Poster Session: Inorganic Pharmacology

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A Biological Study on the Palladium(II) and Platinum-(II) Complexes with Heterocyclic Ligands

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In recent work [1] we studied the inhibitory activity of some ML_2X_2 complexes (M = Pd(II), Pt-(II), L = isox and its derivatives, X = Cl, Br) on the Ca, Mg dependent ATP-ase.

We have now examined the inhibitory effect of the palladium(II) and platinum(II) complexes with benzoxazole (BO) and 2-methylbenzoxazole (MeBO), the palladium compounds with N-ethylimidazole (N-EtIm), N-propylimidazole (N-PropIm) and the palladium(II) oxalato complexes with heterocyclic ligands.

The extraction method of the sarcoplasmatic reticulum (SR) containing Ca, Mg dependent ATP-ase and the inhibitory activity of the complexes towards the ferment and the SH groups determinations by amperometric titrations were published previously [2, 3].

Regarding the benzoxazole and 2-methylbenzoxazole complexes [4], the inhibitory activity in aqueous solution with respect to the Ca, Mg dependent ATP-ase of the palladium(II) is greater than that of the platinum(II) complexes. The chloride derivatives show a greater effect with respect to the bromide for the high lability of the former in comparison with the latter ion. The introduction of a methyl group in position two of the BO ring does not seem to modify the inhibitory effect of the Pd(II) compounds.

As regards the N-EtIm and N-PropIm palladium(II) complexes [4] the inhibitory effect in salt aqueous solutions of the N-PropIm compounds is higher than the N-EtIm complexes. This fact can be explained by the length of the N-PropIm chain which renders the complex soluble in the enzyme lipidic part. The $[Pd(N\text{-}PropIm)_2Cl_2]$ has an activity almost double that of $[Pd(N\text{-}PropIm)_4]Cl_2$, because in the latter case it is difficult to substitute the ligands with water molecules and successively with thiolic groups. The $[Pd(L)_4]X_2$ derivatives have an activity which increases in the sequence I > Br > Cl.

These results are compared with the activity of the platinum(II) complexes in aqueous solution [5].

Because the oxalato complexes are soluble in water and are very important in biological systems, we have studied the monomeric, water-soluble $[Pd(ox)(L)_2]$ (where L = imidazole and aminoisoxazole derivatives or L_2 = en) and the dimeric, almost insoluble in water, Pd(ox)(L) (where L = isox, 3,5-diMeisox, BO and its methyl derivatives) [6].

The inhibitory activity of the $Pd(ox)(L)_2$ decreases in the order N-PropIm > N-EtIm > N-MeIm because the greater length of the ligand chain renders the respective complex more soluble in the ATP-ase lipidic part. The Pd(ox)(en) has no inhibitory effect for the presence of strong bonds of the chelating en. In the Pd(ox)(L) derivatives this effect is generally higher than in $Pd(ox)(L)_2$, because the L bridging ligand is easily substituted with water molecules and with thiol groups of the enzyme.

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Technetium-99m Chelates as Tumor Visualizing Agents

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For scintigraphic visualization of tissues and organs, Tc-99m is an ideal radionuclide because of its optimal half life and good quality scintigrams. There

is at present no outstanding Tc-99m radiopharmaceutical for the imaging of various malignant tumors. A need exists for such agents.

Hoping to find good radiotracers for tumors, we prepared Tc-99m complexes of substances which were expected to have affinity for tumor tissues such as amino acids, peptides, and porphyrins and studied the scintigraphic behaviors in experimental animals bearing spontaneous or transplanted tumors.

In the course of the study, we found that S-containing amino acids and peptides were complexed with Tc-99m in high yield, and the images of transplanted Ehrlich tumors in mice were visualized with the complexes of cysteine, S-carboxymethylcysteine, and glutathione. Recently the Tc-99m complex of ethylenediamine-N,N-diacetic acid (EDDA) was found to give much more satisfactory scintigrams of Ehrlich tumor in mice. Sequential scintigrams show that the image of the tumor was recognized in 1 hr and visualized very clearly 2–5 hr after the i.v. administration of Tc-99m complex of EDDA. The radioactivity was not accumulated in any specific organ other than the tumor and excreted through kidneys. The Tc-99m EDDA complex was also effective for scintigraphic visualization of other malignant tumors in experimental animals.

A number of chelating ligands structurally related to EDDA were examined for Tc-99m labeled radiotracers for tumors. Among the Tc-99m complexes examined, those of ethylenediamine-N,N′-diacetic acid, N-hydroxyethyliminodiacetic acid, and propylene-1,3-diamine-N,N-diacetic acid achieved clear visualization of Ehrlich tumors.

Studies on the scintigraphic visualization of human tumors and on the mechanism of the concentration in the tumor tissues of the Tc-99m complexes are in progress in our laboratories.

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Technetium in Biology and Medicine

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Ever since the availability on a large scale [1] of technetium-99m and its application in science and technology [2], followed by an increasing use of technetium-99m in non-invasive diagnostic nuclear medicine [3], there has been great interest in the biological behaviour of this element in animals and humans [4]. Formerly the use of technetium-99m in functional imaging of different organs and tissues was based on its very favourable physical properties: pure gamma emission of 140 Kev, and short half-life of 6 h, ideal for external imaging, with low radiation risk both to the patient and to the nuclear medicine department personnel. During the past 20 years since its first use in nuclear medicine, it has been increasingly realized that for the synthesis of new technetium-99m radiopharmaceuticals and for evaluations of their biological behaviour a rigorous knowledge of the aqueous solution chemistry of technetium-99m in its various oxidation states, from −1 to +7, is needed. For pertechnetate-99m ion, now widely used for the imaging of the thyroid glands, brain, stomach and salivary glands, and also forming the starting material for the synthesis of other technetium-99m radiopharmaceuticals, little solution chemistry and consequently biological behaviour is known [5]. We have shown that the presence of a small amount (~4 ppm) of free aluminum in the generator-produced pertechnetate-99m eluate not only gives false images of the thyroid gland, but also produces impure technetium-99m radiopharmaceuticals [4–6]. These inconveniences are easily avoided by chromatographic quality control of generator-produced pertechnetate-99m eluate before its administration for radionuclidic imaging, or before its use for the preparation of other radiopharmaceuticals. The results we have explained by complexation of the pertechnetate-99m ion with free Al^{3+} present in the generator column. These conclusions are supported by the chromatographic and electrophoretic examinations of all eluates during the useful life of the generator. Chromatography and electrophoresis are the only techniques which lend themselves to the study of solution chemistry of technetium-99m at the radiopharmaceutical concentration level (which is of the order of nanomolar).

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