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Kinetics of substitution at ternary titanium(IV)–cyclopentadienyl, pyronato or pyridinato–halide or alkoxide complexes

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Rate laws and kinetic parameters are reported for substitution at titanium(IV) complexes $Ti(LL)_2X_2$, where LLH = cyclopentadiene, the 4-pyrone ethylmaltol, several 4-pyridinones, and related ligands, and X = halide or alkoxide, in acetonitrile solution at 298.2 K. Reactivities are discussed in terms of the nature of the leaving group, the entering group and the non-leaving ligand LL^-. Activation volumes of −15 and −12 $cm^3 mol^{-1}$ have been determined for thiocyanate attack at $Ti(cp)_2Cl_2$ and $Ti(etmalt)_2Cl_2$ respectively. Substitution mechanisms are discussed in the light of the kinetic parameters obtained.

Keywords: Titanium(IV) complexes, antitumour agents, ligand substitution, kinetics, mechanism, activation volume

INTRODUCTION

Several series of titanium(IV) compounds of the general type $Ti(LL)_2X_2$, where LL is a bidentate anionic ligand and X is a halide or alkoxide, have been shown to possess antitumour activity.[1–4] The cyclopentadienyl compound $Ti(cp)_2Cl_2$ has been much studied in this respect, with such properties as organ distribution and kinetic characteristics established.[5–9] It has been suggested that the antitumour activity of this compound resides in the cyclopentadienyl group rather than its $>TiCl_2$ moiety, but other similar titanium compounds, particularly with LL = β-diketonate, also show marked antitumour activity. The most successful of these at present is the benzoylacetonato complex budotitane, $Ti(bzac)_2(OEt)_2$.[10] This has reached the stage of successful clinical trials, with particular efficacy against colonic tumours otherwise difficult to treat by chemotherapy. However, this compound does have the disadvantages of being somewhat hepatotoxic and nephrotoxic,[11] so it seems worthwhile to investigate other similar compounds to seek a replacement retaining the therapeutic value of budotitane but with reduced side effects. Two attractive groups of ligands are pyrones **1** and pyridinones **2**. The pyrones with R = Me, Et (maltol and ethylmaltol respectively) are permitted food additives;[12] the anions of ligands of type **1** and **2** prove to form stable titanium(IV) complexes $Ti(LL)_2X_2$, with X = halide or alkoxide. These complexes undergo solvolysis and substitution at rates dependent on, *inter alia*, the nature of the leaving group and non-leaving bidentate ligand. In view of the apparent importance of time scales for substitution in determining antitumour properties of these, as of analogous platinum antitumour agents,[13] kinetic parameters for substitution at $Ti(cp)_2Cl_2$ have been established in aqueous,[8] acetonitrile[14] and dimethyl sulphoxide[15] media. We have extended these kinetic studies, both to a fuller examination of substitution at $Ti(cp)_2Cl_2$ and to series of titanium(IV) complexes containing pyronato and pyridinato ligands and halide or alkoxide leaving groups. We report and discuss our results in the present paper, both for their intrinsic interest and for their possible relevance to drug design.

The formulae of compounds discussed in this paper are shown in Scheme 1, together with the abbreviations employed here.

EXPERIMENTAL

Preparation of ligands

The pyrones **1** with R = Me or Et were used as purchased, and were also used as starting materials for the synthesis of the pyridinones used in preparing respective complexes.

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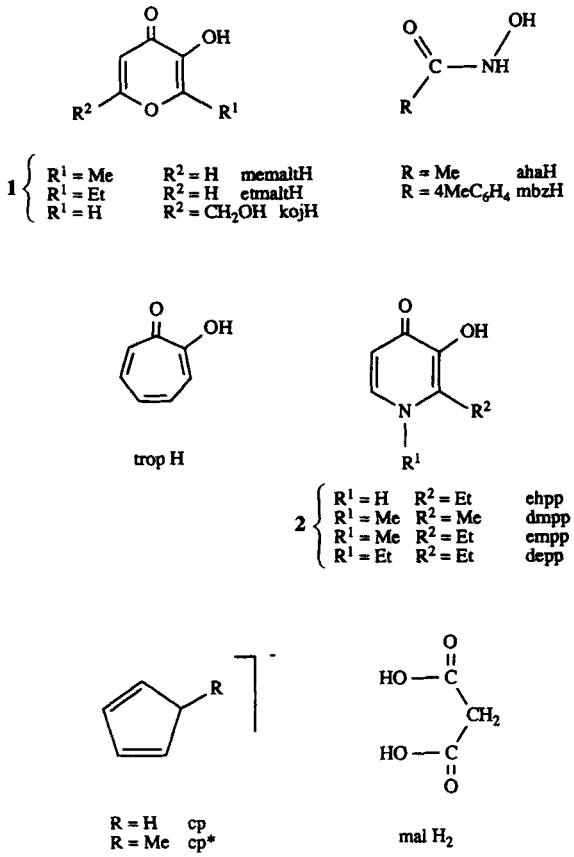

Scheme 1 Formulated abbreviations.

