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The interaction of organotins with native DNA

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The compounds R_2SnCl_2 and R_3SnCl (R = Me, Et, nBu, nOct, Ph, in ethanol solution) as well as the aqueous species $[Me_2Sn(OH_2)_n]^{2+}$ and $[Me_3Sn(OH_2)_2]^+$, react with aqueous native DNA, yielding solid phases. According to the point-charge model treatment of the ^{119}Sn Mössbauer parameter nuclear quadrupole splitting, *trans*-octahedral $R_2Sn(O_2PXY)_2$, and trigonal-bipyramidal $R_3Sn(O_2PXY)$, (R = Me, Et, nBu), would occur in the pellets, the tin atoms being coordinated by phosphodiester groups of the nucleic acid. The precipitates from Ph_2Sn^{IV} would consist of the DNA complex as well as of the Ph_2Sn^{IV} distannoxane obtained by hydrolysis of the reactant, whilst $nOct_2SnCl_2$, $nOct_3SnCl$ and Ph_3SnCl would mainly yield stannoxanes and hydroxides. The water-soluble hydrolyzed species $[Me_2Sn(OH)(OH_2)_n]^+$, $Me_2Sn(OH)_2$ and $Me_3Sn(OH)(OH_2)$ do not show any interaction with native DNA, although they are possibly coordinated by phosphate oxygen atoms in model aqueous systems, in the presence of excess ligand.

These trends have been rationalized by QSAR approach (Quantitative Structure–Activity Relationships) in terms of electronic factors related to tin–oxygen (phosphate) Coulomb interactions, as well as the lipophilicity of R in the R_nSn^{IV} moieties.

Keywords: Organotin, DNA, Mössbauer

INTRODUCTION

In a preceding paper,[1] the structure and bonding in the environment of tin atoms in the systems: organotin–human erythrocytes, –erythrocyte ghosts, and –rat and –feline hemoglobin have been discussed on the basis of ^{119}Sn Mössbauer spectroscopic parameters, as well as by the point-charge model treatment of ^{119}Sn nuclear quadrupole splittings. These studies have been subsequently extended to the interaction of di- and tri-organotin moieties with native DNA, selected as the principal constituent of cell nuclei, and preliminary results obtained in *in vitro* investigations are described in the present paper.

Mutagenic and genotoxic effects due to nBu_2Sn^{IV} and $nOct_2Sn^{IV}$ derivatives have been ascribed to coordination by nucleic acids;[2,3] the latter has been subsequently excluded for $nOct_2Sn^{IV}$.[4] The moieties R_2Sn^{IV} and R_3Sn^{IV} (R = Me, Et, nBu, nOct, Ph) have been shown to interact with aqueous calf thymus DNA, eventually forming condensates, characterized by Coulomb interaction between the oxygen atoms of phosphodiester groups and the tin centers.[5,6] Stoichiometries $R_2Sn(DNA\ phosphate)_2$ and $R_3Sn(DNA\ phosphate)$ have been assumed for the methyl- and ethyl-tin derivatives, where the metal atom would be embedded into *trans*-octahedral and trigonal-bipyramidal environments respectively.[5,6]

EXPERIMENTAL

Calf thymus DNA, 20–50 μmol in monomer units [from stock solutions, 15–25 mmol dm^{-3} in 1 mmol dm^{-3} Tris, 0.1 mmol dm^{-3} EDTA, pH = 8, the concentration being determined by UV spectrophotometry;[5,6] Tris stands for the buffer tris(hydroxymethyl)aminomethane, and EDTA is ethylenediaminetetra-acetic acid, disodium salt] was added with the correct proportional volumes of 0.1 mol dm^{-3} ethanol solutions of R_nSnCl_{4-n} ($n = 2$ and 3), or of Me_3Sn^{IV} and Me_2Sn^{IV} (10–20 mmol dm^{-3}) in aqueous solution at varying pH in a given range of molar ratios r ($r = [Sn]/[DNA\ phosphate]$).

