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SYNTHESIS AND REACTIVITY OF BIS-4-PYRONE AND BIS-4-PYRIDINONE DICHLOROTIN(IV) COMPOUNDS

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Abstract—A number of tin(IV) complexes, $Sn(LL)_2X_2$, have been prepared in which LL is a 4-pyronate or 4-pyridinonate ligand and X is chloride or alkoxide. UV–vis, IR and NMR (^1H, ^{13}C, ^{119}Sn) spectra are reported for these complexes. Reactivities have been established through kinetic studies of nucleophilic substitution in acetonitrile solution. Ligand effects on spectra and reactivity are discussed and compared with those for similar metal(IV) complexes, especially of titanium.

The pyrones kojic acid (**1**) and maltol (**2**) are naturally occurring ligands. Maltol was first isolated from larch bark; kojic acid is derived from bacterial fermentation of carbohydrates, for instance of starch by *Aspergillus oryzae*.[1] Maltol (**2**) and ethylmaltol (**3**) are permitted food additives (E636 and E637) used in the baking industry. They are thus attractive ligands for use either in controlling metal ion concentrations in the human body, or for the introduction of appropriate isotopes for diagnosis or therapy.[2] In practice the closely related 4-pyridinones (e.g. **4**–**6**) are proving more suitable,[3] both since they form significantly more stable complexes and also since, with two variable groups R and R′, they can be tailored more readily than the pyrones.[4] Almost all present and potential applications involve the tris-ligand complexes of metal(III) cations, as for example in the administration of iron(III) complexes for the treatment of anaemia, the use of the ligand L1 (**4**) in clinical trials for dealing with iron overload in thalassaemia[3] and the proposal to use such ligands in the control of aluminium levels in the hope that the progress of senile dementias might at least be slowed.[5] Ligands of these types may also prove of value for the introduction of, for instance, complexes containing gadolinium(III) to act as contrast-enhancing agents in magnetic resonance imaging (MRI)[6] or $^{90}Y^{3+}$ for tumour targetting and destructive irradiation.[7] The most recent application of promise involves vanadium(IV), with the bis-maltolato complex $VO(malt)_2$ claimed to be of value in the treatment of diabetes.[8] In all these applications one of the biggest attractions is the possibility of oral administration.

Several β-diketone complexes of metal(IV) ions of the $M(\beta\text{-dik})_2X_2$ type have shown promise as anti-tumour agents.[9] In particular the benzoylacetonate (bzac) (**7**) compound $Ti(bzac)_2(OEt)_2$, budotitane, is showing considerable promise in the treatment of colon cancers.[10] A number of tin(IV) compounds,[11,12] including the dibenzoylmethanato complex $Sn(bzbz)_2Cl_2$,[13] have also shown some promise in this respect. We therefore felt that synthesis and study of a series of tin(IV) compounds, $Sn(LL)_2X_2$, with LL = a pyronate or pyridinonate ligand [known to form stable complexes, $Si(LL)_3^+$, with silicon[14]] and X = halide or alkoxide, would be interesting and possibly provide one or more compounds of pharmacological value. A further matter of interest to us was the kinetic behaviour of this type of complex, for which rather little information appears to be available. There is rate constant, activation parameter ($\Delta H^\ddagger$, $\Delta S^\ddagger$, $\Delta V^\ddagger$) and solvent effect information on racemization of $Ge(acac)_3^+$ (acacH = acetylacetone = pentane-2,4-dione, **8**)[15] and some kinetic information on intramolecular rearrangements within $Sn(\beta\text{-diketonate})_2Cl_2$ complexes,[16–18] but very little on kinetics of ligand replacement. For tin the only such data appear to be a few results on the relatively slow chloride exchange at $Sn(acac)_2Cl_2$ in chloroform[19] and kinetic parameters for hydrolysis of six dihalogenotin(IV) β-diketonates.[20]

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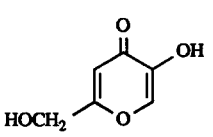
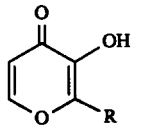
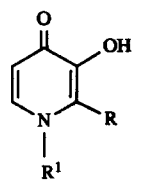