Table 1 Properties of the titanium complexes

Complex	Melting point (°C)	ν(Ti–X) (cm^{-1})	λ_{max} (nm)
$Ti(cp)_2Cl_2$[a]	289		391
$Ti(etmalt)_2Cl_2$	251	315, 340	372
$Ti(memalt)_2Cl_2$	253	310, 330	374
$Ti(aha)_2Cl_2$	220	290, 315	376
$Ti(koj)_2Cl_2$	241	295[b]	380
$Ti(mbz)_2Cl_2$	231	290[b]	391
$Ti(trop)_2Cl_2$	244	295, 320	370
$Ti(depp)_2Cl_2$	260	295, 310	360
$Ti(empp)_2Cl_2$	260	290, 310	375
$Ti(ehpp)_2Cl_2$	267	280, 305	395
$Ti(dmpp)_2Cl_2$	271	270, 305	400
$Ti(etmalt)_2F_2$	200	290, 310	394
$Ti(etmalt)_2(OMe)_2$	241		388
$Ti(etmalt)_2(OEt)_2$	247		386
$Ti(etmalt)_2(OiPr)_2$	251		380
$Ti(etmalt)_2(OPh)_2$	175		367
$Ti(etmalt)_2(Mal)$	232		366

[a] From Ref. 17. [b] Broad.

Preparation and characterization of complexes

$Ti(cp)_2Cl_2$ was prepared as described earlier.[16] All the complexes of the type $Ti(LL)_2Cl_2$ were prepared by a method analogous to the preparation of $Ti(etmalt)_2Cl_2$ described below. Ethyl maltol (2.8 g; 0.02 mol) was stirred in anhydrous THF solution at room temperature. $TiCl_4$ (1.9 g; 0.01 mol) was added dropwise to the solution, which formed an orange precipitate instantly. The solution was stirred for 30 min, then filtered and the product was washed with diethyl ether. The crude product was recrystallized from dichloromethane/40–60 petroleum ether. This yielded orange crystals (3.6 g; 90%) which were shown to be pure by C, H, N analysis and ^1H NMR. $Ti(etmalt)_2(OR)_2$ (OR = OMe, OEt, O^iPr) were prepared using the tetra-alkoxide starting material (Aldrich). The complex $Ti(etmalt)_2(OPh)_2$ was prepared from $Ti(OPh)_4$, which itself was prepared as described previously.[18]

$Ti(etmalt)_2(mal)$ was prepared by the reaction of $Ti(etmalt)_2Cl_2$ (0.4 g; 0.001 mol) and malonic acid (0.1 g; 0.001 mol) in dry dichloromethane. The solution was refluxed for 12 h, the solvent was removed and the product recrystallized from dichloromethane/40–60 petroleum ether. This yielded 0.23 g (52%) of orange solid, which was characterized by NMR and fast atom bombardment–mass spectroscopy (FAB MS).

Melting points, titanium–halide stretching frequencies in the infrared region and wavelengths of maximum absorption in the visible–ultraviolet region are given in Table 1.

Other materials

All materials used were analytical grade: potassium thiocyanate (Hopkins and Williams), lithium bromide and lithium iodide (BDH), tetraethylammonium cyanide (Fluka), pyrazine (Janssen), 2,2′-bipyridyl (Aldrich), 4,4′-bipyridyl, malonic acid (Lancaster) and ethylmaltol (Pfizer).

Acetonitrile, methanol, ethanol and isopropanol were dried, distilled, and stored over molecular sieves.

Kinetic measurements

Kinetic measurements at atmospheric pressure were carried out using standard methods des-

Table 2 Observed first-order rate constants for the first stage of substitution at $Ti(cp)_2Cl_2$ by various incoming ligands Y in acetonitrile solution at 298.2 K

	10^3k_{obs} (s^{-1})				
	[Y](mol dm^{-3}):				
Y	0.005	0.05	0.10	0.15	0.20
Br^-	10				
Pyrazine		3.0	5.0		
4,4'-Bipyridyl		2.5	3.7		5.4
2,2'-Bipyridyl		2.3	3.5		5.1
Ethylmaltol		1.4	1.8	2.4	3.1

cribed earlier.[19] Runs were carried out in the thermostated cell compartment of a Pye–Unicam SP1800 spectrophotometer. Rate constants were computed for the first 2.5 half-lives using a standard least-mean-squares program on a coupled IBM PC.

