TRI-ARYLTIN FUNGICIDES: STRUCTURE-ACTIVITY RELATIONS INVOLVING SUBSTITUENT EFFECTS

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ABSTRACT

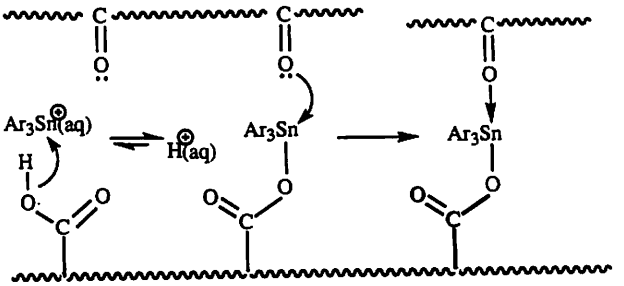
Triphenyltins (Ph_3SnOAc, Ph_3SnOH) have been used for many years as agricultural fungicides on many tropical and temperate crops including those of importance to Quebec, e.g. potatoes, strawberries etc., but their mode of action is still not fully understood. In this study, a series of tri-aryltins [Ar_3SnOAc, Ar_3SnOH, $(Ar_3Sn)_2O$, where Ar = o/m/p-substituted phenyl] has been synthesised in order to assess both steric and electronic effects on the biocidal activity of these systems. Our results indicate that fungicidal effectiveness correlates with the ability of the Ar_3Sn moiety to achieve a trans-bidentate 5-coördinate geometry as exemplified by X-ray diffraction studies of model compounds. A mechanism will be outlined for the mode of action of tri-aryltin fungicides consistent with this result and the picture generally accepted in the literature.

Triphenyltins (Ph_3SnOAc, Ph_3SnOH) have been used for many years as agricultural fungicides for many tropical and temperate crops including those of importance to Quebec, e.g. potatoes, strawberries etc. Early results from the 1970s' showed that the "Ph_3Sn" moiety acted to inhibit ATP formation or hydrolysis in mitochondria by interacting with the enzyme ATPase. However, the nature of the binding site in this enzyme for the tri-organotin species remained unknown.

In this study, a series of tri-aryltins [Ar_3SnOAc, Ar_3SnOH, $(Ar_3Sn)_2O$, where Ar = o/m/p-substituted phenyl] was synthesised in order to assess both steric and electronic effects on the biocidal activity of these systems. Our results indicated that fungicidal effectiveness correlated with the ability of the Ar_3Sn moiety to achieve a *trans*-bidentate 5-coördinate geometry as exemplified by X-ray diffraction studies of model compounds. Thus, Ar_3SnOAc (Ar = *p*-$CH_3OC_6H_4$ or 2,4,6-$(CH_3)_3C_6H_2$) which are monomeric with 4-coördinate tin are completely ineffectual as fungicides unlike Ph_3SnOAc, the commercial agent, which has five-coördinate tin with bridging acetate groups. However, (*o*-$CH_3C_6H_4)_3SnOAc$ which is monomeric in the solid state also shows fungicidal activity but (*o*-$CH_3C_6H_4)_3SnX$ can form adducts provided the ligand L is sterically undemanding.

Recent studies in the literature, show that F-ATPase, the catalyst for ATP synthesis or hydrolysis, consists of two very complex units, F_1, protruding into the mitochondrion and the catalytic sector of the enzyme , and F_0, comprised of sub-units *a*, *b*, and *c*, bridging the membrane of the organelle and responsible for the proton transfer associated with the above two processes. Inhibition by R_3SnX occurs in F_0 by them binding to at least one of the *c* sub-units. In addition, molecular flexibility of the sub-units in F_0 may be required for the rapid proton transfer needed for multisite ATP synthesis or hydrolysis, the process that is inhibited by R_3SnX. It has been proposed that "R_3Sn" freeze the structure of F_0 so that rapid proton transfer is disallowed but that the slow proton transfer rate required for uninhibited unisite processes is still permitted.

The mechanism we propose for the mode of action of tri-aryltin fungicides consistent with our results and the picture generally accepted in the literature is shown in the Figure below.



Penetration by $Ar_3Sn^+(aq)$ or perhaps Ar_3SnX, since the environment is partly hydrophobic, of the a-helical peptide chains forming sub-unit *c* of the F_0 unit of ATP-ase, occurs until carboxyl groups on Asp or Glu residues are reached. Here the Ar_3Sn^+ ion can replace a proton but the tin is occupying a **labile** monodentate site with four-coördinate geometry and thus would not effectively impede the low proton flux required for unisite processes.

However the high proton flux resulting from the greater ATP reactivity using the multisite pathway may induce more extensive molecular motions in the F_0 unit which can cause a donor atom e.g. from a carbonyl group in a neighbouring chain, to approach and further coördinate an already bound Ar_3Sn moiety in a manner equivalent to a giant chelate ligand, giving rise to a strong binding site with five-coördinate geometry. This effectively irreversible change would enable the Ar_3SnX to freeze the F_0 unit in a state so that the rapid proton flux required for the multisite pathway would be disallowed, thus inhibiting the ATP synthesis or hydrolysis needed for the mitochondrion and the cell to function.