Complexes of acylated thioamides and related compounds with copper(I) and nickel(II) ions and their antimycobacterial activity

[a]J. MOLLIN, [a]K. POLÁŠKOVÁ, [b]Ž. ODLEROVÁ, and [a]Z. ŠINDELÁŘ

[a]*Department of Inorganic and Physical Chemistry, Faculty of Natural Sciences, Palacký University, CS-771 46 Olomouc*

[b]*Research Institute of Preventive Medicine, CS-833 01 Bratislava*

Received 30 September 1987

Copper(I) and nickel(II) complexes of acylated thioamides and thioacylated thioureas have been prepared. Measurements of their antimycobacterial activity showed that the ligand has not lost its antimycobacterial activity by entering the complex. The relation between complex-forming ability and antimycobacterial activity has been discussed.

Получены комплексы меди(I) и никеля(II) с ацилированными тиоамидами и тиоацилированными тиомочевинами. Измерение их антимикобактериальной активности показало, что лиганд не лишается своей антимикобактериальной активности при включении в комплекс. Обсуждается взаимосвязь между комплекс-образующей способностью и антимикобактериальной активностью.

Biological properties of thioamides and their reaction products as well as their complex-forming ability have been permanently followed in the literature [1—12]. Unfortunately, only little attention has been paid to biological activity of complexes of thioamides so far [12]. The reason is probably the fact that most of metal complexes of thioamides are formed in nonaqueous media [13] or in concentrated solutions [14, 15]. The chelates of thioamides, conditioned by suitable substitution of the ligand, have been studied in more detail only lately [7—11, 16]. Successful addition of thioamides to isothiocyanates [16] and acylation of thioamides, accompanied by measurement of antimycobacterial activity [4], enabled to prepare metal chelates of substituted thioamides and compare their antimycobacterial activity with that of the ligands themselves. In the previous communication [12] it was stated that the activity of copper(I) complexes was in many cases considerably higher than that of the ligand, however, this effect was not reasoned. At the same time, it is known that copper complexes play an important role in biological processes (see *e.g.* [17]). In order to find out to what extent are the complex-forming ability of the ligand and oxidation properties of the complex itself contributing to the resulting antimycobacterial activity, in the present work we have chosen Cu^+ and Ni^{2+} as the

central atoms, the latter of which does not undergo redox processes at biological conditions.

Experimental

The ligands used herein were prepared in our previous work [4], 1-phenyl-3-acetylthiourea (*I*) and 1-phenyl-3-benzoylthiourea (*II*) [18, 19] as well as the brown complexes of Ni^{2+} with the derivatives of *N*-(thiocarbamoyl)thiobenzamide of the NiL_2 type [16] were prepared according to the literature. The same method [16] was used to prepare Ni^{2+} complexes with *N*-acylthioamides, which were also brown complexes of the general formula NiL_2. When preparing the complex, to the solution of *N*-acylthiobenzamide (0.01 mol) in minimum amount of acetone nickel(II) acetate (0.01 mol) in ethanol was added under stirring. The brown bischelate crystallized immediately. It was sucked and washed with acetone and ethanol. The copper(I) complexes were prepared according to the method used earlier [12, 13] by stirring the saturated aqueous solution of copper(II) acetate, anal. grade (0.01 mol) (Lachema, Brno) with saturated ethanolic solution of *N*-acylthioamide or *N*-acylthiourea (0.01 mol). The brown (in the case of *II* yellow) precipitates were sucked, washed with ethanol, and analyzed.

The visible and UV spectra of complexes in ethanolic solutions ($c = 10^{-4}$ and 10^{-5} mol dm^{-3}) were measured with a Pye Unicam SP 8-100 spectrometer in 1 cm silica cells. IR spectra were measured, due to low solubility of complexes in common solvents, in nujol with a Specord IR-75 spectrometer. Magnetic-chemical measurements were carried out by the method described earlier [12].

The compounds were tested for microbiological activity using the diluting *in vitro* method on the liquid Šula medium against pathogenic strains of *Mycobacterium tuberculosis* $H_{37}R_v$ and *Mycobacterium Kansassii PKG 8*. The substrates were dissolved in DMSO to obtain solutions of different concentrations and were added to the media with the *Mycobacterium* so that the DMSO concentration was below 5 %. The minimal inhibitory concentration (MIC) was the lowest concentration of the substrate at which growth of mycobacteria was not observed after 14-day cultivation at 37 °C.

Results and discussion

The results of analyses of the newly prepared complexes are presented in Table 1. Besides the new compounds also known complexes [16] $[C_6H_5—C(\bar{S})=N—C(S)—NH—CH_3]_2 \cdot Ni$ (*XIII*) and $[C_6H_5—C(\bar{S})=N—C(S)—NH—C_6H_5]_2 \cdot Ni$ (*XIV*) were prepared. Easy preparation of the complexes *III*—*VIII* allows to suggest that the —C(S̄)=N—C(O)— grouping forms with Ni^{2+} stable chelates similarly as the —C(S̄)=N—C(S)— grouping [16], however, quantitative comparison of both groups of complexes has not been reported hitherto.

