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Organotin carboxylates: from structures to antitumour activities

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Abstract: An overview is given of the research on organotin carboxylates, including architecture formation, molecular and supramolecular architectural styles, spectra studies and antitumour activities. The development of antitumour organotin carboxylates is discussed for selected classes. They show high activities but the therapeutic potential is deeply hampered by their solubility in water and side effects. Further research to develop novel antitumour organotin carboxylates and effective methods to achieve higher water solubility need to be carried out.

Key words: Organotin carboxylate; molecular structure; supramolecular structure; antitumour activity; Tin NMR study.

Introduction

Organotin carboxylate is widely used as PVC (polyvi-nyl chloride) stabilizers added in adhesive, sealant, elas-tomer, molded foam etc (1-3). It is well known as catalysts for polyurethane foams, room temperature vulcanisation of silicon rubbers, transesterifications, acetylations of alcohols, and for dehydrations of alcohols to ethers (4-9). But the most attractive is its biological activity used as biocides and anti-tumour agents (10-13). And the ka-leidoscopic fascinating structures of them appeal chemists to explore and study the whole time (14-17).

Organotin carboxylates can be classified as mono-, di-, and tri-organotin carboxylates according to the number of alkyl groups on tin. For the various structures, dibutyltin carboxylate and triphenyltin carboxylate make a primary contribution. Most typical structures like macrocycle, lad-der and polymeric chain are di- or tri-organtin carboxy-lates (1, 14-16). The extraordinary molecular architec-tures about them are still being quested and discovered.

The first in vivo antitumour test was carried out on P388 and L1210 performed by National Cancer Institute (NCI) (18). Results indicate that dibutyltin carboxylate and triphenyltin carboxylate show high antitumour acti-vity against cancer cell lines, which has received univer-sal attention. Today, the tests are replaced by the in vitro experiment (19, 20).

The therapeutic potential is deeply hampered by poor solubility in water and side effects. Polar substituents can improve the water solubility but not effective for all or-ganotin carboxylates. Using ionic groups to improve the ionicity of complex may contributes to the in vivo test. Finding potential encapsulation to enhance the drugs to tumor sites, or using drug combination is practical me-thods to reduce side effects and improve their efficacy.

This paper reports an overview about the molecular and supramolecular structure, antitumour activity, and tin NMR study of di- and tri-organtin carboxylates.

Molecular Structure

Di- and tri-organtin carboxylates can be synthesized by condensing diorganotin oxides and triorganotin hy-droxides with carboxylic acids respectively (1). Depen-ding on the organotin/carboxylic acid molar ratio and the molecular configurations of organotin and carboxylic acid, distinct types of structures can be obtained.

Triorganotin carboxylate

This family usually possesses two main types of struc-tures: (a) chain structures; (b) discrete structures, and ano-ther rare one: (c) macrocycles.

Polymeric chain structures are the most common struc-tural types known for triorganotin carboxylates. When a monocarboxylic acid is used as ligand to coordinate with organotin and the organotin carboxylic acid molar ratio is 2:1, following polymeric chain structures (Figure 1).

If dicarboxylic acid is ligand and the molar ratio is 1:1, following structure (Figure 2).

Macrocycles are known for some triorganotin car-boxylates and they are all tetra- or hexa-nuclear without exception (Figure 3) (21).

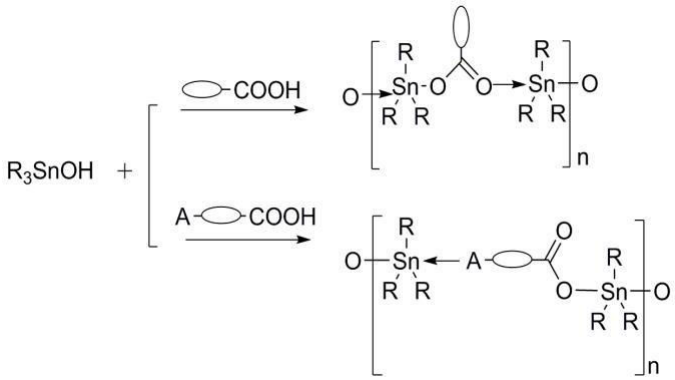

Figure 1. 1:2 formation of chain structures in triorganotin carboxy-lates.

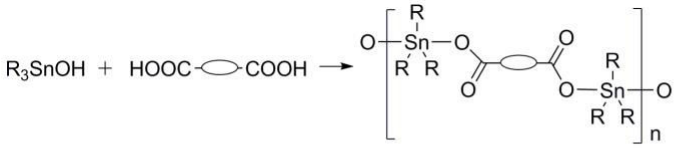

Figure 2. 1:1 formation of chain structure in triorganotin carboxylates.