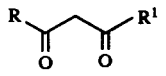
1 kojH



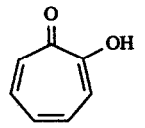
2 R=Me, memaltH
3 R=Et, etmaltH



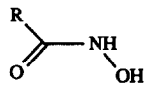
4 R=R¹=Me, dmppH
5 R=Et, R¹=Me, emppH
6 R=R¹=Et, deppH



7 R=Me, R¹=Ph, bzacH
8 R=R¹=Me, acacH



9 tropH



10 R=Me, ahaH
11 R=4MeC$_6$H$_4$, mbzH

We have, therefore, prepared a number of complexes of the $Sn(LL)_2Cl_2$ type, with LL = 4-pyronate or 4-pyridinonate, and characterized them, particularly by NMR and IR spectroscopy. We have also measured rates of ligand replacement in a range of conditions. We report our results here and discuss them in relation to other complexes, particularly of similar bidentate ligands such as β-diketonates (e.g. **7** and **8**), tropolonate (**9**) and hydroxamates (**10** and **11**).

EXPERIMENTAL

Preparation of complexes

The ethylmaltolate complex $Sn(etmalt)_2Cl_2$ was prepared from tin tetrachloride. Ethylmaltol (2.8 g, 0.02 mol) was dissolved in anhydrous acetone at room temperature. $SnCl_4$ (2.6 g, 0.01 mol) was added dropwise with stirring. The solution was refluxed for 30 min during which time a white precipitate formed. This was filtered and washed with diethyl ether. The crude product was recrystallized from dichloromethane/40–60 petroleum ether, to give 3.4 g of white crystals (85% yield). All the other complexes were prepared in an analogous manner. Their melting points, CHN analyses and UV–vis absorption maxima are given in Table 1, IR frequencies in Tables 2 and 3 and NMR data in Table 4.

Apparatus and techniques

IR spectra were obtained using Nujol mulls on a Perkin–Elmer FTIR instrument, NMR spectra on a Bruker AM300 and UV-vis spectra on a Pye–

Table 1. Melting points, wavelengths of maximum absorption and CHN microanalyses for compounds $Sn(LL)_2Cl_2$

Compound	λ_{max} (nm)	M.p. (°C)	(Calc.) Found (%) C	H	N
$Sn(etmalt)_2Cl_2$	337	142	(36.1) 37.0	(3.0) 3.1	
$Sn(memalt)_2Cl_2$	341	138	(27.0) 27.5	(2.3) 2.3	
$Sn(aha)_2Cl_2$	337	liq			
$Sn(mbz)_2Cl_2$	311	180[a]	(39.1) 38.7	(3.3) 3.3	(5.7) 5.4
$Sn(trop)_2Cl_2$	348	201	(36.1) 36.7	(3.7) 2.4	
$Sn(depp)_2Cl_2$	319	249[a]	(36.6) 36.0	(4.0) 4.0	(3.8) 3.4
$Sn(empp)_2Cl_2$	351	238	(36.5) 36.8	(3.8) 4.0	(5.3) 5.2
$Sn(dmpp)_2Cl_2$	360	258	(37.8) 37.3	(3.7) 4.0	(5.8) 5.8

[a] Decomposed.

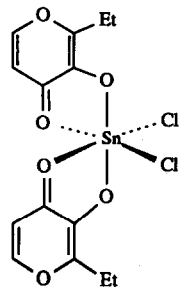
Table 2. IR data for compounds $Sn(LL)_2Cl_2$