The following effects have been detected.[5,6]

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Table 1 ^{119}Sn Mössbauer parameters of the systems organotin(IV)–calf thymus DNA[a]

System	Organotin compounds reacted with DNA[b]	r[c]	δ[d] (mm s^{-1})	ΔE[d] (mm s^{-1})	Γ_1, Γ_2[d] (mm s^{-1})
(A) $R_2SnCl_2(C_2H_5OH)_2$; pellets					
1	Me_2SnCl_2[e]	0.40; 1.00	1.26; 1.33	4.39; 4.44	0.79–0.91
2	Et_2SnCl_2[f]	0.60–2.40	1.39–1.50	4.40–4.49	0.74–0.99
3	nBu_2SnCl_2	0.48–1.00	1.37–1.45	3.72–3.88	1.08–1.32
4	nBu_2SnCl_2	2.40	1.43	3.41	0.92; 0.92
5	$nOct_2SnCl_2$[g]	0.50	1.35	3.23	0.86; 0.93
6	$nOct_2SnCl_2$	2.40	1.61	3.33	1.00; 0.93
7	Ph_2SnCl_2	0.48	1.13	3.23	1.45; 1.22
8	Ph_2SnCl_2	1.00	1.05	2.96	1.63; 1.22
9	Ph_2SnCl_2	2.40	1.07	2.83	1.24; 1.01
(B) $R_3SnCl(C_2H_5OH)$; pellets					
10	Me_3SnCl[h]	2.40	1.31	3.77	0.89; 0.82
11	Et_3SnCl[i]	1.00–2.40	1.47–1.50	3.83–3.89	0.80–0.90
12	nBu_3SnCl	0.96; 2.40	1.50; 1.45	3.85; 3.79	0.92–1.09
13	$nOct_3SnCl$	1.00–2.40	1.39–1.56	3.42–3.53	0.66–0.97
14	Ph_3SnCl	1.00–2.40	1.24–1.29	2.85–3.08	0.94–1.22
(C) $[Me_2Sn(OH)(OH_2)_n]^+$ and $[Me_3Sn(OH_2)_2]^+$[j]					
15	Me_2Sn^{IV}; solution	0.38; 1.00	1.15; 1.14	3.44; 3.11	0.94–1.51
16	Me_3Sn^{IV}; solution	1.20–1.56	1.25–1.37	3.75–3.88	0.65–0.96
17	Me_3Sn^{IV}; pellet[k]	2.40	1.38	3.84	0.93; 0.75
(D) $Me_2Sn(OH)_2$ and $Me_3Sn(OH)(OH_2)^{(l)}$; solutions					
18	Me_2Sn^{IV}	0.20–0.66	0.92–0.96	2.24–2.33	0.79–1.41
19	Me_3Sn^{IV}	0.20–1.00	1.22–1.26	2.83–2.96	0.69–0.93

[a] At liquid-nitrogen temperature. Data from Refs 5–7, and this work.

[b] The absorber samples 1–19 were prepared as described in the Experimental section of this paper. See Table 2 of Ref. 1 for the parameters of the reactant organotin species in ethanol and aqueous solutions.

[c] r = [Sn]/[DNA phosphate].

[d] See Table 1, footnotes c, d, and Table 2, footnote d, of Ref. 1. Γ's are working values from computer fitting.

[e] Percent resonant effect data, ε%, r = 1.0: pellet, $\varepsilon_1 = 0.46$, $\varepsilon_2 = 0.42$; supernatant, $\varepsilon_1 = 0.31$, $\varepsilon_2 = 0.33\%$.[5]

[f] ε% data, r = 1.0: pellet, $\varepsilon_1 = 0.63$, $\varepsilon_2 = 0.58$; supernatant, $\varepsilon_1 = 0.28$, $\varepsilon_2 = 0.30\%$.[6]

[g] The precipitate does not contain DNA.[6]

[h] ε% data: pellet, $\varepsilon_1 = 0.59$, $\varepsilon_2 = 0.63$; supernatant, $\varepsilon_1 = 0.38$, $\varepsilon_2 = 0.39\%$.[6]

[i] ε% data, r = 2.4: pellet, $\varepsilon_1 = 1.24$, $\varepsilon_2 = 1.33$; supernatant, $\varepsilon_1 = 0.40$, $\varepsilon_2 = 0.32\%$.[6]

[j] Aqueous Me_2SnCl_2 or Me_3SnCl, 20 mmol dm^{-3}, pH ≈ 5, is added to DNA; pH = 3.5–5.0 after addition.[5,6]

