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Studies on organometallic compounds: An approach towards characterisation of structure and activity of triorganostannyl 2-(arylazo)benzenecarboxylates in relation to the bacterial cell wall

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Abstract. Organostannyl 2-(arylazo)benzenecarboxylates have shown great promise in inhibiting the growth of Gram-positive bacteria. A possible explanation for the structure–activity relationship (SAR) has been discussed through an intercalation mechanism. The intercalative binding mechanism finds support from spectral, chemical as well as X-ray computer molecular modelling evidences. An interpretation of the activity against various microorganisms has also been made in the present investigation.

Keywords. Organometallics; triorganostannyl 2-(arylazo)benzenecarboxylates; tri-*n*-butylstannyl carboxylates; biologically active; intercalation; CPK space-filling models; computer molecular model.

1. Introduction

Organostannyl carboxylates constitute an important class of organometallics known since the 1950's both for their biocidal properties and unique structural features (Coates *et al* 1967; Polster and Halacka 1972; Soracco and Pope 1983; Powell 1988). With this in view, we have focussed attention on molecules of the general formula (*I*) containing elements of structural rigidity, because rigidity restricts conformational options and reduces the ambiguity in stereochemical assignments for functional groups.

In continuation of our earlier work (Maji *et al* 1989) on the syntheses and the microbiological activities of triorganostannyl 2-(arylazo)benzenecarboxylates, we wished to augment our study with X-ray structure determination and computer modelling to correlate their unique structural properties with their activities.

Because of the complexity of biological macromolecules and consequent difficulties in their study, the use of model compounds which have the property of forming a

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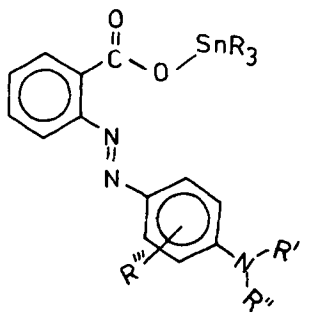

(I)

receptor-substrate pair with the compound under investigation can be used to study activity. Amino acids and oligopeptides have proved to be good model compounds and have thus drawn the attention of researchers during the last few decades for understanding the biological activities of a wide variety of compounds. Our findings indicate that the structural specificities of triorganostannyl 2-(arylazo)benzenecarboxylates can be understood in terms of interactions based on two different combinations of functional groups with peptide units of enzymatic proteins by intercalation.

2. Materials and methods

The syntheses and characterisation of the compounds under investigation have been described previously in detail (Maji *et al* 1989). The test compounds were screened *in vitro* for their microbiological activity by using Agar-Cup method (Mackie and McCartney 1959). Spectrophotometric measurements were performed with a Cary 17 D spectrophotometer. The stereochemistry of the intercalative binding geometry was tested by computer modelling using an IRIS molecular modelling workstation (Silicon Graphics).

3. Results and discussion

Organostannyl 2-(arylazo)benzenecarboxylates under investigation were screened *in vitro* for their biological activity against several microorganisms using Agar-Cup method. These compounds were found to exhibit considerable activity against several Gram-positive bacteria (table 1). From the results, it was found that the nature of the substituents (R′, R″, R‴) at various positions in the phenyl ring was found either to increase or to decrease the biological activity of the organostannyl 2-(arylazo)benzenecarboxylates. The results may be explained as being due to the variation of electron density on the β-azoic nitrogen brought about by the substituents. These observations led us to consider the β-azoic nitrogen to be the active site in organostannyl carboxylates under investigation. This is not surprising, because the azoic nitrogen is capable of forming a hydrogen bond as was well established in this series of 2-(arylazo)-benzenecarboxylic acids by our IR, UV-Vis and ^{1}H-NMR spectral studies.

Table 1. Antimicrobial activity of organostannyl 2-(arylazo)-benzenecarboxylates.

Compound	R	R′	R″	R‴	*S.a.*	*B.m.*	*S.l.*	*B.p.*	*M.f.*	*B.s.*
1	Ph	H	Me	3-Cl	15·0	15·0	13·0	15·0	15·0	14·0
2	*n*-Bu	H	Me	3-Cl	15·0	15·0	15·0	15·0	15·0	15·0
3	Ph	H	Me	3-Me	15·0	15·0	15·0	15·0	15·0	15·0
4	*n*-Bu	H	Me	3-Me	15·0	16·0	15·0	16·0	15·0	15·0
5	Ph	Me	Me	2-Cl	15·0	15·0	16·0	16·0	16·0	15·0
6	*n*-Bu	Me	Me	2-Cl	16·0	16·0	16·0	17·0	17·0	16·0
7	Ph	Me	Me	2-Br	16·0	17·0	18·0	17·0	17·0	18·0
8	*n*-Bu	Me	Me	2-Br	19·0	19·0	19·0	19·0	19·0	18·0
9	Ph	Et	Et	H	19·0	18·0	18·0	19·0	19·0	19·0
10	*n*-Bu	Et	Et	H	19·0	19·0	20·0	19·0	19·0	19·0
11	Ph	Et	Et	2-Me	20·0	19·0	20·0	19·0	19·0	20·0
12	*n*-Bu	Et	Et	2-Me	20·0	20·0	21·0	19·0	20·0	21·0

S.a.: *Staphylococcus aureus*; *B.m.*: *Bacillus cereus* var. *mycoides*; *S.l.*: *Sarcina lutea*; *B.p.*: *Bacillus pumilus*; *M.f.*: *Micrococcus flavus*; *B.s.*: *Bacillus subtilis*;

Table 2. UV-Vis spectra of organostannyl 2-(arylazo)benzenecarboxylates in different nucleophilic solvents [λ_{max}(nm)].