Compound	ν(C—O) ν(C—R)	σ(C—H)	σ(ring)	ν(C—R)	π(C—H)	ν(C—R)	ν(M—O)	ν(M—X)
$Sn(etmalt)_2Cl_2$	1604	1331	1261	1044	844	722	540	390
	1548			942	824		480	338
	1504							
$Sn(memalt)_2Cl_2$	1558	1322	1263	1027	842	720	538	385
	1540		1185				459	330
	1506							
$Sn(aha)_2Cl_2$	1616	1339		1093	810	722	540	370
	1520						458	
	1456							
$Sn(mbz)_2Cl_2$	1611	1401	1197	1085	830	721	542	
	1570						450	
$Sn(trop)_2Cl_2$	1558	1338	1261	1016	801	722	540	340
	1540						427	328
	1506							
$Sn(depp)_2Cl_2$	1607	1327	1237	1034	846	722	539	340
	1564			942			481	295
	1511							
$Sn(empp)_2Cl_2$	1609	1332	1253	1030	845	722	539	360
	1549				820		480	345
	1511							
$Sn(dmpp)_2Cl_2$	1575	1351	1260	1020			541	330
	1558						495	285
	1506							

Unicam SP1800. This last instrument, which was equipped with a thermostatted cell holder and PC for data analysis, was also used for the kinetic measurements.

RESULTS AND DISCUSSION

In all cases the product obtained was *cis*-bis-pyronato- or bis-pyridinato-dichlorotin(IV), as was clear from analysis (see above) and from IR and NMR spectroscopy (see below). In the case of the ethylmaltol (**3**) derivative a crystal of product of suitable quality for X-ray structural determination[21] was obtained. This was confirmed to be the expected *cis*-dichloro isomer, with its unsymmetrical bidentate ligands disposed as shown in **12**.



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IR spectroscopy

IR frequencies and their assignments are given in Table 2, while tin–chloride stretching frequencies for these and a number of related complexes are

Table 3. Tin(IV)–chloride stretching frequencies

	ν(Sn—Cl) (cm^{-1})		ν(Sn—Cl) (cm^{-1})	Ref.
$Sn(etmalt)_2Cl_2$	390, 338	$Sn(koj)_2Cl_2$	336, 331(sh)	22
$Sn(memalt)_2Cl_2$	385, 330	$Sn(acac)_2Cl_2$	334, 264	16, 18, 23
$Sn(aha)_2Cl_2$	370	$Sn(bzac)_2Cl_2$	336, 314	13
$Sn(trop)_2Cl_2$	339, 328	$Sn(bzbz)_2Cl_2$	347, 334	13
$Sn(depp)_2Cl_2$	345, 295	$Sn(cp)_2Cl_2$	358, 336	24
$Sn(empp)_2Cl_2$	340, 295	$SnCl_6^{2-}$	300	25
$Sn(dmpp)_2Cl_2$	330, 285			

Table 4. NMR data for compounds $Sn(LL)_2Cl_2$

Compound	^1H NMR (ppm)	^{13}C NMR (ppm)	^{119}Sn NMR (ppm)	$J(^{119}Sn—^{13}C)$ (Hz)
$Sn(etmalt)_2Cl_2$	H_a 8.1, 7.9, H_b 6.9, 6.7, H_c 2.9, H_d 1.4 $CDCl_3$	C^1 10.6, C^2 22.7, C^3 146.1, C^4 160.9, C^5 172.3, C^6 110.0, C^7 155.9	−467.71 (3) −473.33 (1)	$^2J(Sn—C^5)$ 23.0 $^3J(Sn—C^6)$ 71.4
$Sn(memalt)_2Cl_2$	H_a 8.1, H_b 6.9, H_c 2.6 d^6 acetone		−465.51 (3) −471.62 (1)	
$Sn(aha)_2Cl_2$	H_a 4.1, H_b 6.0 d^6 acetone	C^1 17.8, C^2 165.8	−518.01 (2) −534.25 (2) −549.30 (1)	$^2J(Sn—C^1)$ 23.9 $^3J(Sn—C^2)$ 28.5
$Sn(mbz)_2Cl_2$	H_a 8.0, 7.9, H_b 7.3, H_c 2.4, H_d 5.2 d^6 acetone	C^1 21.5, C^2 128.9, C^3 128.1, C^4 130.0, C^5 130.2, C^6 130.7, C^7 143.4, C^8 168.3	−467.63 (3) −473.53 (1)	$^3J(Sn—C^7)$ 48.44
$Sn(trop)_2Cl_2$	H_a 7.4, H_b 6.8 d^6 acetone		−466.64 (3) −472.43 (1)	
$Sn(depp)_2Cl_2$	H_a 8.0, 7.9, 7.8, H_b 6.85, 6.7, H_c 3.1, H_d 1.33, He 4.4, H_f 1.55 d^6 acetone	C^1 11.1, C^2 20.6, C^3 135.8, C^4 149.5, C^5 164.7, C^6 109.2, C^7 158.1, C^8 51.5, C^9 17.5	−531.32	$^2J(Sn—C^4)$ 42.7 $^2J(Sn—C^5)$ 44.5 $^3J(Sn—C^6)$ 70.7 $^3J(Sn—C^3)$ 48.9
$Sn(empp)_2Cl_2$	H_a 7.7, H_b 6.65, H_c 2.9, H_d 1.3, He 3.7 d^6 acetone	C^1 11.8, C^2 20.7, C^3 136.5, C^4 149.5, C^5 164.3, C^6 109.2, C^7 140.9, C^8 43.6	−531.43	$^3J(Sn—C^6)$ 87.64 $\{^4J(Sn—H_b)$ 15$\}$
$Sn(dmpp)_2Cl_2$	H_a 7.8, H_b 6.9, H_c 3.0, H_d 1.2, He 4.0 d^6 acetone		−520.22	

