PS5.68 — TU

HELMUT SIGEL
ROGER TRIBOLET
Institute of Inorganic Chemistry
University of Basel
Spitalstrasse 51, CH-4056 Basel
Switzerland

SYNERGISM IN THE METAL ION PROMOTED HYDROLYSIS OF ADENOSINE 5'-TRIPHOSPHATE

The enzyme-catalyzed transfers of phosphoryl or nucleotidyl groups depend on the presence of divalent metal ions, and the various stages of information transfer in genetic processes, DNA replication, RNA synthesis, and protein synthesis all require metal ions [1]. Hence, it is not surprising that the metal ion promoted dephosphorylation of nucleoside 5'-triphosphates, especially of adenosine 5'-triphosphate (ATP^{4-}), has long been recognized [2]. The simplest of these processes is the transfer of a phosphoryl group to water, and some insight into the mechanism of this reaction with ATP has been gained [3,4].

Many enzyme-nucleotide systems involve two (or more) metal ions [1]. Therefore, we are attempting to elucidate the influence of different metal ion mixtures on the dephosphorylation rate of ATP [5]. So far, the initial rates of dephosphorylation (*i.e.*, $v_o = d[PO_4]/dt$) of ATP (10^{-3} M) in the mixed metal ion systems $Cu^{2+}/ATP/Mg^{2+}$, Ni^{2+} or Zn^{2+} with the ratio 1:1:5 have been measured at pH 5.5 and compared with the binary ATP/M^{2+} 1:6 systems (see Table).

The remarkable result is that addition of Mg^{2+} to a Cu^{2+}/ATP 1:1 system accelerates the dephosphorylation rate significantly more than the same amounts of Mg^{2+} accelerate the reaction in a Mg^{2+}/ATP 1:1 system. The same synergism, based also on the Cu^{2+}/ATP 1:1 system is observed with Ni^{2+}, but not with Zn^{2+}. We attribute this observation, based on previous results [4], to the formation of a pre-reactive complex in the Cu^{2+}/ATP 1:1 system, *i.e.* of a $[Cu(ATP)]_2^{4-}$ dimer which involves purine-stacking and a Cu^{2+}/N-7 interaction; the inherent reactivity in this dimer may be triggered by the addition of Mg^{2+} or Ni^{2+}. Furthermore, we suggest that in the Zn^{2+}/ATP 1:1 system a corresponding pre-reactive state is formed and that therefore no synergism with Cu^{2+} is observed.

Table

Evidence for Synergistic Effects in the Dephosphorylation of ATP (10^{-3} M) at pH 5.5 by Mixed Metal Ion Systems ($I = 0.1$, $NaClO_4$; 50°C). The Effect of the Second Metal Ion on M^{2+}/ATP 1:1 Systems is Expressed by Rate Enhancement Factors (= REF)[a]. All Initial Rates are Given as $v_0 \times 10^8$ M s^{-1}

Effect of	system 1:1	system 1:1:5	v_o for 1:1	v_o for 1:1:5	REF [a]
Mg^{2+}	Mg/ATP		0.096		
		Mg/ATP/Mg		0.13	1.4
	Cu/ATP		2.5		
		Cu/ATP/Mg		9.7	4
Ni^{2+}	Ni/ATP		0.075		
		Ni/ATP/Ni		0.18	2.4
	Cu/ATP		2.5		
		Cu/ATP/Ni		9.5	4
Zn^{2+}	Zn/ATP		0.15		
		Zn/ATP/Zn		0.92	6
	Cu/ATP		2.5		
		Cu/ATP/Zn		14	6

a) REF = v_o of a 1:1:5 system divided by v_o of the corresponding 1:1 system; *e.g.*, 0.13/0.096 = 1.4 or 9.7/2.5 = 4. The rate data are summarized from several of our studies [3-7].

In accord with this interpretation are the results of preliminary experiments which suggest that there is also a very pronounced synergism in $Zn^{2+}/ATP/Mg^{2+}$ systems at pH 7.5. This is interesting because, *e.g.*, DNA and RNA polymerase [1] contain tightly bound Zn^{2+} and use nucleoside 5'-triphosphates as substrates, but for activity the enzymes require in addition Mg^{2+}.