The initial concentration of the titanium complex $Ti(LL)_2X_2$ was 10^{-4} mol dm^{-3} in all runs. Absorbances were monitored at the wavelength of maximum absorption for $Ti(LL)_2X_2$ for the first stage of reaction with the nucleophile, and at the wavelength of maximum absorption of the intermediate $Ti(LL)_2(nucl)X$ for the second stage. The spectra of the starting complex, intermediate, and final product differed considerably, so that the absorbance being monitored decreased by at least 50% in every run.

Kinetic measurements at high pressure were carried out in a thermostated vessel built into the observation compartment of a Pye–Unicam SP8-100 spectrophotometer. Reaction solutions of approximately 15 cm^3 are contained in a stainless-steel bomb equipped with sapphire windows to give a 5 mm pathlength. The temperature of the solution is monitored by a built-in thermocouple. Pressures of up to 1 kbar are applied by a hydraulic system connected to an appropriately adapted RIIC press originally constructed for KBr disc preparation for infrared spectroscopy. The apparatus, and the detailed procedure for obtaining the kinetic data, are described elsewhere.[20]

Cytotoxicity

In vitro screening of $Ti(etmalt)_2X_2$ with X = Cl and OEt and of $Ti(depp)_2Cl_2$ against a variety of cell lines gave IC_{50} values (IC_{50} = drug concentration at which 50% cell kill is achieved) in the region of 30 μg cm^{-3} for three murine adenocarcinomas. They were less effective against the eight other cell lines tested. These levels of activity were deemed too low for further compound development.

RESULTS

Substitution reactions for all the complexes in this investigation take place in two kinetically distinct steps, for example:

$$Ti(LL)_2Cl_2 \xrightarrow{Y^-} Ti(LL)_2YCl \xrightarrow{Y^-} Ti(LL)_2Y_2$$

The rate constant for the second step is always at least 10 times, generally more than 30 times, slower than that for the first step. There is thus negligible coupling between the two stages, and rate constants may be determined independently. In some cases we have been able to establish

Table 3 Observed first-order rate constants for the second stage of substitution at $Ti(cp)_2Cl_2$ by various incoming ligands Y in acetonitrile solution at 298.2 K

	$10^3k_{obs}(s^{-1})$							
	[Y](mol dm^{-3}):							
Y	0.03	0.05	0.08	0.10	0.15	0.20	0.50	1.00
NCS^-[a]	8.5	11.2	19.6	23	33	40		
I^-	3.0	3.6	3.7	3.8	4.9	5.4		
Br^-	2.5	2.8		2.9	3.4	3.9		
Pyrazine								15
2,2'-Bipyridyl								0.54
Ethylmaltol						0.30	0.24	0.30

[a] Also 3.9×10^{-3} at $[NCS^-] = 0.01$.

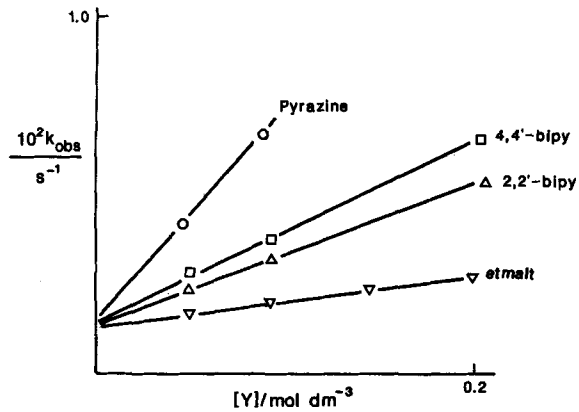

Figure 1 Observed first-order rate constants for the first stage in nucleophilic attack at $Ti(cp)_2Cl_2$ in acetonitrile solution at 298.2 K.

kinetic data for both steps, but often either the first or the second step proved to be impracticably fast or slow. In all kinetic runs the nucleophile was present in large excess, so first-order kinetics were always observed.

Rate constants for the first and second stages of substitution at $Ti(cp)_2Cl_2$ are reported in Tables 2 and 3 respectively, with the results plotted as a function of incoming nucleophile concentration in Figs 1 and 2. Analogous series of kinetic results for $Ti(etmalt)_2Cl_2$ are reported in Table 4 and depicted in Figs 3 and 4. The effects of varying the leaving group in $Ti(etmalt)_2X_2$ are reported and illustrated in Table 5 and Fig. 5, while the effects of the non-leaving ligands LL in $Ti(LL)_2Cl_2$ are documented in Table 6 and Fig. 6. As is apparent