collected together in Table 3.[22–25] In all cases, except for the broad band observed for the acethydroxamate complex and the single Sn—Cl stretch for $SnCl_6^{2-}$, two distinct bands assignable to ν(Sn—Cl) in *cis* geometry are found. The ν(Sn—Cl) for our complexes are similar to those for Sn(β-diketonate)$_2Cl_2$ and indeed for $Sn(cp)_2Cl_2$ and $SnCl_6^{2-}$, as is clear from the following order of mean ν(Sn—Cl) values (pyrone and pyridinone complexes in bold type) for complexes $Sn(LL)_2Cl_2$:

aha > **etmalt** > **memalt** > cp > bzbz > **koj** =

trop > bzac > **depp** > **empp** > acac > **dmpp**.

The more weakly bonding pyronate ligands produce higher ν(Sn—Cl) than pyridinonates; the most strongly bonding pyridinonate, dmpp, is associated with the lowest ν(Sn—Cl). The values for the β-diketonate complexes are consistent with this sequence. These IR results are correlated with kinetic results in the appropriate section later.

Discussion of ν(Sn—O) is potentially more complicated, since the bonds in question are incorporated in chelate rings. In practice ν(Sn—O) values are identical within experimental uncertainty for all the pyrone and pyridinone complexes (Table 2; values for the kojate complex are available already[22]). There are, however, significant differences between this very short range of values for the pyrone and pyridinone complexes and the ranges characteristic of tropolonates,[26] β-diketonates[27] and 8-hydroxyquinolinates[28] in complexes $Sn(LL)_2XY$.

NMR spectroscopy

The ^1H, ^{13}C and ^{119}Sn chemical shifts are listed in Table 4, which also includes $^{119}Sn—^{13}C$ coupling constants. Very few direct comparisons with published data appear to be possible.[29] ^1H, ^{13}C and ^{119}Sn chemical shifts and coupling constants are available for one $Sn(koj)_2X_2$ compound,[22,30] but here X = methyl rather than chloride. There is only limited proton NMR information on β-diketonate complexes, Sn(β-dik)$_2X_2$.[16,18]

Kinetics and mechanism

The complexes are indefinitely stable in solution in dry acetonitrile, but addition of water, thio-

Table 5. Observed first-order rate constants for the second stage of reactions of $Sn(LL)_2Cl_2$ with nucleophiles, in acetonitrile solution at 298.2 K