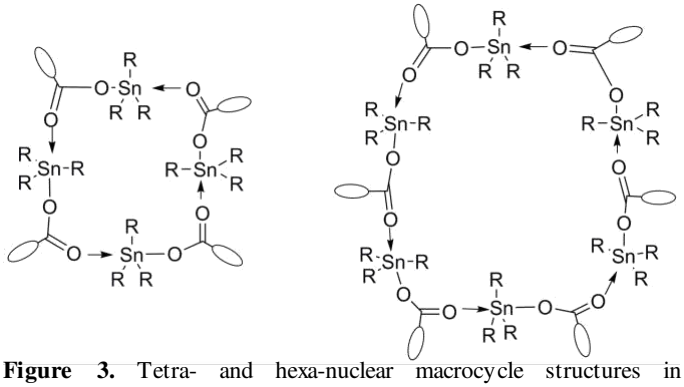

Figure 3. Tetra- and hexa-nuclear macrocycle structures in triorganotin carboxylates.

Diorganotin carboxylate

The simplest structure of diorganotin carboxylate consist of 1:2 organotin and carboxylic acid. Central atom "Sn" coordinates with two carboxyl groups and the geo-metry can be described as a skew-trapezoidal bipyramid or bicapped tetrahedron (22). In general, this type of struc-ture is discrete molecule.

While ladder structure of diorganotin carboxylate is composed of [R2SnO]n and the carboxylic acid by diffe-rent molar ratio (23). The structures vary depending on subtle variation of the coordination of the carboxylate ligands. The shortest ladder is tetra-nuclear three-fold. Some typical types among the shortest are depicted in Fi-gure 4. The common structural motif of the ladder is a central four-membered Sn2O2 ring.

The length of ladder will increase with "n" in [R2SnO] n part. Most of the ladder are three- and four- fold. The longest known for now is a nona-nuclear eight-fold lad-der (24). All the ladder structures can be divided into two categories: double-ladder and single-ladder. They could be macrocycles or not (Figure 5), and the ligands in macrocy-

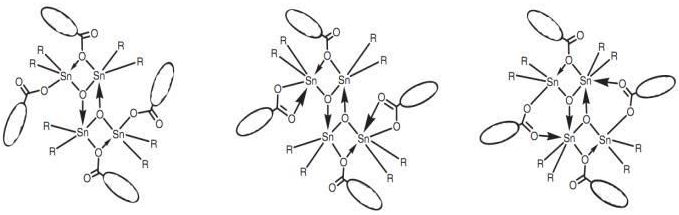

Figure 4. Typical tetra-nuclear three-fold ladder structures in diorgano-tin carboxylates.

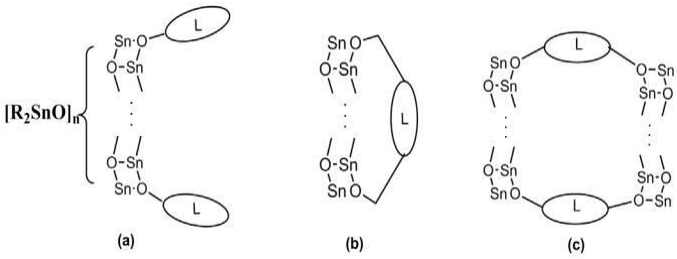

Figure 5. Ladder structures in diorganotin carboxylates: (a) non-macro-cycle single ladder (as structures in Figure 4) (b) macrocycle contains a single ladder (c) macrocycle contains double ladders. All the R- and COO- groups are omitted for clarity.

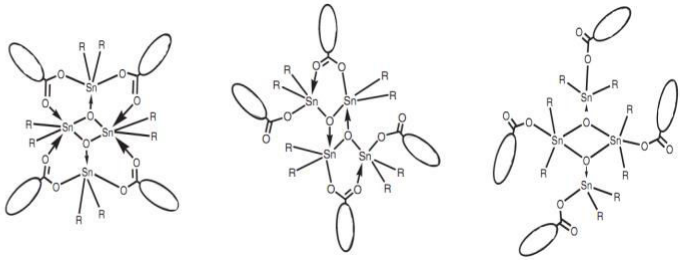

Figure 6. Typical central four-membered Sn_2O_2 structures in diorgano-tin carboxylates.

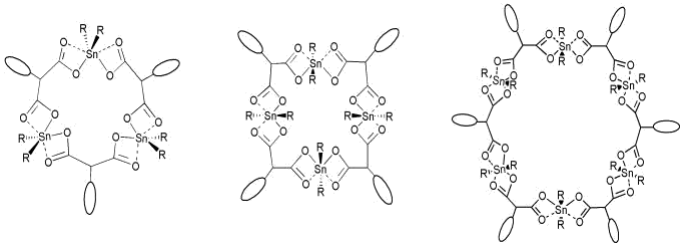

Figure 7. Tri-, tera- and hexa-nuclear macrocycle structures in diorganotin carboxylates.

