Carbon Monoxide Antidote as the Necessary Item for the First-Aid Automobile Kit

B. A. TROFIMOV, L. V. BAYKALOVA, V. A. BARINOV and KH. KH. BABANIYAZOV

Favorskiy Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, Ul. Favorskogo 1, Irkutsk 664033 (Russia)

E-mail: ludabaik@irioch.irk.ru

Abstract

A complex compound bis(1-vinylimidazole)zincdiacetate is proposed for use as a prophylactic and curative antihypoxic means against poisoning with CO and other products formed as a result of incomplete combustion of fuel in an automobile engine. An efficient method of its manufacture was developed; its molecular structure was revealed. It was determined that, in addition, the preparation possesses antidote properties.

One of the urgent ecological problems at present is intensive air pollution with automobile emissions. A continuous increase in the number of automobiles on roads is accompanied by an increase in exhaust content of urban air, which, according to the data of the State Committee on Ecology of RF, accounts for 90 % of the total amount over the city and contains more than 200 various chemical compounds among which carbon monoxide CO is prevailing. It was established that motor exhausts contribute more than 700 thousand tons of emitted compounds per year to the atmosphere; among them, CO accounts for about 600 thousand tons, nitrogen oxides for nearly 40 thousand tons, and hydrocarbons for more than 110 thousand tons.

Formed as a result of incomplete combustion of hydrocarbons in fuel, CO binds itself to hemoglobin in blood replacing oxygen from it, which results in anoxemia. Carbon monoxide causes poisoning due to inactivation of a number of iron-containing porphyrins of blood and tissues, firstly hemoglobin to which it has much higher affinity than oxygen does. Thus, blockade of oxygen transport by hemoglobin and myoglobin causes a decrease in the oxygen content of blood. Small amounts of CO cause giddiness, headache, tiredness and inhibited drivers' reaction. Even a short-time action of the high concentrations of CO can cause death.

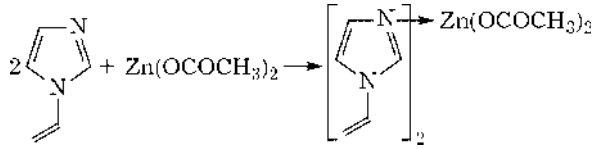
Pathogenetic treatment of poisoning with carbon monoxide is aimed at the acceleration of removal of this toxicant from an organism. No specific medicines for prophylactics and treatment of poisoning with CO and other combustion products have been existing till recently. The main method of protection from CO is still the use of an isolating gas-mask; the only method of treatment is expensive hyperbaric oxygenation in special pressure chambers.

While working on this problem, we discovered a complex compound of zinc diacetate and 1-vinylimidazole the use of which will allow one to decrease the effect of carbon monoxide and other products present in exhaust.

One of the most important and complicated problems of modern pharmacology is development and introduction of promising remedies incorporating the coordination compounds of a number of vitally important microelements (metal complexes) in which the ligand systems, being parts of biologically active systems of an organism, would possess sufficient activity for the realization of their physiological effect at the molecular level. The outlooks of using these remedies are due to their broad range of directional operation ; thus they stabilize the homeostasis. In addition, they are low-toxic, easily measurable, and, most important, they are very efficient. As a result

of the joint research carried out at the Irkutsk Institute of Chemistry, SB RAS, and the 1st Central Research Institute of MD RF (St. Petersburg) into unsaturated heteroatomic compounds and their metal complexes of new biologically active substances, it was established that many complex compounds of metals, in particular zinc, copper, iron and cobalt, have prophylactic protective effect against acute lethal poisoning with CO. The same complexes based on nitrogen-containing heterocycles exhibit a wide range of antihypoxic action, especially zinc compounds because they not only exceed the compounds of other metals in activity but also are less toxic and can be excreted in case of excess introduction. In addition, zinc is necessary in microscale amounts for a human organism. When testing with the model of hemic hypoxia, it was established that the coordination compounds of zinc possess generally higher protective activity in case of acute poisoning with CO than its salts. In addition, complex formation between the zinc ion and an organic ligand causing no antihypoxic action provides a substantial increase in the protective effect of this ion.

As a result of investigation of a broad range of various metal complexes based on nitrogen-containing heterocycles, we discovered a compound bis-(1-vinylimidazole)zinc diacetate (conventionally called Acyzol) possessing the highest protective action [1–3]. The method of obtaining bis-(1-vinylimidazole)zinc diacetate is based on the interaction of an available ligand 1-vinylimidazole with zinc diacetate (salt), both in the solution in an organic solvent (ethanol, acetone, ether) and without a solvent [4]. A simple synthesis method allows one to obtain Acyzol with the quantitative yield and high purity (99.5 %).



