Functionalized Oxovanadium Alkoxides – Potential Haptens

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Several new oxovanadium alkoxides and alkoxides/chlorides of the composition $VOCl_{3-n}(OR)_n$ (n = 1, R = CPh_3; n = 2 and 3, R = CPh_3, *i*Bu, cyclopentyl, *tert*-pentyl, octyl; n = 3, R = dodecyl, 3-methylbutyl) and the mixed ester $VO(OiBu)(OCPh_3)_2$ have been prepared. The compounds $VO(OiBu)_2OR'$ have been synthesized, where R' is a functionalized long-chain alkyl group [$-(CH_2)_8OH$, $-(CH_2)_6NH(FMOC)$, $-(CH_2)_6NH_2$, $-C(O)(CH_2)_5C(O)OMe$, p-C_6H_4CN, p-$C_6H_4NH_2$]. The chloride/carboxylate $VOCl_2\{O_2C(CH_2)_5CO_2H\}$ has also been obtained. The compounds are characterized, inter alia, by ^{51}V-NMR spectroscopy. Typical ^{51}V shift ranges are observed for specific ligand functionalities (chloride, alkoxide, carboxylate). $\delta(^{51}V)$ values also depend on the steric requirement of the groups R and the coordination number. The importance of the functionalized esters as potential triggers for the production of abzymes with phosphatase activity is discussed.

The enzymatic cleavage and formation of phosphoester bonds in biological systems proceeds via a transition state, in which phosphorus is assumed to display a trigonal bipyramidal geometry. We have shown that this transition state can be mimicked by oxovanadium alkoxides (i.e. esters of the hypothetic orthovanadium acid which, in the solid state, are dimers with vanadium in a slightly distorted trigonal bipyramidal environment[1]). This geometry has also been found for a mixed alkoxide/chloride[2] and proposed, on the basis of ^{51}V-NMR studies, for the association of the esters in non-aqueous solution[1], the weak associates formed between vanadate and diols or lactic acid in aqueous solutions[3] and the ternary complexes vanadate/uridine/ribonuclease-A[4] and vanadate/inosine/ribonuclease-T_1[5]. In contrast to phosphorus, vanadium has available energetically low-lying d orbitals which allow the formation of stable coordination compounds with coordination numbers >4 and hence can give rise to stable transition-state analogues. These have been made responsible for the inhibitory action of vanadate (under physiological conditions this is $H_2VO_4^-$) towards enzymes involved in phosphorylation reactions, such as ribonucleases[4] and ATP-ases[6]. The regulation of phosphate metabolizing enzymes[7] is part of the now well established overall biological function of vanadium[8].

The bio-analogy between phosphate and vanadate in ester formation[8] on the one hand, and the different stabilities of the esters on the other hand, paired with the ability of vanadium to extend its coordination sphere have prompted us to investigate the potential of oxovanadium esters with anchor groups, to be employed as haptens for carrier proteins. Such proteins with oxovanadium groups attached to their surface might be able to trigger the formation of so-called abzymes, antibodies with enzymatic (here: phosphatase) activity.

In this paper, we present results on esters with and without dangling functions.

Results and Discussion

General and Esters Derived from Monoalcohols

Oxovanadium alkoxides and mixed alkoxides/chlorides of the general formula $VOCl_{3-n}(OR)_n$ (n = 1–3) are usually liquids at ambient temperatures. Their structural and spectroscopic features have been described comprehensively for common groups R[1,9,10] and for esters formed with diols[1]. Solid-state structures have been reported for n = 3, R = Me[11] and CH_2CH_2Cl[1], and for n = 2, R = pinacolate[2], showing their dimeric, OR-bridged nature in the crystalline state. ^{51}V-NMR[1,9], ^1H-NMR[12], ^{35}Cl-NQR studies[10], cryoscopic measurements[13], and mass spectra[14] have revealed that the triesters also associate in the neat liquid state and in solution. The extent of association depends on the bulkiness of the groups R and, in solution, on concentration, temperature, and the nature of the solvent. Association possibly occurs through OR bridges. A sensitive tool to determine the extent of association is ^{51}V-NMR spectroscopy[15]. With increasing association of $VO(OR)_3$, shielding of the ^{51}V nucleus decreases as a consequence of an increase in the coordination number[1,16a]. With very bulky groups R, such as *t*Bu, there is no association at all and a limiting high-field shift of $\delta = -685$ is observed. Apart from this steric influence on $\delta(^{51}V)$, shielding is determined by the electronegativity of the substituents attached to vanadium, in that Cl gives rise to a deshielding relative to O functions (so-called inverse electronegativity dependence of metal shielding). In Table 1 relevant data on compounds derived from monoalcohols and described here mostly for the first time are listed. ^{51}V shielding clearly increases as (i) the number of chlorine atoms in $VOCl_3$ is successively replaced by alkoxy residues, and (ii) as the bulkiness of R increases[16b].