Compound	Nucleophile conc:	$10^3 k_{obs}$ ($dm^3 mol^{-1} s^{-1}$) 0.0005	0.001	0.002	0.005	0.01	0.015
$Sn(etmalt)_2Cl_2$	H_2O		3.0		7.4	12.3	
$Sn(etmalt)_2Cl_2$	Pyrazine				2.8	4.4	6.3
$Sn(etmalt)_2Cl_2$	NCS^-	7.35	15.1				
$Sn(memalt)_2Cl_2$	NCS^-	6.2	12.6				
$Sn(aha)_2Cl_2$	NCS^-	3.6	5.1	9.8			
$Sn(mbz)_2Cl_2$	NCS^-		3.1	4.0	8.1	14.3	
$Sn(trop)_2Cl_2$	NCS^-		2.6		5.11	10.1	15.0
$Sn(depp)_2Cl_2$	NCS^-		2.5	2.9	5.1	9.0	14.2
$Sn(empp)_2Cl_2$	NCS^-		2.3	2.6	4.9	7.7	12.5
$Sn(dmpp)_2Cl_2$	NCS^-		1.3	1.6	2.2	3.8	4.9

cyanate, pyrazine or other potential nucleophiles results in instant reaction. Such reactions are complete within the time needed to mix solutions and run their UV–vis spectra on a conventional spectrophotometer. Thereafter, there is a much slower second reaction, occurring on a time scale appropriate for kinetic monitoring. The products of the second stage are the bis-nucleophile complexes $Sn(LL)_2(nucl)_2$; we are able to obtain rate constants for the reactions:

$$Sn(LL)_2Cl(nucl)^+ + nucl \rightarrow Sn(LL)_2(nucl)_2^{2+} + Cl^-.$$

As both reactants on the left-hand side of this equation vary with the nature of the nucleophile it is not possible to establish relative reactivities for various incoming groups in the way that we were able to do with titanium(IV) analogues.[31] We have, therefore, carried out only a few runs comparing reactivities of water, thiocyanate and pyrazine as nucleophiles and have concentrated our kinetic investigations on the effects of the nature of the non-leaving ligands LL on reactivities with one nucleophile, viz. thiocyanate.

All kinetic runs were conducted in acetonitrile solution, at 298.2 K, with the incoming nucleophile present in considerable excess over the tin compound. First-order kinetics were followed in every run; observed first-order rate constants, computed from absorbance data collected over the first 2.5 half-lives, are reported as a function of nucleophile concentration in Table 5. In each series of runs over a range of nucleophile concentrations a plot of observed rate constant against nucleophile concentration was linear, but with a positive intercept

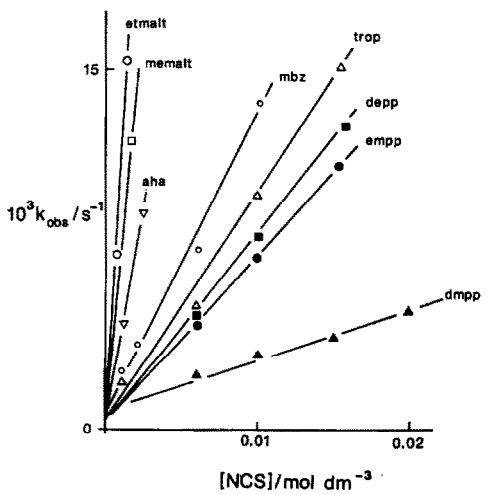

Fig. 1. Dependence of first-order rate constants on thiocyanate concentration for reactions of $Sn(LL)_2(NCS)Cl$ plus thiocyanate, in acetonitrile solution at 298.2 K.

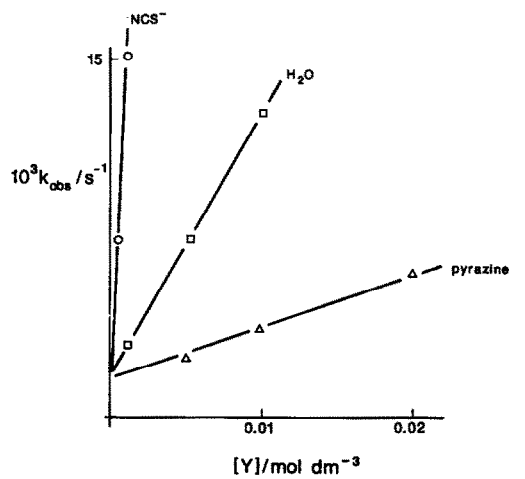

Fig. 2. Dependence of first-order rate constants on incoming nucleophile concentration for the second stage of the reactions of $Sn(etmalt)_2Cl_2$ with thiocyanate, water and pyrazine, in acetonitrile solution at 298.2 K.