The crystal and molecular structure of the complex compound bis-(1-vinyl-imidazole)zinc diacetate was established by means of X-ray structural analysis (R_1 = 0.0335 for 8902 independent reflections with $I > 2\sigma$ (I) and $wR_2 = 0.0931$ for all the 10752 independent reflections) [5]. The triclinic cell of Acyzol crystals contains two independent molecules of the complex under investigation (A and B) (Fig. 1). The vertices of distorted tetrahedrons of zinc atoms in molecules A and B are occupied by nitrogen atoms of vinyl imidazole ligands and oxygen atoms of acetate groups. The Zn–N and Zn–O bonds with three acetate groups are characterized by the usual length, Å: 2.023(1)±0.004 and 1.957(1)±0.00, respectively. In one of the acetate groups in

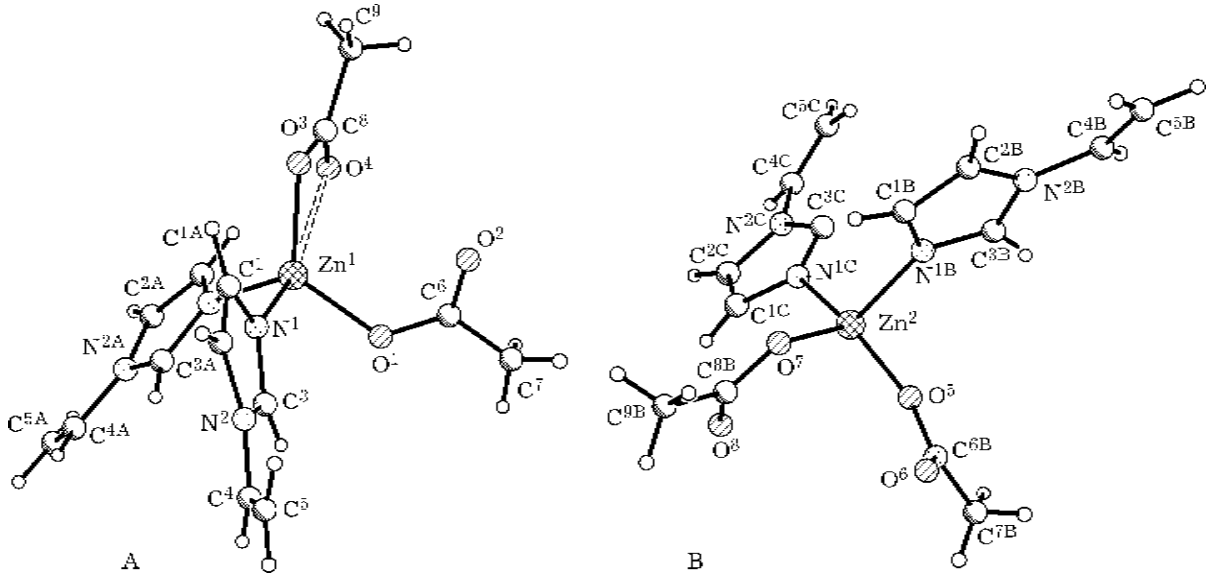


Fig. 1. Structure of the complex compound bis-(1-vinylimidazole)zinc diacetate.

molecule A, the Zn–O(3) bond (2.009(1) Å) is a little longer. In addition, there is an additional contact of the zinc atom with the carbonyl oxygen atom of this group (Zn–O(4) (2.498 Å)).

The packing of molecules A and B in the crystal of acyzol structure is shown in Fig. 2. There are short contacts O...H–C between A and B molecules; their geometric parameters allow one to interpret them as hydrogen bonds forming the framework structure in crystals.

Medical and biological tests showed that the antidote action of Acyzol against poisoning with CO is due to the ability of this preparation to decrease the relative affinity of hemoglobin to CO, which is exhibited as a decrease in Douglas constant and acceleration of CO elimination from the organism. Acyzol decreases the cooperative interaction of hemoglobin subunits, which is exhibited as a decrease in Hill constant and clinically manifests itself as the elimination of Haldane effect. It was shown that the action of Acyzol increases the affinity of hemoglobin to oxygen and causes the shift of oxyhemoglobin dissociation curve to the left/ Therefore, Acyzol is not only an antidote for CO but also an antihypoxant, which is able to protect an organism in case of low oxygen partial pressure in the environment and insufficient oxygenation of hemoglobin. The results of investigation provide evidence that acyzol increases the antihypoxic stability of the organs that are most sensitive to the deficit of oxygen (brain, myocardium, liver) and fills the lack of zinc in he organism. The preparation has been recommended by the Pharmacological Committee of the Ministry of Health RF for use in medicine as the antihypoxic means in case of poisoning with CO and other combustion products (registration certificate R No. 001936/ 01–2002 of 02.12.2002, FSP for the preparation substance 42-040902691–02). The dosage form was developed (a 6 % aqueous solution,