Diamagnetism found with all compounds described herein leads to the

Table 1

Composition and analyses of the prepared complexes

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%				
			Metal	C	H	N	S
III	$[C_6H_5—C(\bar{S})=N—C(O)—CH_3]_2 \cdot Ni$	415.14	14.14	52.07	3.88	6.74	15.44
			14.27	51.70	3.84	6.42	15.67
IV	$[C_6H_5—C(\bar{S})=N—C(O)—C_2H_5]_2 \cdot Ni$	443.22	13.25	54.20	4.55	6.32	14.47
			13.55	53.85	4.32	6.06	14.22
V	$[C_6H_5—C(\bar{S})=N—C(O)—C_3H_7]_2 \cdot Ni$	471.25	12.46	56.06	5.13	5.94	13.61
			12.13	55.79	5.45	5.61	14.02
VI	$[p\text{-}Cl—C_6H_4—C(\bar{S})=N—C(O)—C_2H_5]_2 \cdot Ni$	512.10	11.46	46.91	3.54	5.47	12.52
			11.20	47.29	3.78	5.55	12.30
VII	$[p\text{-}CH_3O—C_6H_4—C(\bar{S})=N—C(O)—C_2H_5]_2 \cdot Ni$	503.25	11.67	52.50	4.81	5.57	12.74
			11.85	52.86	4.65	5.32	12.46
VIII	$[p\text{-}CH_3—C_6H_4—C(\bar{S})=N—C(O)—C_2H_5]_2 \cdot Ni$	471.25	12.46	56.07	5.13	5.94	13.61
			12.73	55.64	5.12	5.67	13.85
IX	$[C_6H_5—C(S)—NH—C(O)—C_2H_5] \cdot CuOH$	273.83	23.22	43.87	4.05	5.11	11.71
			24.01	44.07	3.65	5.19	11.56
X	$[C_6H_5—C(S)—NH—C(O)—C_3H_7] \cdot CuOH$	287.83	22.09	45.90	4.90	4.86	11.14
			22.46	45.32	4.32	4.82	10.90
XI	$[C_6H_5—N(CO—CH_3)—C(\bar{S})=NH]\ Cu$	244.77	24.75	42.09	3.53	10.91	13.10
			24.56	41.43	2.98	11.36	12.92
XII	$[C_6H_5—NH—C(S)—NH—C(O)—C_6H_5]_3 \cdot Cu_2 \cdot (CO—CH_3)_2$	1013.78	12.54	54.45	4.18	8.29	9.49
			12.84	55.09	3.95	8.65	10.01

conclusion that nickel complexes are square planar [20]. This conclusion is in good agreement with the results of measurements of electronic spectra in the visible region. The absorption bands in the region of about $\tilde{\nu} = 20\,000\ \mathrm{cm}^{-1}$ can be assigned to *d*—*d* transitions $^1A_{2g} \rightarrow {}^1A_{1g}$ and the band at $\tilde{\nu} = 27\,000\ \mathrm{cm}^{-1}$ to $^1B_{1g} \rightarrow {}^1A_{1g}$ transition [21]. The found diamagnetism confirmed that copper is in the prepared complexes monovalent, which is a consequence of redox reactions of Cu^{2+} with the sulfhydryl groups of thioamides, as it was reported earlier [12]. Due to complexity of the IR spectra of the complexes the bands observed could not be assigned unambiguously. The diffuse band with the maximum at about $\tilde{\nu} = 3300\ \mathrm{cm}^{-1}$, observed with all compounds, belongs probably to the stretching vibration ν(NH). In the region of about $\tilde{\nu} = 1400\ \mathrm{cm}^{-1}$ an intensive band ascribed to δ(NH) appeared and at $\tilde{\nu} = 1550$—$1600\ \mathrm{cm}^{-1}$ an intensive band belonging to ν(C=N) [22] was observed. Assignment of further bands appearing mainly at lower wavenumbers has not been substantiated experimentally.

The results of antimycobacterial tests are presented in Table 2. The use of the same medium and the same microbial strain as in the previous works [4, 6, 12] and the found monovalence of copper allow to compare the individual results.

Table 2

Minimal inhibitory concentrations of the compounds prepared

Compound	MIC $10^4/(\mathrm{mol\,dm^{-3}})$ Against *Mycobacterium*		Compound	MIC · $10^4/(\mathrm{mol\,dm^{-3}})$ Against *Mycobacterium*	
	tuberculosis $H_{37}R_v$	*Kansassii* *PKG 8*		*tuberculosis* $H_{37}R_v$	*Kansassii* *PKG 8*
I	3.3	10	*IX*	1.1	10
II	1.1	3.3	*X*	0.37	1.1
III	0.37	1.1	*XI*	1.1	3.3
IV	1.1	3.3	*XII*	0.041	0.37
V	0.37	3.3	*XIII*	0.12	1.1
VI	0.37	3.3	*XVI*	0.12	1.1
VII	0.12	1.1	Ethionamide	0.12	1.1
VIII	1.1	3.3	INH[a]	0.041	3.3

a) Isonicotinohydrazide.