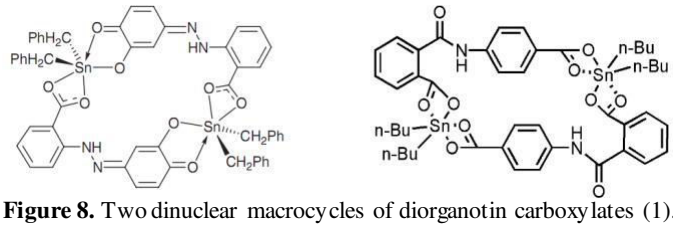

Figure 8. Two dinuclear macrocycles of diorganotin carboxylates (1).

cle structure are always dicarboxylic acid.

There are still a group contains a central four-membe-red Sn2O2 ring. The carboxylic acids in them adopt various coordination modes. Representative examples are shown in Figure 6.

In addition to the above, macrocycles linked by diorganotins and ligands alternately are synthesized gra-dually. Most are tri-, tera- and hexa-nuclear (Figure 7), several are dinuclear (Figure 8) (1, 21).

Compared with other metals, only few macrocycles are reported about tin. And based on the various coordination modes of tin, more novel molecular constructions will be fond. The structure of organotin carboxylate still has unexplored fields so far.

Supramolecular Structure

Discussion on supramolecular structure of organotin carboxylate crystal is limited. The 2D or 3D supramolecu-lar structures are built by intermolecular interactions such as H-bond, C-H···π, Sn···O and π···π ineractions (21, 22, 24). There is no rules for the construction of multi-dimen-sional structure. It changes sensitively with the substituent group of ligand, the alkyl group of organotin, the growth rate of crystal and the environment of cultivate room.

Generally the organotin carboxylate molecules make up irregular macrocycles through intermolecular inte-ractions, and the macrocycles connect with each other to form the fantastic multi-dimensional structure. In these multi-dimensional structures reported, the molecular re-cognition to solvent molecules occurs frequently (Figure
9) (21, 22). Moreover, it can be concluded that similar or-ganotin carboxylate molecules tend to form similar mul-ti-dimensional configurations (Figure 10) (24).

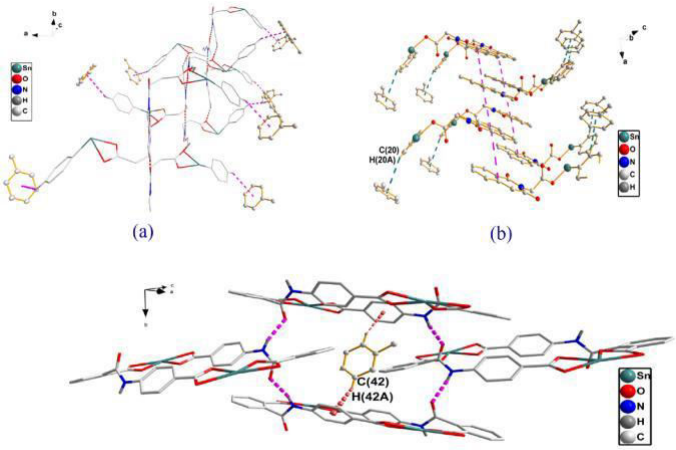

Figure 9. C-H···π interactions between solvent benzene molecules and organotin carboxylates in the supramolecular structure [(a, b): (22), (c): (21)].

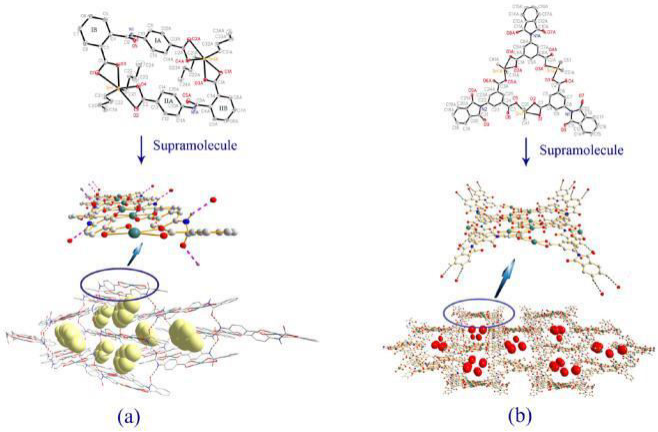

Figure 10. Similar organotin carboxylate macrocycles show similar multi-dimensional structures (21).

Tin NMR Study

Tin has many stable isotopes. Two of them owing a spin 1/2 can be identified in Sn NMR. For organotin car-boxylate, the increase in the coordination number of Sn is accompanied by an obvious increase in 119Sn nuclear shielding. A large number of examples have proven to consist with this observation (14). And the weak intra- or inter-molecular interactions, the solvent, temperature, or even the steric requirements of remote substituents will affect the δ119Sn values (1, 11).