Esters Derived from Functionalized Alcohols

Diols, when treated with $VOCl_3$, may form chelate (glycol, 1,2-butanediol) or bridging structures (1,3- and 1,4-butane-

  0009–2940/91/1010–2249 $ 3.50+.25/0

Table 1. Spectroscopic data on oxovanadium alkoxides and mixed alkoxides/chlorides[a]

Compound	B.p.[b] [°C]	$\delta(^{51}V)$[c]	$\nu(V=O)$[d] [cm^{-1}]	$\nu(V-Cl)$[d] [cm^{-1}]
$VOCl_3$	127	0	1040	510
$VOCl_2OCPh_3$	dec.	−327	1025	498
$VOCl(OR)_2$				
R = Octyl	dec.	−482	1019	455
*i*Bu	90 (hv)	−482	1015	463
Cyp[e]	110 (hv)	−498	1015	463
*i*Pr	36 (hv)	−509	1014	460
$OCPh_3$	dec.	−511	1013	460
tert-Pentyl	dec.	−538	1013	461
$VO(OR)_3$				
R = *i*Bu	98 (hv)	−597	1008	
3-Methylbutyl	109 (hv)	−599	1006	
Dodecyl	60 (m.p.)	−600, −611[f]	1007	
Octyl	[g]	−603	[g]	
Cyp	−10 (m.p.)	−618	1004	
*i*Pr	60 (hv)	−629	1004	
tert-Pentyl	128 (hv)	−685	1001	
$VO(OiBu)(OCPh_3)_2$	[g]	−670	1001	

[a] Except for R = *i*Pr and *i*Bu, the compounds have not been reported before. For additional information see Experimental (Table 3). — [b] Boiling point (hv = high vacuum), if not mentioned otherwise. — [c] In CD_3Cl_3 except for R = CPh_3 (toluene). — [d] Neat for liquids, or in nujol suspension. — [e] Cyp = cyclopentyl. — [f] We have no explanation for the observation of two resonances (intensity ratio −600/−611 = 1.8/1). At 55°C, there is but one signal at δ = −580. — [g] Not determined.

Table 2. $\delta(^{51}V)$ values for oxovanadium compounds carrying a functionalized substituent (FMOC = 9-fluorenylmethyleneoxycarbonyl)

Compound	$\delta(^{51}V)$/phase
$VO(OR)O(CH_2)_8OH$	
R = *i*Bu	−594/THF-$CDCl_3$
tert-Pentyl	−618/$CDCl_3$;
*i*Pr	−593/THF-$CDCl_3$
	−618/$CDCl_3$
$VO(OiBu)_2O(CH_2)_6NH(FMOC)$	−589/$CDCl_3$;
	−601/THF-$CDCl_3$
$VO(OiBu)_2O(CH_2)_6NH_2$	−569/$CDCl_3$;
	−556/THF;
	−568/DMSO
$VO(OiBu)_2OC_6H_4CN$-(*p*)	−603/THF;
	−608/CD_3Cl
$VO(OiBu)_2OC_6H_4NH_2$-(*p*)	−597/THF
$VO(OiBu)_2O(CH_2)_3CO_2H$[a]	−628/THF
$VOCl_{3-n}\{O_2C(CH_2)_5CO_2H\}_n$	
n = 1	−168/THF
n = 2[a]	−356/THF
$VO(O\text{-}tert\text{-}pentyl)_2\{O_2C(CH_2)_5CO_2H\}$[a]	−620/THF
$VO(OR)_2\{O_2C(CH_2)_5C(O)OMe\}$	
R = *i*Bu	−593/THF
R = *i*Pr[a]	−621/$CDCl_3$

[a] Not isolated; detected in a mixture with other components only.

diol), usually in mixtures with acyclic compounds carrying a dangling OH[1]. As with monoalcohols, a maximum of two chlorine atoms can be substituted in a simple reaction mixture of the two components. To remove the last chlorine in $VOCl_3$, the lithium alcoholates can be employed. Alternatively, the reaction mixture can be treated with ammonia[17].

We have obtained the compounds $VO(OR)_2\{O(CH_2)_8OH\}$ by reaction of $VO(OR)_2Cl$ with the monolithium salt of 1,8-octanediol [eq. (1); for ^{51}V-NMR data see Table 2]. Figure 1 illustrates the incomplete conversion in the case of R = *i*Pr as depicted by the ^{51}V-NMR spectrum. A pure (determined by ^{51}V-NMR and elemental analysis) complex has been isolated in the case of R = *i*Bu. The yields depend on the nature of R: with R = Et, the product is isolated in 85% yield after a reaction time of 20 h, while the yield drops to 30% when $VO(O\text{-}tert\text{-}pentyl)_2Cl$ is employed. The reaction is apparently sterically hindered. When the diol itself is applied and NH_3 passed over the reaction mixture, almost complete exchange of Cl for $O(CH_2)_8OH$ occurs within a few minutes [eq. (2)] and without any apparent steric influences on the kinetics. The product is composed of several complexes, however: For R = *i*Bu, four NMR signals in the region of the triesters are observed, possibly belonging to the complexes $VO(OiBu)_{3-n}\{O(CH_2)_8OH\}_n$, $n = 0-3$.