[k] ε% data: pellet, $\varepsilon_1 = 0.17$, $\varepsilon_2 = 0.18$; supernatant, $\varepsilon_1 = 0.66$, $\varepsilon_2 = 0.63\%$.[6]

[l] Aqueous Me_2SnCl_2 or Me_3SnCl, adjusted to pH = 7.4 with NaOH, is added to DNA.[5,7]

Reaction with ethanolic organotins

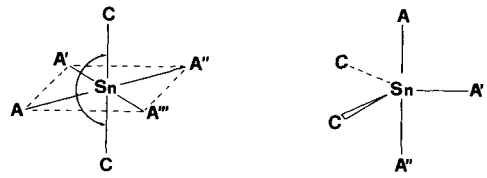
R_2Sn^{IV}–DNA, $r \approx 0.5$, and R_3Sn^{IV}–DNA, $r \approx 1.0$
No condensates are obtained for R = Me and R = nOct; a solid not containing DNA is formed with $nOct_2Sn^{IV}$; pellets consisting of organotin and DNA are obtained with R = Et, nBu, Ph.

Me_2Sn^{IV}–DNA, $r \approx 0.5$
Condensates containing Me_2Sn^{IV} and DNA are obtained by further treatment with 0.1 mol dm^{-3} HCl until pH ≈ 3.5, as well as by addition of NaCl 1 mol dm^{-3}, (till μ = 0.1) and 2–3 volumes of neat C_2H_5OH.

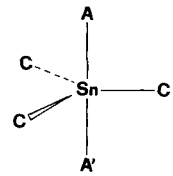
R_2Sn^{IV}–DNA, $r \geq 1.0$, and R_3Sn^{IV}–DNA, $r \approx 2.0$
Pellets are formed for all organotins.

Reaction with aqueous methyltins

No pellets are obtained for $r \leq 1.50$, pH ≈ 5.0–7.4; condensates are formed by adjusting the pH to ≈2.5–3.5 with 0.1 mol dm^{-3} HCl (e.g., Me_3Sn^{IV}–DNA, r = 2.4).



System	Angle C–Sn–C (°)	System	Angle C–Sn–C (°)
1, 2	180	4	131
3	150–157	5	126
4	140	6	129
7	143	7–9	139–127



System	Angle C–Sn–A (°)
10–13, 16, 17	90
14	96–90

Figure 1 The structures assigned[5,6] to the organotin–DNA systems through fingerprint criteria (Table 1 of Ref. 1) concerning experimental values of nuclear quadrupole splitting ΔE (Table 1), and point-charge model calculations of angles according to the procedure II.[1] A′, A″ and A‴ are electronegative bonding atoms (e.g. phosphate oxygen).

RESULTS AND DISCUSSION

Interactions between organotins and DNA are mainly monitored in the formation of condensates in the systems methyl- and ethyl-tin–DNA, by using Mössbauer spectra, and the composition of the pellets estimated through resonance effect data (ε%) of the ^{119}Sn signals in the pellets compared with the related supernatants;[5,6] the latter is feasible only for methyl- and ethyl-tins, which are water-soluble species. According to this simplified approach, the reactions with DNA of ethanolic Me_2SnCl_2, Et_2SnCl_2, Me_3SnCl and Et_3SnCl yield complexes $Alk_2Sn(DNA\ phosphate)_2$ and $Alk_3Sn(DNA\ phosphate)$, characterized by *trans*-octahedral and trigonal-bipyramidal structures respectively [1, 2, 10, 11, Table 1 and Fig. 1], corresponding to data for the solid-state phosphate complexes $Alk_2Sn(PO_2XY)_2$ and $Alk_3Sn(PO_2XY)$ [structures **III** and **IV**, Fig. 7 in Ref. 1]. A regular trigonal-bipyramidal complex could also occur in the condensate obtained from aqueous $[Me_3Sn(OH_2)_2]^+$, possibly $Me_3Sn(DNA\ phosphate)$ [system **17**, Table 1 and Fig. 1]; the same could be advanced for the solution 16, where, on the other hand, the ΔE parameter strictly corresponds to the value for the reactant species [Table 2(B) in Ref. 1].