From the comparison it follows that conversion of thioamides into both nickel(II) and copper(I) complexes does not bring about a loss of their antimycobacterial activity. This finding completes our previous observation [12]. From the previous study of copper(I) complexes it was not clear whether the central Cu^+

ion of complexes was or was not oxidized in oxidation processes proceeding in cells [17] under release of thioamides. Release of the ligand from Ni^{2+} chelates by biological processes appears to be less probable. Therefore, in accordance with the known high activity of very strong Cu complexes of dithiocarbamates [23], we assume that the activity of the prepared complexes is due to themselves and not to the ligands released on decomposition. From Table 2 it is evident that valence or redox reactions of the central ion are not decisive. The small differences in minimal inhibitory concentrations presented in Table 2 are conditioned probably by other factors of which mainly lipophility is significant [24]. It seems that the complex-forming ability is connected with antimycobacterial activity of thioamides only secondarily. The experiments of the previous works [4, 6] led to the conclusion that antimycobacterial activity is, beside other factors, influenced also by polarity of bonds of the functional group. The polarity of bonds is, however, connected with the stability of complexes [12]. Therefore, we assume that, though both effects could not be separated from each other, the polarity of bonds is of primary significance for antimycobacterial activity.

Of the set of complexes studied the copper(I) complex of 1-phenyl-3--benzoylthiourea is noticeable for its composition and partly for its minimal inhibitory concentration. However, the latter factor is evidently connected with the number of ligands in the molecule. When multiplying MIC of *XII* by 3, we obtain values corresponding to Ethionamide. This is in agreement with the previous observation [12], according to which the MIC of copper(I) chelates of thioamides is approximately the same as MIC of Ethionamide. It appears that, with regard to antimycobacterial activity, this compound does not differ either from the other compounds presented in Table 2 and in the previous communication [12].

The experimental material presented above allows to assume that the change in antimycobacterial activity of thioamides after entering the complex is more probably due to their changed ability to penetrate cells than due to changed biochemical mechanism of their action.

References

1. Cashman, J. R. and Hanzlik, R. P., *J. Org. Chem. 47*, 4645 (1982).
2. Bukowski, L., *Pol. J. Pharmacol. Pharm. 36*, 683 (1984).
3. Bukowski, L., *Pol. J. Pharmacol. Pharm. 38*, 91 (1986).
4. Mollin, J., Polášková, K., Odlerová, Ž., and Bekárek, V., *Collect. Czechoslov. Chem. Commun. 52*, 2087 (1987).
5. Mollin, J., Polášková, K., and Odlerová, Ž., *Chem. Papers 42*, 811 (1988).
6. Mollin, J., Paukertová, H., and Odlerová, Ž., *Chem. Zvesti 38*, 629 (1984).
7. Pal, T. and Das, J., *Talanta 30*, 519 (1983).

8. Fahmi, A. A., Naoum, M. M., Tadros, M. A., and Shawali, A. S., *Indian J. Chem. 23A*, 824 (1984).
9. Barsoum, B. N. and Naoum, M. M., *Indian J. Chem. 24A*, 533 (1985).
10. Naoum, M. M. and Barsoum, B. N., *Indian J. Chem. 24A*, 983 (1985).
11. Naoum, M. M. and Barsoum, B. N., *Indian J. Chem. 25A*, 398 (1986).
12. Mollin, J., Kašpárek, F., Odlerová, Ž., and Šindelář, Z., *Chem. Papers 40*, 239 (1986).
13. Kašpárek, F. and Mollin, J., *Collect. Czechoslov. Chem. Commun. 25*, 2919 (1960).
14. Rolies, M. M. and De Ranter, C. J., *Cryst. Struct. Commun. 6*, 275 (1977).
15. Rolies, M. M. and De Ranter, C. J., *Acta Crystallogr. B 34*, 3216 (1978).
16. Hartmann, A., Uhlemann, E., Walter, M., and Hoyer, E., *Z. Chem. 21*, 271 (1981).
17. Lehninger, A. I., *Biochemistry*, p. 493. Worth Publishers, New York, 1975.
18. Hugershoff, A., *Ber. Dtsch. Chem. Ges. 32*, 3649 (1899).
19. Kaválek, J., Jirman, J., and Štěrba, V., *Collect. Czechoslov. Chem. Commun. 50*, 766 (1985).
20. Bondreaux, E. A. and Mulay, L. N., *Theory and Applications of Molecular Paramagnetism*, p. 226. J. Wiley, New York, 1976.
21. Levert, B. P., *Inorganic Electronic Spectroscopy*. Elsevier, London, 1968.
22. Papoušek, D. and Horák, M., *IR spektra a struktura molekul.* (IR Spectra and Molecular Structure.) P. 706. Academia, Prague, 1976.
23. Liebermeister, K., *Z. Naturforsch. 5*, 79 (1950).
24. Waisser, K., Čeladník, M., Palát, K., Karlíček, R., Odlerová, Ž., Bartoš, F., and Dršata, J., *Pharmazie 38*, 874 (1983).

Translated by A. Kardošová