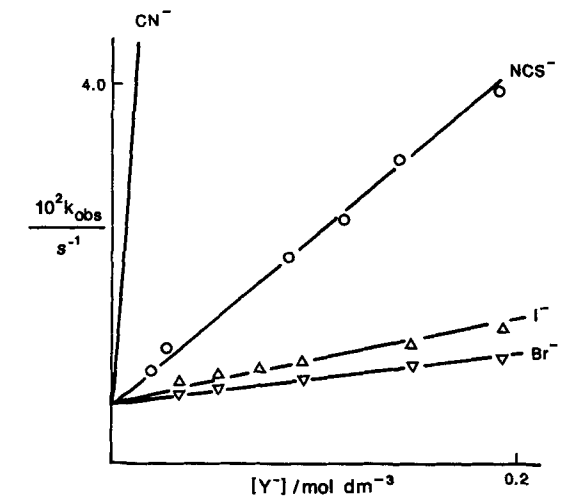

Figure 2 Observed first-order rate constants for the second stage in nucleophilic attack at $Ti(cp)_2Cl_2$ in acetonitrile solution at 298.2 K.

from Figs 1–6, in all cases the rate law is a two-term expression,

$$-d[complex]/dt = \{k_1 + k_2[Y]\}[complex] \quad [1]$$

Values of k_1 and k_2 have been obtained from the best straight lines in all cases where this is feasible, and are given in Tables 7–9. Pressure effects on rate constants, and derived activation volumes, are reported in Table 10.

DISCUSSION

Earlier investigations of the kinetics of substitution at $Ti(cp)_2Cl_2$ in our laboratories[14] and elsewhere[5,7] identified a single kinetic step. We have now, by reducing the concentrations of incoming groups, slowed some substitutions sufficiently to detect a relatively rapid first stage preceding the previously studied process, which is now seen to be the replacement of the second chloride (at least in acetonitrile solution). Figure 1 shows the conformance of the kinetic results for replacement of the first chloride in $Ti(cp)_2Cl_2$ to the rate law

$$-d[Ti(cp)_2Cl_2]/dt = \{k_1 + k_2[Y]\}[Ti(cp)_2Cl_2] \quad [2]$$

The k_1 values (Fig. 1 and Table 7) are essentially equal, consistent with this term in the rate law of Eqn [2] arising from a common rate-limiting solvolysis pathway. The k_2 values (Table 7) define the relative affinity of the ligands studied for the titanium in this complex. Discussion of the second-stage k_1 and k_2 values is complicated by the fact that the starting complexes $Ti(cp)_2ClY^+$ are different—indeed the solvolysis pathway rate constants (k_1) differ slightly but significantly (see Fig. 2) for Y = Br and Y = I (the only two ligands for which a reasonable approximation for k_1 can be obtained). What is most interesting about the second stage is that the rate constants (k_{obs}) for the nucleophiles 2,2'-bipyridyl and ethylmaltol are considerably less than the solvolysis, k_1, rate constants for the second stage. This suggests that the second kinetic step is rate-limiting ring closure to give a product "$Ti(cp)_2(LL)$", not reaction with a second molecule of entering group to give a bis(monodentate product) "$Ti(cp)_2(LL)_2$". This question is addressed below.

Kinetic data for the analogous reaction of $Ti(etmalt)_2Cl_2$ (Table 4 plus Figs 3 and 4) also

Table 4 Observed first-order rate constants for substitution at $Ti(etmalt)_2Cl_2$ by various incoming ligands Y in acetonitrile solution at 298.2 K

	$10^3k_{obs}(s^{-1})$							
	[Y](mol dm^{-3}):							
Y	0.001	0.005	0.010	0.05	0.10	0.20	0.30	0.50
	Second stage							
CN^-	(~46)							
NCS^-	2.6	4.8	7.1					
Water	0.9		1.1	2.2	5.0	9.6		
	First stage				*Second stage*			
MeOH	2.8	7.8	12.1		2.4	7.9	13.2	
EtOH	2.7	7.0	10.1		2.1	6.1	10.9	
iPrOH	2.4	4.9	7.9		2.0	5.3	9.2	
Pyrazine	0.85	2.8	5.2					
2,2'-Bipyridyl	0.82	2.2	4.1					
Malonic acid	0.70	1.3	1.7					

conform to parallel solvolysis and bimolecular nucleophilic attack for both stages. However, in this case the intercepts of k_{obs} versus incoming nucleophile concentration plots for the first stage (Fig. 3) are not quite independent of the nature of the nucleophile (Fig. 3 and Table 8), as would be expected for common rate-limiting dissociation of

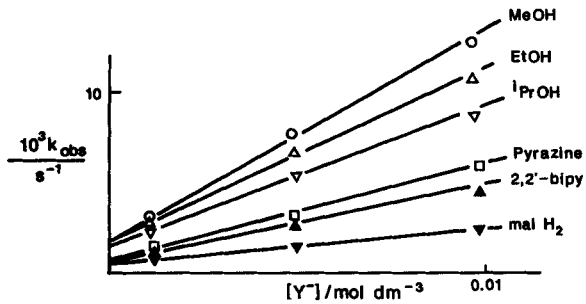

Figure 3 Observed first-order rate constants for the first stage in nucleophilic attack at $Ti(etmalt)_2Cl_2$ in acetonitrile solution at 298.2 K.