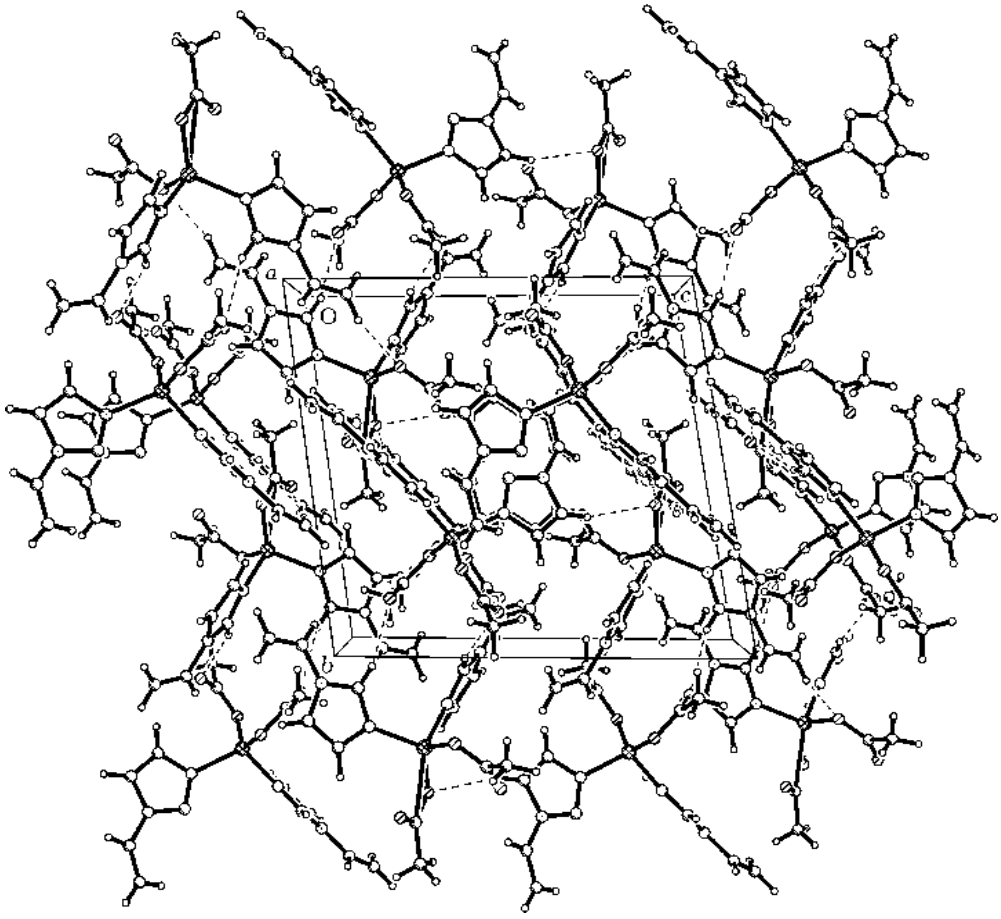


Fig. 2. Packing of A and B molecules of bis-(1-vinylimidazole)zinc diacetate complex in the crystal (projection on the *yz*-plane).

ampoules of 1 ml) for intramuscular introduction. The compositions of experimental acyzol samples in the form of capsules and syrup are being developed. The protective index of acyzol for parenteral introduction is 1.4–1.45. Oral introduction of Acyzol increases the prophylactic and curative action of the preparation with respect to CO, and the protective index increases to 1.6–1.8.

Thus, in order to decrease the action of a flow of toxicants from auto exhaust on a driver's organism, substantially helpful substance will be the highly efficient CO antidote and antihypoxant Acyzol developed by us; it is necessary in the automobile first aid kits. There are no analogues for Acyzol in the world practice in the efficiency of therapeutic action and in antihypoxic activity.

REFERENCES

1 V. Baikalova, B. A. Trofimov, V. A. Barinov *et al.*, *Nauka – Proizvodstvu*, 6 (2003) 23.
2 Pat. 2070201 RF, 1996.
3 Pat. 2204392 RF, 2003.
4 Pat. 2254337 RF, 2005.
5 L. V. Baikalova, V. I. Sokol, V. N. Khrustalev *et al.*, *Zh. Obshch. Khim.*,75 (2005) 1542.