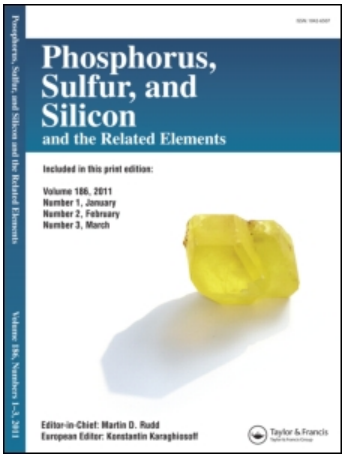

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THE INTERACTION OF BIS[2-MERCAPTOETHANESULFONATO(2⁻)-S], BIS[L-CYSTEINATO(1⁻)-S], AND BIS[L-PENICILLAMINATO(1⁻)-S]-DIMETHYLTIN (IV), WITH RAT HEMOGLOBIN: A ^{119}Sn MÖSSBAUER SPECTROSCOPIC STUDY

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The title compounds, representative of classes of diorganotin (IV) derivatives active against murine leukemia P-388, interact with rat hemoglobin (selected as a model protein) by: i) co-crystallization, with formation of microcrystalline pellets, and: ii) diffusion into hemoglobin crystals from the supernatant solution (as determined for the 2-mercaptoethanesulfonato derivative). The nature of the Me_2Sn^{IV} species in hemoglobin has been investigated by ^{119}Sn Mössbauer spectroscopy, and a C_2SnS_2 tetrahedral geometry has been assigned by the point-charge model rationalization of the nuclear quadrupole splitting parameter.

Binding into crystalline hemoglobin has been ascribed to Coulomb interactions and to hydrogen bonding between the sulfonate and the aminoacid tails of the organotin (IV) derivatives and functional groups of the globin.

Key words: Mössbauer spectra; rat hemoglobin; dimethyltin (IV).

INTRODUCTION

The binding of triethyltin (IV) to rat and cat hemoglobin, employed as model proteins, has been widely investigated, in order to interpret on a molecular basis its ample biological activity.[1,2] The studies in this field have been recently extended to dimethyltin (IV) derivatives, whose interaction with rat hemoglobin has been investigated by ^{119}Sn Mössbauer spectroscopy,[3] in the context of a research program on the anti-leukemia activity of diorganotins and the related structure–activity relationship.[4] The occurrence of covalent binding by a thiol sulfur of a cysteine side chain (and possibly also by a nitrogen atom from histidine) on tin in dimethyltin (IV) moieties and in [L-cysteinato(2⁻)-S,N-dimethyltin (IV)], has been proposed,[3] by analogy with findings on triethyltins.[5,6]

Amongst the compounds more active against murine leukemia P-388, are anions bis[2-mercaptoethanesulfonato(2⁻)-S]-diorganotin (IV),[4] where the metal atom is formally neutral and involves two strongly covalent bonds with thiol sulfur.[4,7] We planned to investigate the nature of the interaction with the model

protein (rat hemoglobin) by compounds of this type, and report in this paper ^{119}Sn Mössbauer spectroscopic studies on the systems bis(2-mercapto-ethanesulfonato)-, bis(L-cysteinato)-, bis(L-penicillaminato)-dimethyltin (IV)-rat hemoglobin.

EXPERIMENTAL

The sodium and guanidinium salts of 2-mercaptoethane sulfonates, $[Me_2Sn(SCH_2CH_2SO_3)_2]^{2-}$, (1) and (2) respectively, and the L-cysteinate and L-penicillaminate, $Me_2Sn[SCH_2CH(NH_3^+)COO^-]_2$, (3), and $Me_2Sn[SC(CH_3)_2CH(NH_3^+)COO^-]_2$, (4), were prepared according to literature reports.[4,8] Aqueous solutions of 10 mM with respect to the Me_2Sn^{IV} moiety in Hepes buffer (N-2-hydroxyethyl-piperazine-N' -2-ethanesulfonic acid) 0.2 M, adjusted to pH 7.4 with NaOH, were prepared from solid samples of the compounds listed above, or from Me_2SnCl_2 and ligands in the molar ratio 1:2; these were employed for the synthesis of the hemoglobin derivatives, soon after the preparation, in order to avoid ligand oxidation and related processes detected to occur on standing.[7,9]

Rat hemoglobin was obtained and analyzed according to the literature method,[10] and the lysate was immediately employed in the synthesis of the dimethyltin (IV) derivatives, which was carried out by the procedure reported earlier.[3,6] The Mössbauer spectra were determined at 77.3°K on absorber samples consisting of 0.5–1.0 g of pellet of the hemoglobin complexes ($\varepsilon\%$ effect $\simeq 0.3$), which were pre-frozen by immersion into liquid N_2 before insertion into the cryostat.[3,6] A spectrometer based on a 4096 channels analyzer (Master 4000, Laben, Milano) and related electronics[3] was employed. The sources (e.g., Ca $^{119}SnO_3$, 10 mCi, R.C., Amersham, England) moved at linear velocity and constant acceleration. Data reduction was effected by computer fitting with Lorentzian lineshapes.[3]

RESULTS AND DISCUSSION

The quality of the Mössbauer spectra here determined is shown in Figure 1, while the Mössbauer parameters of the hemoglobin complexes are summarized in Table I. It is observed that the spectra are well-formed, suitable for computer fitting and determination of the parameters δ, ΔE and Γ, despite the low percent effect for resonant absorption of γ rays. Moreover, the narrowness of the lines suggests the occurrence of single tin sites.