The ΔE data for the solution from $[Me_2Sn(OH)(OH_2)_n]^+ + DNA$ (system 15), and for the solution of the reactant (Table 2(B) in Ref. 1) are quite similar;[5,6] on the other hand, these ΔE data consistently differ from the value for the (assumed) pellet $Me_2Sn(DNA\ phosphate)_2$ (system 1), which would imply that the hydrolyzed species $[Me_2Sn(OH)(OH_2)_n]^+$ does not interact with DNA in our experimental conditions. This holds also for $Me_2Sn(OH)_2$ and $Me_3Sn(OH)(OH_2)$; in fact, the parameters ΔE of the frozen solutions 18 and 19 are invariant with respect to data for the reactants (Table 2 in Ref. 1) even in the presence of excess DNA phosphate [which would be expected to increase ΔE significantly upon coordination of tin by phosphodiester oxygen atoms, according to the model systems (**I** and **II**, Fig. 6 of Ref. 1, and **I–III**, Fig. 2, this paper). These results are in line with a report on the lack of interaction between Et_3Sn^{IV} and calf thymus DNA in phosphate buffer.[8]

In conclusion, the data discussed above point to the occurrence of Coulomb interactions between the phosphodiester group and the cations

Alk_2Sn^{2+} and Alk_3Sn^+, the latter originating by dissociation of the ethanolic chlorides upon addition to aqueous DNA, or already present in aqueous phase (Me_3Sn^+, pH ≈ 5).[5,6]

The systems $R_2SnCl_2(C_2H_5OH)_2$–DNA and $R_3SnCl(C_2H_5OH)$–DNA (R = nBu, nOct, Ph, systems 3–9 and 12–14, Table 1) yield condensates (see the Experimental section). Additionally, these reactants are likely to form the water-insoluble hydrolysis products[6] listed in Table 2(C) of Ref. 1. They show the following trends of ΔE parameters:

$R_2SnCl_2(C_2H_5OH)_2$ + DNA, systems 3–9

The ΔE values of the reactants, typical of *trans*-octahedral species [Table 2(A) of Ref. 1], decrease in the products as a function also of increasing molar ratio r = [Sn]/[DNA phosphate] for a given R. Structures assigned according to fingerprint criteria (Table 1 of Ref. 1) gradually tend to trigonal-bipyramidal (Fig. 1). The angles C–Sn–C (Fig. 1) gradually approximate to the values inherent to diorganochlorostannoxanes (Fig. 1 of Ref. 1); these latter hydrolysis products would then be eventually formed, and not the oxides (Table 2(C) of Ref. 1). The nBu_2Sn^{IV}-DNA pellet (system 3) seems to consist of the octahedral complex, although distorted (Fig. 1). In Ph_2Sn^{IV}-DNA, (systems nos 7 and 8) a mixture of octahedral- and trigonal-bipyramidal species would occur (Fig. 1), the presence of multiple tin sites being suggested by the large Γ values (Table 1). The $nOct_2Sn^{IV}$ precipitates would instead consist of the stannoxane;[6] in fact, system 5 does not contain DNA, and this is in conformity with the lack of coordinative interaction between $nOct_2Sn^{IV}$ and DNA proposed earlier.[4]

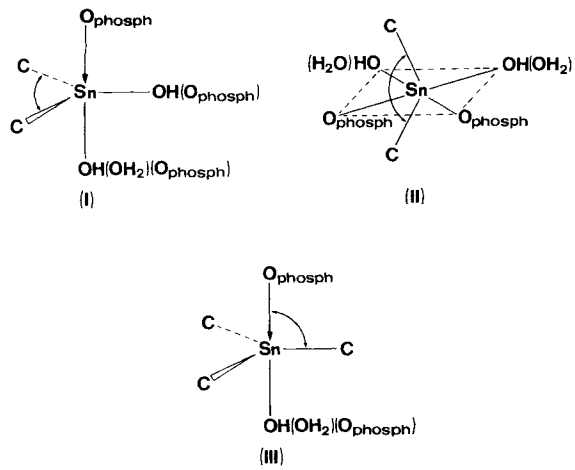


Figure 2 Possible tin environments in $Me_2Sn(OH)_2$ and $Me_3Sn(OH)(OH_2)$ in presence of excess phosphate (HPO_4^{2-}, $H_2PO_4^-$) and D-ribose-5-phosphate (characterized by the group RPO_3H^-), in aqueous solution at physiological pH.[7] Angles CSnC and CSnO from ΔE data[7] and point-charge model II estimates:[1]