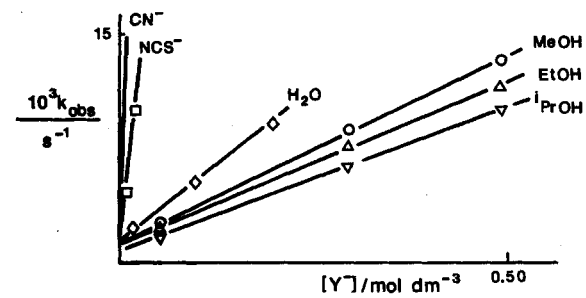

Figure 4 Observed first-order rate consants for the second stage in nucleophilic attack at $Ti(etmalt)_2Cl_2$ in acetonitrile solution at 298.2 K.

Table 5 Observed first-order rate constants for the second stage of substitution at $Ti(etmalt)_2X_2$ by thiocyanate in acetonitrile solution at 298.2 K

	$10^3k_{obs}(s^{-1})$			
	[NCS^-](mol dm^{-3}):			
X_2	0.005	0.01	0.05	0.10
Cl_2	4.8	7.1		
F_2	1.9	2.9	6.9	11
$(OMe)_2$	1.9	2.6	4.9	8.7
$(OEt)_2$	1.4	1.7	4.0	6.3
$(O^iPr)_2$	1.4	1.7	4.0	6.3
$(OPh)_2$	1.3	1.5	2.1	3.0
mal	2.4	4.4	8.7	

the first chloride ligand. The intercepts for pyrazine, 2,2'-bipyridyl and malonic acid are in fact identical, but the intercepts for isopropanol, ethanol and methanol are successively slightly greater. It may well be that, even at the low concentrations of alcohols used here, there are small but significant rate enhancements which can be attributed to favourable interaction with the leaving chloride ligand. In this connection it may be recalled that the rate constant for t-butyl chloride solvolysis in alcohol–water mixtures is very sensitive to particularly favourable solvation of the leaving chloride, e.g. solvolysis is nearly six times faster in ethanol containing 5% water than in pure ethanol.[21] The relative values of k_2 for the first and second stages are as expected for the range of nucleophiles studied.

In terms of the Hard and Soft Acids and Bases (HSAB) concept,[22] one might expect tita-

nium(IV) to display the characteristics of a hard centre, but the presence of the cyclopentadienyl ligands in $Ti(cp)_2Cl_2$ might well soften it considerably. In practice, the order of affinity of incoming groups for substitution at this compound (cf. Table 7) is

$$O,O\text{ ligand} < N,N < Br^- < I^- < SCN^-$$

Such an order is characteristic of a soft centre, but the range of reactivities is very much less than for the substitution of such ligands at, for example, platinum(II).[23] We therefore conclude that the titanium(IV) in $Ti(cp)_2Cl_2$ is only marginally soft. The situation for $Ti(etmalt)_2Cl_2$ is less clear, though the somewhat greater affinity of the alcohols than the N-donor ligands suggests that titanium(IV) in this complex is just on the hard side of the HSAB borderline.

The relative reactivities of different leaving ligands are documented in the left-hand half of Table 9. There is a surprisingly small range of rate constants for the dissociative (k_1) pathway for the loss of halide or alkoxide (X^-) from $Ti(etmalt)_2(NCS)X$, but rate constants (k_2) for the dominant bimolecular pathway cover a range of over 20-fold for the complexes studied. The fluoride complex reacts more slowly (k_1 and k_2) than the chloride, consistent with stronger Ti–F bonding. Whether the order of k_2 values for the alkoxides arises from the relative ease of stretching the Ti–O bonds in transition-state formation or from steric effects of varying bulk of —OR groups is not clear.

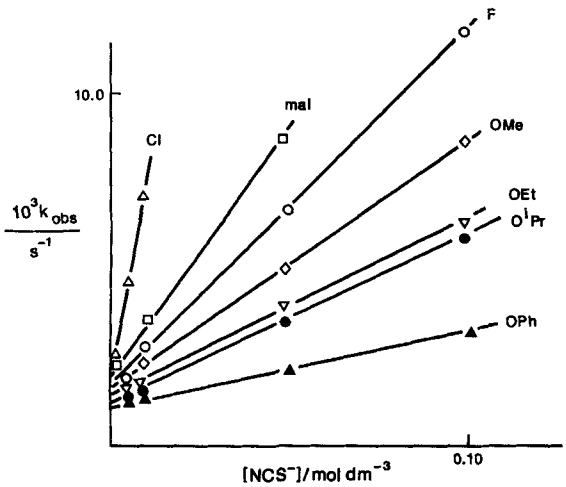

Figure 5 Effect of leaving group variation: observed first-order rate constants for the second stage in nucleophilic attack at $Ti(etmalt)_2X_2$ in acetonitrile solution at 298.2 K.