Compound	R	R′	R″	R‴	MeOH	Pyridine	DMSO
1	Ph	H	Me	3-Cl	391	397	398
2	*n*-Bu	H	Me	3-Cl	395	395	401
3	Ph	H	Me	3-Me	400	405	410
4	*n*-Bu	H	Me	3-Me	402	400	407
5	Ph	Me	Me	2-Cl	407	415	421
					498	—	—
6	*n*-Bu	Me	Me	2-Cl	412	412	416
					500	—	—
7	Ph	Me	Me	2-Br	410	417	418
					510	—	—
8	*n*-Bu	Me	Me	2-Br	410	420	421
					512	—	—
9	Ph	Et	Et	H	412	432	422
					510	518	—
10	*n*-Bu	Et	Et	H	415	432	420
					512	510	—

The significant inhibition of bacterial growth by organostannyl 2-(arylazo)benzenecarboxylates in the present study also proved the presence of the metal in the reactive site of the substrate. The observed enhanced biological activity of the organostannyl carboxylates as compared to that of their corresponding 2-(arylazo)benzenecarboxylic acids and the complete loss of the biological potency of the corresponding methyl carboxylates provide further support to this view.

The unique structural feature of the organostannyl 2-(arylazo)benzenecarboxylates (Das *et al* 1993), which is involved in complexation with solvents of variable nucleophilicity as evidenced from UV-Vis spectra (table 2), can perhaps be successfully exploited in explaining similar coordination with the enzymatic protein molecules also. The enzymatic proteins in their relatively rigid planar peptide structures possess

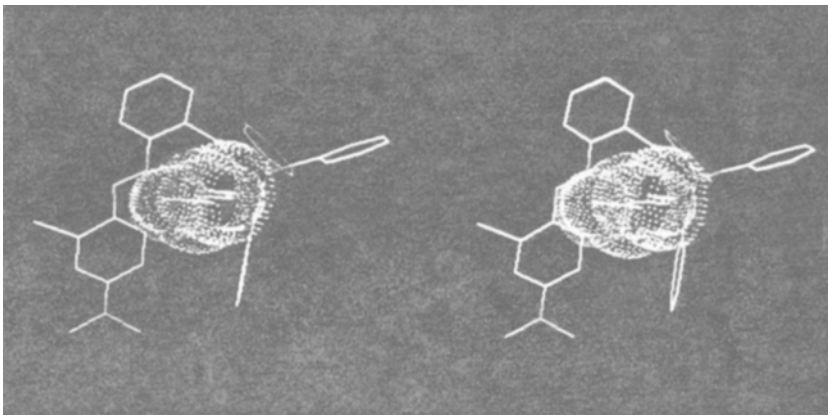

Figure 1. Stereo computer simulated molecular model with van der waal radii net of the mode of attachment of peptide unit (Gly–Gly) with crystallographic structure of triphenyl 2-[2-bromo-4-(dimethylamino)phenylazo]benzenecarboxylate.

carbonyl group capable of forming metal–oxygen bond with the stannyl groups of organostannyl carboxylate and this bond formation is further augmented by the nearby β-azoic nitrogen and stannyl carboxylate carbonyl oxygens which form bifurcated hydrogen bonds with the peptide N–H groups (N–H...N = 2·97 Å, N–H...O = 3·29 Å), thus enhancing the electron density on the peptide oxygen. The binding through peptide oxygen is not unusual since the affinity of stannyl group for oxygen coordination (Ho *et al* 1980) is believed to be greater than that of peptide nitrogen.

This sort of complexation of the organostannyl carboxylates and enzymes may thus easily account for its property of arresting bacterial growth.

The above possibility seems to be quite reasonable from an examination of Dreiding, CPK space-filling models and finally from computer graphics (Silicon Graphics) of the novel compound, triphenylstannyl 2-[2-bromo-4-(dimethylamino)phenylazo]-benzenecarboxylate (figure 1), that allows the planar peptide unit of a dipeptide (Gly–Gly or Gly–Ser) to fit well into the organostannyl carboxylate molecule by intercalation.

Spectral evidence in favour of this picture lies in the variation of λ_{max} along with ϵ values of the above organostannyl carboxylate with time in presence of the simplest dipeptide (Gly–Ser) in the UV-Vis spectroscopy in methanol. This arises from the preferred coordination of this stannyl atom with the relatively more nucleophilic peptide oxygen and the formation of a hydrogen bond involving the peptide N–H, the β-azoic nitrogen and the stannyl carboxylate carbonyl oxygen as well. A rapid change in λ_{max} and ϵ values can also be attained simply by slight warming which enhances the intercalation due to "thermal breathing" of the organostannyl carboxylate molecule.

Inclusion of a methoxy group at the 2-position overpowers the chelating property of the solvent molecule and a rigid cagelike structure is formed through chelation with the tin atom simultaneously by both the β-azoic nitrogen and C_2 oxygen atom. This is likely to prevent the intercalation of the peptide linkage into the organostannyl carboxylate molecule which is supported by the complete lack of biological potency of the 2-methoxy organostannyl carboxylate compound.

This fact corroborates our view about the structural specificity of the organostannyl carboxylates in question.

On thorough examination, it was observed that while these organostannyl carboxylates are active against Gram-positive bacteria, none possess any activity against Gram-negative bacteria and pathogenic fungi.

Gram-negative bacteria are resistant to this group of organostannyl carboxylates possibly due to the inability of these large polar molecules to cross the outer membrane and reach the target site.

It has been found that ergosterol biosynthesis is inhibited by all antifungal agents. Organostannyl carboxylates in our case probably do not in any way inhibit the biosynthesis of ergosterol in fungal cells and hence these compounds under investigation have no fungicidal properties.

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