I: [D-ribose-5-phosphate]/[$Me_2Sn(OH)_2$] = 9.08; ΔE_{exp} = 3.06 mm s^{-1}; C–Sn–C = 122°.[7]

II: [Phosphate]/[$Me_2Sn(OH)_2$] = 10.0; ΔE_{exp} = 3.75 mm s^{-1}; C–Sn–C = 152°.[7]

III: [Ligand]/[$Me_3Sn(OH)(OH_2)$] = 10.0, 9.14; ΔE_{exp} = 3.59 mm s^{-1}, 3.63 mm s^{-1}; C–Sn–O = 102°, 101°.[7]

$R_3SnCl(C_2H_5OH)$ + DNA, systems 12–14

Quasi-regular trigonal-bipyramidal species would occur (Fig. 1) analogously to the reactants [Table 2(A) of Ref. 1]. The eventual hydrolysis products formed in these systems would then be the hydroxides rather than the stannoxanes (Table 2(C) of Ref. 1.) In any case, nBu_3Sn^{IV}–DNA (system 12), shows a ΔE value consistently larger than that of the related hydroxide, being of the order of that in the phosphates $Alk_3Sn(O_2PXY)$, and this suggests the formation of DNA complexes. On the contrary, ΔE of Ph_3Sn^{IV}–DNA, (system 14), is quite close to the Ph_3SnOH value, the corresponding data for $nOct_3Sn^{IV}$ being intermediate: a mixture of R_3Sn^{IV}–DNA and R_3SnOH may be assumed to occur in these systems.

QSAR Treatment of ΔE data

In the present context, it is our opinion that the assumed Coulomb interactions, R_nSn^{IV}–DNA phosphate, in conjunction with effects originated by the radicals R, may be rationalized through the application of the QSAR approach (Quantitative Structure–Activity Relationships) by Hansch and Leo[9] and Rekker,[10] which may be summarized by Eqn [1].

$$BA = a + b\pi + c\pi^2 + d\sigma + eE_s + gS \qquad [1]$$

where BA is the activity (biological) of a given compound, π is a hydrophobic parameter, σ is an electronic parameter, E_s is a steric factor, and S is a structural parameter. In our systems, the two congeneric series of compounds R_2Sn^{IV} and R_3Sn^{IV} could be taken into account. The electronic factor, σ in Eqn [1], would be concerned with the extent of acid–base (Lewis) interaction $Sn^{+2,+1}$–O^{-1}, which would be an increasing function of r = [Sn]/[DNA phosphate], favouring the

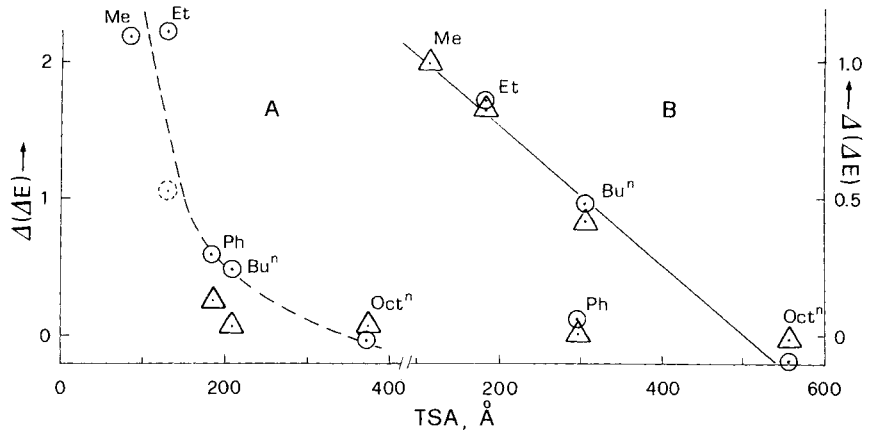


Figure 3 The correlation of normalized nuclear quadrupole splitting data, $\Delta(\Delta E)$, of the condensates: (A) R_2Sn^{IV}–DNA; (B) R_3Sn^{IV}–DNA, with the total surface area of R_nSn^{IV} moieties, TSA[12]. Values $\Delta(\Delta E)$ are obtained from ΔE_{exp} of pellet R_nSn^{IV}–DNA, by subtracting ΔE_{exp} for the corresponding (same R) hydrolyzed (or anyway water-insoluble) species; the latter are listed below.

