015.

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