Table 6. Derived first-order and second-order rate constants, with their attendant uncertainties, for the second stage of reactions of $Sn(LL)_2Cl_2$ with nucleophiles, in acetonitrile solution at 298.2 K

Compound	Nucleophile	$10^3 k_1$ (s^{-1})	σ	k_2 ($M^{-1}s^{-1}$)	σ
$Sn(etmalt)_2Cl_2$	H_2O	1.5	±0.11	1.08	±0.07
$Sn(etmalt)_2Cl_2$	Pyrazine	1.5	±0.13	0.24	±0.03
$Sn(etmalt)_2Cl_2$	NCS^-	1.6		13.3	
$Sn(memalt)_2Cl_2$	NCS^-	1.5		10.9	
$Sn(aha)_2Cl_2$	NCS^-	1.6	±0.01	4.23	±0.1
$Sn(mbz)_2Cl_2$	NCS^-	1.6	±0.08	1.25	±0.06
$Sn(trop)_2Cl_2$	NCS^-	1.4	±0.04	0.91	±0.06
$Sn(depp)_2Cl_2$	NCS^-	1.3	±0.1	0.84	±0.1
$Sn(empp)_2Cl_2$	NCS^-	1.2	±0.05	0.71	±0.02
$Sn(dmpp)_2Cl_2$	NCS^-	1.3	±0.1	0.24	±0.02

on the y (rate constant) axis:

$$k_{obs} = k_1 + k_2[\text{nucleophile}].$$

This is illustrated for the series of reactions with thiocyanate in Fig. 1 and for reaction of the ethylmaltol complex with thiocyanate, pyrazine and water in Fig. 2. Values of k_1 and k_2 are collected together, with their uncertainties, in Table 6.

All the values of k_1 (Table 6) are remarkably similar. For the series of thiocyanate reactions these rate constants correspond to solvolytic dissociation of the second chloride:

$$Sn(LL)_2(NCS)Cl + NCS^- \rightarrow Sn(LL)_2(NCS)_2 + Cl^-.$$

As the ligands LL are all two-oxygen chelators of rather similar properties, it is not unreasonable that non-leaving ligand effects on chloride loss should be small. It is rather more surprising that k_1 values for chloride loss from the three complexes Sn(etmalt)$_2$Cl(NCS), Sn(etmalt)$_2$Cl$(OH_2)^+$ and Sn(etmalt)$_2$Cl(pz)$^+$ are also so similar in value. However, a similarly small range of rate constants has recently been found for analogous titanium(IV) complexes.[31]

The relative reactivities of the series of complexes $Sn(LL)_2(NCS)Cl$ towards nucleophilic attack by thiocyanate (Fig. 1), i.e. the order of k_2 values (Table 6), is the same as that in analogous reactions of titanium(IV) complexes.[31] Indeed rate constants for nucleophilic attack at the tin and titanium complexes correlate well, as shown in Fig. 3. The slope of the correlation line in Fig. 3 is 30, indicating that

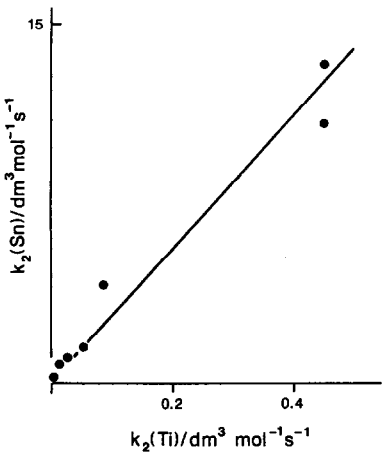

Fig. 3. Correlation of second-order rate constants for thiocyanate attack at tin(IV) and titanium(IV) complexes, $M(LL)_2(NCS)Cl$, under comparable conditions.