The isomer shift values, δ, are typically in the range shown by dimethyltins.[11] The nuclear quadrupole splitting values, ΔE, are discussed in connection with data calculated using the point-charge model,[11] in order to assign bonding and structure of our organotins. Some calculated data are in Figure 2, where partial nuclear quadrupole splittings employed in the calculations are taken from the literature,[11–14] the value of $\{N(R_3)\}^{tba}$ in (II) being that of piperidine.[12]

The ΔE values of disodium and diguanidinium bis[2-mercaptoethane-sulfonato(2^-)-S]-dimethyltin (IV), compounds (1) and (2), are respectively 1.84 and 1.67 mm s^{-1}, in aqueous solution frozen to 77.3°K, which strongly suggests the presence of a tetrahedral configuration around tin, (I) in Figure 2.[7] Since the ΔE values of frozen aqueous bis[cysteinato (1^-)-S]- and bis[penicillaminato(1^-)-S]-dimethyltin (IV), compounds (3) and (4), are 2.40 and 2.59 mm s^{-1} respectively, tetrahedral type structures (I) have been assumed mainly on the basis of the Mössbauer–Zeeman spectra of the Ph_2Sn^{IV} derivatives in the solid state and of their correlation with the data in the frozen aqueous systems.[9]

The addition of Hepes (see Experimental) to the aqueous solutions of compounds (1)–(4) shifts ΔE to 2.16–2.38 mm s^{-1}, which indicates the coordination by Hepes of the tin center, possibly through the tertiary amino nitrogen atom,

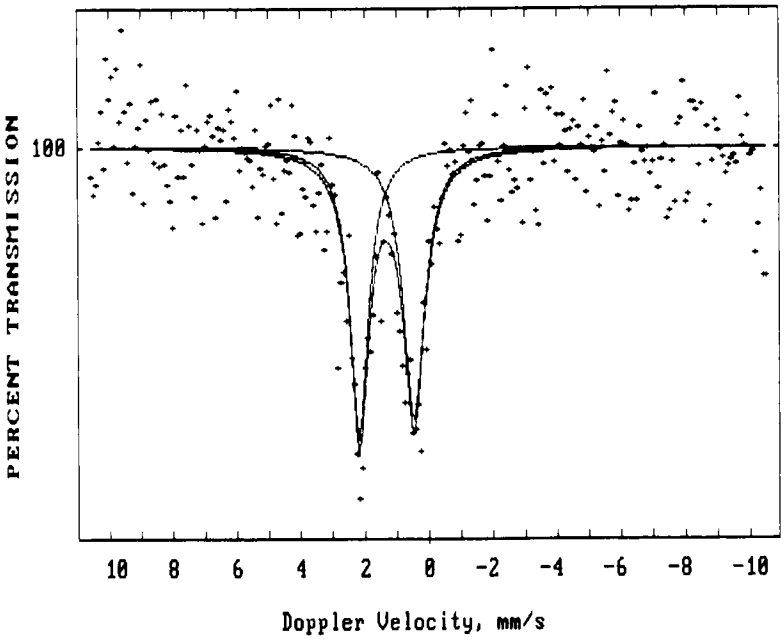

FIGURE 1 The ^{119}Sn Mössbauer spectrum of the rat hemoglobin derivative (pellet) of bis[2-Mercaptoethanesulfonato(2$^-$)-S]-Dimethyltin (IV): experimental data points (+), fitted Lorentzian lineshapes and simulated spectrum (full lines). Percent effect at the dips of the resonant peaks is: $\varepsilon_1 = 0.35$; $\varepsilon_2 = 0.33$.

yielding the trigonal bypyrimidal species (II), Figure 2, according to the point-charge ΔE value.[3,7,9] In fact, experimental and calculated ΔE values agree within 0.4 mm s^{-1}.[15] It is noteworthy that the Hepes complexes of (1)–(4) are clearly characterized by the same structure of the tin environment (according to the near coincidence of the corresponding ΔE values), which implies that the

TABLE I

^{119}Sn Mössbauer parameters at 77.3°K of bis[2-mercaptoethanesulfonato(2$^-$)-S]-, bis[L-cysteinato(1$^-$)-S]- and bis[L-penicillaminato(1$^-$)-S]-dimethyltin (IV) into crystalline rat hemoglobin