Compound or System	ΔE (mm s^{-1})	Refs.
$Me_2Sn(OH)_2$	2.24	13
$(Et_2SnO)_n$	2.10; 2.25[a]; 2.33[a]	14; 6[a]
$(Et_2SnCl)_2O$	3.34; 3.41	14; 15
$Me_3Sn(OH)(OH_2)$	2.80	16
$Et_3Sn(OH)(OH_2)$	2.98; 3.02[b]	16; 6[b]
$R_nSnCl_{4-n} + H_2O$(n = 2, 3)	see Table 2, Ref. (6)	

[a] Solids obtained from 10 mmol dm^{-3} Et_2SnCl_2 in H_2O, as well as from 10 mmol dm^{-3} Et_2SnCl_2 in Tris-EDTA, 10% C_2H_5OH (v/v), both adjusted to pH 7.4.
[b] 20 mmol dm^{-3} Et_3SnCl in 20% C_2H_5OH–H_2O (v/v), with Tris-EDTA, adjusted to pH 7.4.

Average ΔE values have been eventually employed, these are taken from Table 1, this work, and from Ref. (6).

(A): ⊙: R = Me, Et; r = [Sn]/[DNA phosphate] = 0.4–2.4; R = nBu; r = 0.48–1.0; R = nOct, Ph, $r \approx 0.5$. △: R = nBu; r = 2.4; R = nOct, Ph; r = 1.0–2.4. Data points for R = Et: ⊙, referred to $(Et_2SnO)_n$; ⊙, referred to $(Et_2SnCl)_2O$.
(B): ⊙: r = 0.96–1.2; △: r = 2.4.

formation of R_nSn^{IV}–DNA condensates at high r (*vide supra*). In this context, the lack of interaction with DNA of the covalent species $Me_2Sn(OH)_2$ and $Me_3Sn(OH)(OH_2)$[5–7] could be attributed to an insufficient partial positive charge on the tin atom. The lipophilicity parameter π would be concerned with the radicals R bound to the metal, which increases in the series Me < Et < Ph < nBu < nOct, according e.g. to estimates employing fragmental constants.[10]

The circumstance that the tendency to yield condensates R_nSn^{IV}–DNA (taken as a measure of the extent of tin–oxygen interaction) appears to be a function of π,[5,6] seems to be in line with Eqn [1]. In fact, hydrophilic Me_2Sn^{IV} and Me_3Sn^{IV} may remain in solution phase (aqueous) at low r values, while lipophilic R (= nBu, nOct, Ph) would induce the preferential precipitation of hydrolysis products (as well as their formation subsequent to the induction of DNA condensation?). It seems worth to note that correlations for Biological Response vs. lipophilicity are quite common for organotins.[11]

The competition between electronic and lipophilic (hydrophobic) factors is evidenced by systems R_nSn^{IV} in excess C_2H_5OH and $\mu = 0.1$ with NaCl: all R_2Sn^{IV} fragments locate in the condensates, while e.g. Me_3Sn^{IV} and nBu_3Sn^{IV} remain in the solution phase.[5,6] Moreover, systems Me_2Sn^{IV} and Me_3Sn^{IV} at corresponding ratio of electrical charge with respect to DNA phosphate (i.e. Me_2Sn^{IV}, $r = 0.5$, and Me_3Sn^{IV}, $r = 1.0$; Me_2Sn^{IV}, $r = 1.0$, and Me_3Sn^{IV}, $r = 2.0$) show a lesser tendency of the more lipophilic

fragment Me_3Sn^{IV} to interact with DNA, monitored by the formation of condensates.[5,6] The trends here discussed are summarized in Fig. 3, where normalized ΔE_{exp} values for R_nSn–DNA condensates are shown to be functions of the total surface area of the moieties R_nSn^{IV}, a parameter correlated to their lipophilicity;[12] Ph_3Sn^{IV} seems to be the only outlier term. Analogous functions are obtained employing Rekker's log *P* data[10] of R in R_nSn^{IV} as estimators of lipophilicity (where *P*'s are partition coefficients in octanol–water).

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