Table 6 Observed first-order rate constants for the second stage of substitution at $Ti(LL)_2Cl_2$ by thiocyanate in acetonitrile solution at 298.2 K

	$10^3 k_{obs}(s^{-1})$				
Ligand (LL)	[NCS$^-$] (mol dm^{-3}): 0.001	0.005	0.01	0.05	0.10
etmalt	2.6	4.8	7.1		
memalt	2.7	5.5	7.2		
aha		1.7	2.2	5.4	9.2
koj		1.1	2.0	4.0	7.1
mbz		1.3	1.5	3.6	6.1
trop			1.2	1.9	3.1
depp			1.09	1.32	1.98
empp			1.07	1.28	1.91
hepp		1.01	1.03	1.08	1.13
dmpp		0.84	0.85	0.88	0.91

Effects of changing non-leaving chelating ligands LL in complexes $Ti(LL)_2Cl_2$ on substitution reactivity are summarized in the right-hand half of Table 9. There is a relatively restricted range of rate constants k_2, and a very restricted range of dissociation rate constants k_1. For both dissociative and associative substitution the pyrone complexes react the most quickly, the pyridinone complexes the most slowly—with cyclopentadienyl, hydroxamate and tropolonate complexes reacting at intermediate rates. The very small effects on bimolecular thiocyanate attack are due to electron withdrawal or release by the chelating ligand assisting or discouraging entry of the incoming thiocyanate nucleophile.

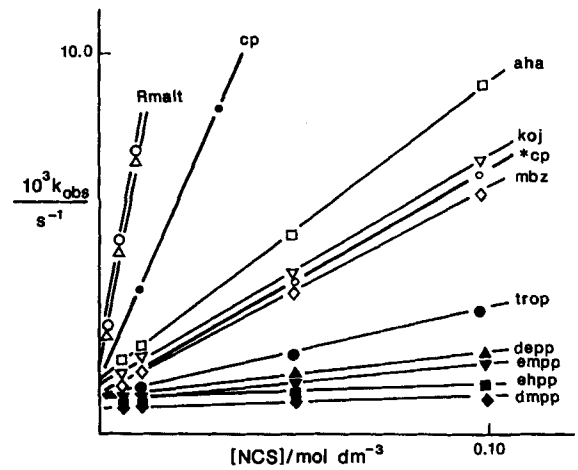

Figure 6 Effect of non-leaving group variation: observed first-order rate constants for the second stage in nucleophilic attack at $Ti(LL)_2Cl_2$ in acetonitrile solution at 298.2 K.

Table 7 Values of k_1 and k_2 for the first and second stages of substitution at $Ti(cp)_2Cl_2$ in acetonitrile solution at 298.2 K[a]

	First stage		Second stage	
	$10^3k_1(s^{-1})$	$k_2(dm^3\,mol^{-1}\,s^{-1})$	$10^3k_1(s^{-1})$	$k_2(dm^3\,mol^{-1}\,s^{-1})$
CN^- [a]				ca. 14
NCS^- [b]			2.5	0.20
I^- [b]			2.7	0.02
Br^- [b]		(0.2)	2.4	0.01
Pyrazine	1.2	0.037		0.012
4,4'-Bipyridyl	1.2	0.021		
2,2'-Bipyridyl	1.2	0.020		
Ethylmaltol	0.9	0.011		

[a] From Ref. 14. [b] Mean results from Ref. 14 and the present investigation.

The smallest k_2 values in Table 9 correspond with those ligands expected to form the most stable complexes. The high degree of σ-electron pair donation associated with strong ligand–metal bonding will increase the net electron density at the titanium, i.e. reduce the effective positive charge on the central metal, and thus discourage nucleophilic attack. The difference in k_2 values between the pyrone and pyridinone complexes corresponds to a difference of about 15 kJ mol^{-1} in the activation barriers, which are about 75 and 90 kJ mol^{-1} respectively.