Rat hemoglobin reacted with the solutions in Hepes buffer of the compounds[a]	[Me_2Sn]/[Hem][b]	δ[c] (mm s^{-1})	ΔE[d] (mm s^{-1})	Γ_1[e] (mm s^{-1})	Γ_2[e] (mm s^{-1})
1) $Na_2[Me_2Sn(SCH_2CH_2SO_3)_2]$	2.07	1.35	1.67	0.71	0.82
1) $Na_2[Me_2Sn(SCH_2CH_2SO_3)_2]$	1.88[f]	1.34[f]	1.71[f]	0.90[f]	1.06[f]
2) $[C(NH_2)_3]_2[Me_2Sn(SCH_2CH_2SO_3)_2]$	1.05	1.33	1.58	0.57	0.75
3) $Me_2Sn[SCH_2CH(NH_3^+)COO^-]_2$	1.45	1.27	2.21	0.83	0.96
4) $Me_2Sn[SC(CH_3)_2CH(NH_3^+)COO^-]_2$	0.97	1.23	2.48	0.70	0.83

[a] Microcrystalline solid obtained by co-crystallization of rat hemoglobin with $Me_2Sn(SR)_2$ in 0.2 M Hepes buffer (N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid, pH = 7.4). Unless otherwise stated.

[b] Molar ratio employed in the crystal formation, or diffusion of the organotin (IV) compound into crystals of hemoglobin (=Hem).

[c] Isomer shift with respect to $CaSnO_3$, average values, at room temperature.

[d] Nuclear quadrupole splitting, ±0.02 mm/s, average values.[3]

[e] Full width at half height of the resonant peaks at lesser and larger velocity that the spectrum centroid respectively, average values.

[f] Data referring to the diffusion of the solution of $Na_2[Me_2Sn(SCH_2CH_2SO_3)_2]$ in Hepes into hemoglobin crystals.

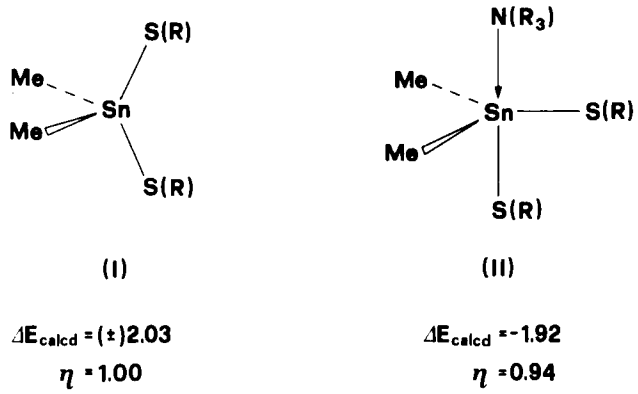

FIGURE 2 The point charge model estimates of Mössbauer nuclear quadrupole splitting ΔE ($mm\,s^{-1}$) and asymmetry parameter $\eta = (Vxx - Vyy)/Vzz$ for possible regular trigonal bipyramidal and tetrahedral structures of the dimethyltin (IV) derivatives, here studied, in aqueous Hepes buffer and in the hemoglobin "phase" (see text).

reason of the abnormally large ΔE's of the presumed tetrahedral bis-cysteinate and bis-penicillaminate in aqueous solution[9] is removed upon complexation by Hepes.

Assuming that compounds (1)–(4) show analogous tin sites also in the "hemoglobin" phase, the tbp species (II) would change to tetrahedral (I) for both co-crystallization of (II) with hemoglobin and diffusion of (II) into hemoglobin crystals. In fact, the ΔE values in Table I approach those in water, at least for the mercaptoethane sulfonates (1) and (2) and the penicillaminate (4) (vide supra). This behavior implies that Hepes does not coordinate to tin in hemoglobin, as is also found in the $Me_2Sn(OH)_2$-Hepes-hemoglobin system.[3] Moreover, the species (1)–(4) do not bind further sulfur ligand sites, as demonstrated by the δ and ΔE values of frozen solutions with Me_2Sn^{IV}-sulfur ligand mole ratios larger than 2.[3,7,9] Perhaps the eventual coordination to tin by a thiol group of a cysteine side-chain of the globin implies the replacement of a cysteine residue already bound to the metal.

In conclusion, it appears to us that the bonding to the globin by dimethyltin(IV)-bis-thiolato compounds (1)–(4) is quite different from the proposals for dimethyltin(IV)-dihydroxyde, -glycylglycinate and -monocysteinate.[3] The amphiphilic species (1)–(4) could bind through Coulombic and hydrogen bonding interactions with the sulfonate and aminoacid groups, in much the same way as has been proposed for *p*-chloromercuribenzenesulfonate and 2-hydroxymercuritoluol-4-sulfonic acid with myoglobin and lysozyme,[16,17] as well as for a series of oligopeptides in human hemoglobin.[18] The Me_2Sn^{IV} moiety would not coordinate further with tin, and act as hydrophobic to the globin.

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