119Sn NMR spectroscopy, together with NMR data, serves most conveniently to monitor molecular rearran-gements and helps to assign unambiguous structures (25).

Antitumour activity

Nowadays, reports on anti-cancer drugs and the mecha-nism become popular (26-30). After the cisplatin was fond antitumour active, some chemistry teams began to investigate the possible therapeutic applications of other metal-based, often organometallic compounds. Organotin carboxylates with a variety of ligands such as benzoates, phenylacetates, and cinnamates, were discovered to be active in vitro and in vivo against tumor cell lines (31). A few examples of organotin carboxylates with antitumor activities are listed in Table 1 (23, 32, 33).

It can be seen that both di- and tri-organotin carboxy-lates have high antitumour activities, and di-n-butytin are often potent, sometimes even more than cisplatin. The high activity mostly owe to the high toxicity of di-n-butyl-tin itself. The di-n-butyltin carboxylate analogue of car-boplatin (Figure 11) was synthesized and screened against MCF-7 and WIDR. The ID50 values are 63 and 121ng/ ml respectively smaller than those of cisplatin (699 and 967ng/ml) (1, 31).

The mechanism of biological action of organotin de-rivatives is still being fond. Some tentative proposals have emerged. These studies provide information on the

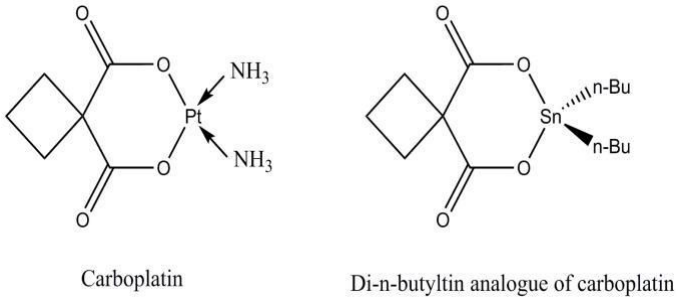

Figure 11. Carboplatin and di-n-butyltin analogue of carboplatin.

Table 1. Concentration of organotin carboxylates to obtain 50% inhibition of HeLa, HT1080 and U87 proliferate ac-tivity.

2,5-H_2L1 = 2,5-dibenzoylterephthalic acid, 2,5-H_2L2 = 2,5-bis(4-methylbenzoyl)terephthalic acid, 2,5-H_2L3 = 2,5-bis(4-ethylbenzoyl)terephthalic acid, 4,6- H_2L1 = 4,6-dibenzoylisophthalic acid, HL5 = (E)-3-(2-nitrophenyl) propenoic acid

mechanism of action of organotin complexes: the lipophi-licity plays an important role (1, 31).

Due to lipophilicity, organotins are membrane-active to attack cytoplasmic membrane. By binding or inser-tion into the membrane, organotin disrupt the integrity of membrane. The cell wall is the dominant target of Sn(IV) in studies of tin interactions with the yeast. Lipophilic interactions augment the toxicity of tri-n-butyltin com-polexes (TBT)) and help to uptake. TBT uptake leads to cell death and extensive K+ leakage. While Sn(IV) uptake had no effect, and trimethyltin complexes (TMT), do not interact with cells. Only TBT changes membrane fluidity among the above three kinds of complexes (1, 31).

Organotins can also act intra-cellularly and disrupte the intact organelles. They dissociates from carboxylate ligand when enters the cytosol, and binds with biological molecules, thiols, peptides, proteins, amino acids, nucleic acids, carbohydrates, and steroids. It is possible that these processes or interaction are involved in the biological ac-tivity of organotin complexes (1, 31).

In addition to the advantages of high activity, com-pared to the platinum compound, tin complexes are much cheaper. So if organotin carboxylate can be used for clini-cal medicine, cost reduction, dosage reduction and effect enhancement will be reached.

However, for the high cytotoxicity, when organotin carboxylates kill the cancer cells, side effects also accom-pany. Normal and healthy cells will be attacked at the same time, cause the inhibition ability of cells growth is not targeted. These lead to strong and inevitable side ef-fects.

Structure-Activity

Few works on structure-activity relationships are re-ported. Some of these investigations support the conclu-sion that the toxicity of organotin complexes is domi-nanted by the nature of organic groups on tin atom and the number of the organic groups. Generally triorganotin complexes show the highest biocidal activities. The nature of the organic group decides the species to which cancer cell the organotin complex is most active (1). Overall, alkyl groups make the complexes more active than aryl groups. To design more effective complexes and study quantitative structure-activity relationship appear to be an interesting strategy to address this problem.

Acknowledgments

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