The activation volumes for thiocyanate attack at $Ti(cp)_2Cl_2$ and at $Ti(etmalt)_2Cl_2$, -15 and $-12\,cm^3\,mol^{-1}$ (Table 10), are of the magnitude expected for a bimolecular process (*ca* $-10\,cm^3\,mol^{-1}$ for organic systems[24]) in the absence of significant solvent effects. Hydration effects have a large effect on activation volumes for bimolecular inorganic reactions involving small hydrophilic anions such as hydroxide or cyanide in aqueous solution.[25,26] Such effects are attributed to extensive desolvation of the anionic nucleophile on it incorporation into a transition state. This situation in acetonitrile will be very different, as dipolar aprotic solvents solvate hydrophilic anions very poorly. The transfer chemical potential of thiocyanate from water to acetonitrile,[27] which is at least +12 kJ mol^{-1}, gives a quantitative indication of the essentially unsolvated state of thiocyanate in acetonitrile. We may therefore expect the solvation contribution to activation volumes for thiocyanate attack at $Ti(cp)_2Cl_2$ or $Ti(etmalt)_2Cl_2$ to be negligible, and the observed negative values to provide strong support for bimolecular attack as the mechanism for the bimolecular k_2 pathway.

The final point for discussion concerns potentially bidentate ligands as nucleophiles. As mentioned above, the second step in the observed kinetics could arise from replacement of the second chloride of $Ti(cp)_2Cl_2$ or $Ti(etmalt)_2Cl_2$ by

Table 8 Values of k_1 and k_2 for the first and second stages of substitution at $Ti(etmalt)_2Cl_2$ in acetonitrile solution at 298.2 K[a]

	First stage		Second stage	
	$10^3k_1(s^{-1})$	$k_2(dm^3\,mol^{-1}\,s^{-1})$	$10^3k_1(s^{-1})$	$k_2(dm^3\,mol^{-1}\,s^{-1})$
CN^-				(50)
NCS^-			2.0	0.45
Water			(1)	0.043
MeOH	2.2	1.0	2.0	0.027
EtOH	2.2	0.9	1.8	0.022
iPrOH	1.8	0.6	1.5	0.018
Pyrazine	0.7	0.43		
2,2'-Bipyridyl	0.7	0.36		
Malonate	0.6	0.12		

[a] Values in brackets are estimates.

Table 9 Effect of leaving ligand and non-leaving ligand on k_1 and k_2 values for the second stage of thiocyanate substitution at $Ti(LL)_2Cl$ in acetonitrile at 298.2 K

$Ti(etmalt)_2X_2$			$Ti(LL)_2Cl_2$		
X_2	$10^3k_1(s^{-1})$	$k_2(dm^3\,mol^{-1}\,s^{-1})$	LL[b]	$10^3k_1(s^{-1})$	$k_2(dm^3\,mol^{-1}\,s^{-1})$
Cl_2	(2)	(0.45)	memalt	2.0	0.45
Malonate	1.8	0.24	etmalt	2.0	0.45
F_2	1.6	0.17	cp[c]	2.5	0.203
$(OMe)_2$	1.7	0.07	aha	1.4	0.078
$(OEt)_2$	1.3	0.05	koj	1.3	0. 061
$(OiPr)_2$	1.1	0.05	cp*[c]	1.2	0.053
$(OPh)_2$	1.1	0.02	mbz	1.3	0.051
			trop	1.0	0.022
			depp	1.0	0.010
			empp	1.0	0.009
			ehpp	1.0	0.0018
			dmpp	0.8	0.001

[a] Values in brackets are approximate.[b] See text for formula and abbreviations. Ref. 14.

a second molecule of incoming group, to give a product containing two of the potentially bidentate ligands actually coordinated in a monodentate manner, e.g.

$$Ti(cp)_2(etmalt)Cl + etmaltH \rightarrow Ti(cp)_2(etmalt)_2 + Cl^- + H^+$$

Alternatively the second step could simply be ring closure:

$$Ti(cp)_2(etmalt)Cl \rightarrow [Ti(Cp)_2{<}\supset]^+ + Cl^-$$

where

$$[{<}\supset = etmalt^-].$$

The question can be resolved by product identification and from kinetic evidence. Thus k_{obs} values for the second step in the reaction of $Ti(cp)_2Cl_2$ with 2,2′-bipyridyl and with ethylmaltol are less than the k_1 values for the solvolytic path (see above). Moreover, for ethylmaltol as nucleophile, k_{obs} is independent of the concentration of the incoming ligand. The kinetic evidence thus firmly indicates rate-limiting ring closure. That the product contains chelated incoming ligand has been shown by FAB MS for the reaction of $Ti(cp)_2Cl_2$ with ethylmaltol and of $Ti(etmalt)_2Cl_2$ with malonate. Bidentate malonate in the product is also indicated by ^1H NMR of the material obtained by refluxing $Ti(etmalt)_2Cl_2$ with malonic acid for 12 h. Of course, such chelate products are to be expected in view of, for example, the fact that reaction of $Ti(cp)_2Cl_2$ with acacH gave $Ti(cp)_2(acac)^+$ under all conditions,[28] and the prevalence of (substituted) malonate complexes of platinum(II) in cancer chemotherapy.[29]