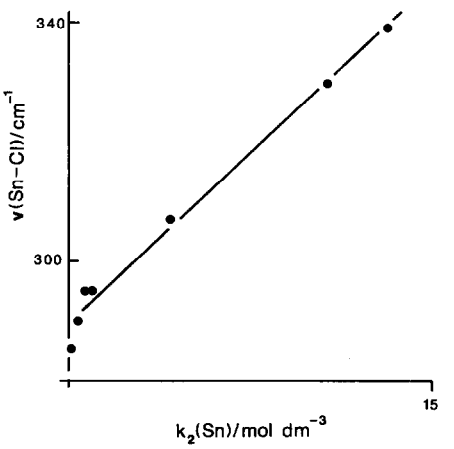

Fig. 4. Correlation of second-order rate constants for thiocyanate attack at complexes of $Sn(LL)_2(NCS)Cl$ with tin–chloride stretching frequencies for the respective complexes $Sn(LL)_2Cl_2$.

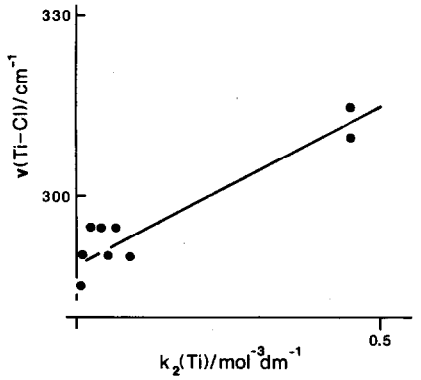

Fig. 5. Correlation of second-order rate constants for thiocyanate attack at complexes of $Ti(LL)_2(NCS)Cl$ with titanium–chloride stretching frequencies for the respective complexes $Ti(LL)_2Cl_2$.

the tin(IV) centre is considerably more reactive than titanium(IV) in this type of complex. This reactivity difference can be ascribed to the different sizes of the tin and the titanium, whose notional ionic radii in six-coordination differ by 8.5 pm, according both to the original Shannon estimates[32] (Sn 69, Ti 60.5 pm) and to the later Shannon and Prewitt values[33] (Sn 83, Ti 74.5 pm). Frazer and Haines found that second-order rate constants were very similar for the three β-diketonate complexes, $Sn(\beta\text{-dik})_2Cl_2$ ($k_2 = 8.8$ for β-dik = acac, 10.3 for bzac and 7.5 $dm^3\ mol^{-1}\ s^{-1}$ for bzbz, in chloroform at 30°C).[20] These values are remarkably close to ours for the ethylmaltol analogue, especially when allowance is made for the differences in solvent (chloroform vs acetonitrile) and in temperature. Frazer and Haines reported activation entropies of around $-50\ J\ K^{-1}\ mol^{-1}$ for the reactions of their three β-diketone complexes, which is consistent with bimolecular water attack at the tin.

Figure 4 shows that there is a strong correlation between IR stretching frequencies, ν(Sn—Cl), and second-order rate constants for thiocyanate attack. Stronger tin–chloride bonding makes attainment of the transition state harder since the bond to the leaving group has to be extended considerably to form the S_N2 transition state. There is a similar correlation for the analogous titanium complexes and reactions.[31]

Anti-tumour activity

The complex $Sn(empp)_2Cl_2$ was tested against a number of cell lines. It was found to have significant but rather modest activity against K562 leukemia and MAC13 murine tumour cells, and rather small activity against two other murine lines and HCT18 and HRT18, human colon and rectal carcinoma lines, respectively. It is interesting that the tin complex shows most activity against the leukemia cells, whereas analogous titanium complexes only appear to show significant activity against colon tumours. Earlier reports[11,34] also suggested greatest activity of complexes of the R_3SnOH, R_2SnO and $R_2SnOSnR_2$ type against P388 leukemia.

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