ACKNOWLEDGEMENTS

The support of this work by the Swiss National Science Foundation is gratefully acknowledged.

REFERENCES

[1] a) G.L. EICHHORN, *Met. Ions Biol. Syst.*, **10**, 1-21 (1980); b) F.Y.-H. WU,C.-W. WU, *Met. Ions Biol. Syst.*, **15**, 157--192 (1983).

[2] C. LIÉBECQ, M. JACQUEMOTTE-LOUIS, *Bull. Soc. Chim. Biol.*, **40**, 67-85 and 759-765 (1958).

[3] H. SIGEL, P.E. AMSLER, *J. Am. Chem. Soc.*, **98**, 7390--7400 (1976).

[4] H. SIGEL, F. HOFSTETTER, R.B. MARTIN, R.M. MILBURN, V. SCHELLER-KRATTIGER, K.H. SCHELLER, *J. Am. Chem. Soc.*, **106**, 7935-7946 (1984).

[5] H. SIGEL, R. TRIBOLET, results to be published.

[6] R.M. MILBURN, M. GAUTAM-BASAK, R. TRIBOLET, H. SIGEL, *J. Am. Chem. Soc.*, **107**, (1985), in press.

[7] P.E. AMSLER, H. SIGEL, *Eur. J. Biochem.*, **63**, 569-581 (1976).

6. *Bioinorganic Therapy*

PS6.1 — MO

RUTH MARGALIT
HARRY B. GRAY
Arthur Amos Noyes Laboratory
California Institute of Technology
Pasadena, California 91125
U.S.A.
MICHAEL CLARKE
Department of Chemistry
Boston College
Chestnut Hill, Massachusetts
U.S.A.
S.C. SRIVASTAVA
Department of Chemistry
Brookhaven National Laboratory
Upton, New York
U.S.A.

BIOLOGICAL TISSUE DISTRIBUTION OF $Ru(NH_3)_5$-BLEOMYCIN

The reaction of $Ru(NH_3)_5H_2O^{2+}$ with the chemotherapeutic agent bleomycin at pH 7.2 gives a Ru-modified derivative. The modified bleomycin has been purified and characterized (by ^1H NMR and differential pulse electrochemistry) as $Ru(NH_3)_5^{3+}$-(pyrimidine)-BLM.
A model compound, $Ru(NH_3)_5His^{3+}$, was found to be effective in the scission of DNA strands, *in vitro*, when combined with a reducing agent. The activity of $Ru(NH_3)_5$BLM in DNA strand scission will be presented and discussed. The distribution of the radioactive drug $^{106}Ru(NH_3)_5$BLM in normal and tumor-bearing mice has been studied.

PS6.2 — TU

M.G. BASALLOTE
E.J.G. CONEJERO
R. VILAPLANA
F. GONZÁLEZ-VÍLCHEZ
Departamento de Química Inorgánica
Facultad de Ciencias
Aptdo. 40, Puerto Real, Cádiz
Spain

PLATINUM COMPLEXES OF EDDA AND ITS ETHYL ESTER: SYNTHESES AND ANTITUMOR PROPERTIES

Structure-activity relationship for antitumor properties of platinum complexes is still not clear, although *cis*-$[PtA_2X_2]$ compounds seem to be active when A ligands are inert and X ligands can be easily replaced in biological media. The nature of A is of great importance for the antitumor activity of the complex, with little changes in its structure leading sometimes to main changes in activity. Therefore we are testing complexes of this type with new structures in order to obtain *cis*-DDP analogs with higher therapeutic indexes.
We have shown recently activity against Ehrlich ascites tumor for some platinum complexes with aminopolycarboxylic ligands [1]. However, $[Pt(EDDA\text{-}H_2)Cl_2]$ was showed to be inactive in a previous study by SPEER *et al.* [2]. One interesting problem in structure-activity relationship is that related to the effect of the charge of the complex, active compounds being normally neutral complexes. So esterification of carboxylic groups in ligands must lead to an increase in the activity of the complexes. However, the results of previous studies with similar ligands [3,4] by other authors are contradictory and new data must be obtained for solving the problem. In this sense, we report in this paper the results of a new test of this compound and of its analog with the ethyl ester of the ligand.