In conclusion, we have shown that the substitution reactivity of titanium(IV) complexes of the type $Ti(LL)_2X_2$ can be tailored over a reasonably wide range by variation of leaving group (X = halide or alkoxide) and non-leaving ligand (cf. Table 9). Fine tuning of reactivity could be achieved by, for instance, methyl substitution in

Table 10 Ratios of rate constants at high pressure (k_p) to the respective value at 1 atm (k_a), and derived activation volumes for the second stage of the substitution in acetonitrile solution at 298.2 K

		$\log_{10}(k_p/k_a)$				
		Pressure (bar):				
Complex	Incoming	250	500	750	1000	$\Delta V\,cm^3\,mol^{-1}$)
$Ti(cp)_2Cl_2$	NCS^-	0.13	0.24	0.36	0.46	-15 ± 0.5
$Ti(etmalt)_2Cl_2$	H_2O	0.09	0.19	0.30	0.39	-12 ± 0.5

the cyclopentadienyl ligands or by alkyl substitution in the pyridinones.

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REFERENCES

1. Kopf, H and Kopf-Maier, P *Angew. Chem.*, 1979, 91: 509; *Angew. Chem. Int. Ed. Engl.*, 1979, 18: 477
2. Kopf, H and Kopf-Maier, P *ACS Symp. Ser.*, 1983, 209: 315
3. Keller, H J, Keppler, B K and Schmahl, H *Arzneim-Forsch./Drug Res.*, 1982, 32: 806
4. Kopf, H and Kopf-Maier, P *Struct. Bond*, 1988, 70: 103
5. Jensen, A and Basolo, F *J. Am. Chem. Soc.*, 1959, 81: 5312
6. Jensen A *Proc. 7th Internat. Conf. Coord. Chem.*, 1962, 254
7. Langford, C E and Aplington, J P *J. Organomet. Chem.*, 1965, 294: 321
8. Toney, J H and Marks, T J *J. Am. Chem. Soc.*, 1985, 107: 947
9. Kopf-Maier, P, Brauchle, U and Hemssler, A *Toxicology*, 1988, 51: 291
10. Keppler, B K, Diez, A and Seigfried, V *Arzneim-Forsch./Drug Res.*, 1985, 35: 12
11. Heim, M H, Flechtner, H and Keppler, B K *Prog. Clin. Biochem. Med.*, 1989, 10: 217
12. Hanssen, M *E for Additives*, Thorsons, Wellingborough, UK, 1987
13. Romeo, R, Lanza, S, Minniti, D and Tobe, M L *Inorg. Chem.*, 1978, 17: 2436
14. Razak bin Ali, Burgess, J and Casey, A T, *J. Organomet. Chem.*, 1989, 362: 305
15. Ye Dakeng, Wang Chengrui, Meng Lingzhi and Liu Daoyu *Kexue Tongbao*, 1987, 32: 1031; *Chem. Abstr.* 108: 204750c
16. Birmingham, J M and Wilkinson, G *J. Am. Chem. Soc.*, 1954, 76: 4281
17 Bercaw, J E, Marvich, R H, Bell, L G and Brintzinger, H H *J. Am. Chem. Soc.*, 1972, 94: 1219
18. Chaudhry, S C, Bhatt, S S, Kumar, A, Bhatt, S S and Sharma, N *Synth. React. Inorg. Met. Org. Chem.*, 1992, 22: 1
19. Blandamer, M J, Burgess, J, Clark, B, Duce, P P, Hakin, A W, Gosal, N, Radulovic, S, Guardado, P, Sanchez, F, Hubbard, C D and Abu-Gharib, E A *J. Chem. Soc., Faraday Trans. 1*, 1986, 82: 1471
20 Hallinan, N, McArdle, P, Burgess, J and Guardado, P *J. Organomet. Chem.*, 1987, 333: 77
21 Wells, P R *Chem. Rev.*, 1963, 63: 171
22. Pearson, R G (ed) *Hard and Soft Acids and Bases*, Dowden, Hutchinson and Ross, Stroudsburg, PA, USA, 1973
23. Belluco, U, Cattalini, L, Basolo, F, Pearson, R G and Turco, A *J. Am. Chem. Soc.*, 1965, 87: 241
24. Asano, T and Le Noble, W J *Chem. Rev.*, 1978, 78: 407
25. Burgess, J, Duffield, A J and Sherry, R *J. Chem. Soc., Chem. Commun.*, 1980, 350
26. Burgess, J, Galema, S A and Hubbard, C D *Polyhedron*, 1991, 10: 703
27 Barraque, C, Vedel, J and Tremillon, R *Bull. Soc. Chim. Fr.*, 1968, 3421
28. Doyle, G and Tobias, R S *Inorg. Chem.*, 1967, 6: 1111
29. Anon *Chem. Brit.*, 1991, 27: 1002