$$VO(OR)_2Cl + LiO(CH_2)_8OH \rightarrow LiCl + VO(OR)_2\{O(CH_2)_8OH\} \quad (1)$$

$$VO(OR)_2Cl + HO(CH_2)_8OH + NH_3 \rightarrow [NH_4]Cl + VO(OR)_2\{O(CH_2)_8OH\} \quad (2)$$

The situation becomes more complex, as one of the functions is an amino group, such as in 6-amino-1-hexanol. In order to establish a clear reaction path, it is necessary to protect the amino group, preferably with FMOC (9-fluorenylmethyleneoxycarbonyl) which can be split off under mild alkaline conditions (the ester bond is susceptible towards splitting by acids[1]). A spectroscopically and analytically pure product of composition $VO(OiBu)_2O(CH_2)_6NH$-(FMOC) has been obtained in 95% yield by treating $(FMOC)NH(CH_2)_6OH$ with $VO(OiBu)_2Cl$ in the presence of NH_3. For data, see Table 2. Alternatively, re-esterification [eq. (3)] also leads to a uniform product; yields, however, are pure. Deblocking of the amino group with piperidine yields $VO(OiBu)O(CH_2)_6NH_2$ [eq. (3)], characterized by $\delta(^{51}V)$ = −569, and a second product with $\delta(^{51}V)$ = −491, possibly

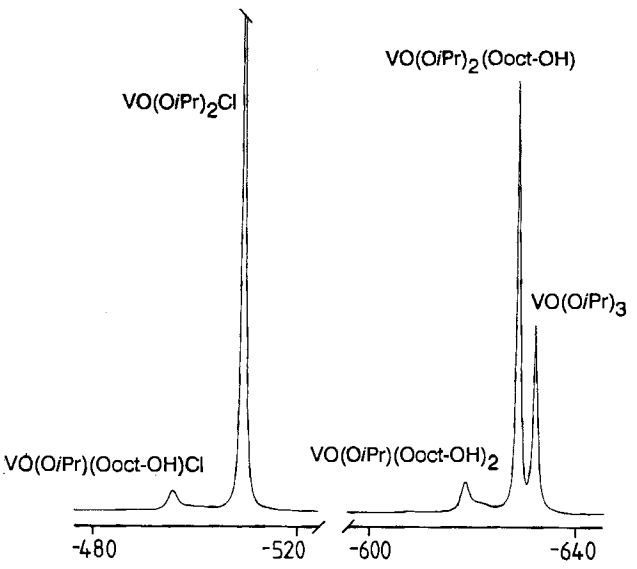
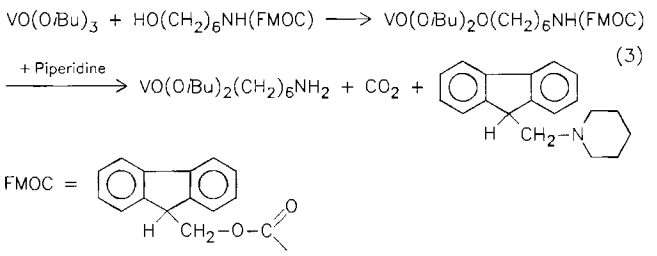


Figure 1. ^{51}V-NMR spectrum ($CDCl_3$) of the products obtained by the reaction of $VO(OiPr)_2Cl$ with $LiO(CH_2)_8OH$. The assignments are based on the data given in Table 1. Relative intensities (from left to right): 1:9:1.5:8.5:4.5

corresponding to a (not identified) octahedral complex of V^{V} [18].

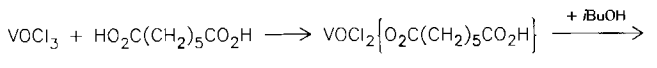


(3)

The reaction between 4-hydroxybenzonitrile and $VO(OiBu)_2Cl$ in the presence of NH_3 yields several products, one of which we have characterized as $VO(OiBu)_2OC_6H_4CN$ by its IR and ^{1}H-NMR patterns and $\delta(^{51}V) = -603$. This compound can also be prepared by re-esterification. A complex product pattern is observed with 4-aminophenol. The reaction becomes clearer as FMOC-protected aminophenol is employed. The ^{51}V-NMR spectrum shows one main component at $\delta(^{51}V) = -597$, which can be allocated to $VO(OiBu)_2OC_6H_4NH_2$. In this case, the basicity of ammonia suffices to deblock the amino group in the course of the reaction. The absence of FMOC in the product has been evidenced by ^{1}H-NMR and IR spectroscopy.

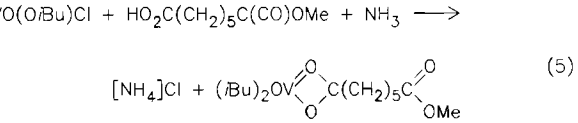
Reaction with 1,7-Heptanedioic (Pimelic) Acid and its Derivatives

The reaction of pimelic acid with $VOCl_3$ in CH_2Cl_2 [eq. (4)] leads to an approximate 1:1 mixture of a charge transfer compound [19] between $VOCl_3$ and the acid [$\delta(^{51}V) = -8$] and a substitution product of the composition $VOCl_2\{O_2C(CH_2)_5CO_2H\}$ [$\delta(^{51}V) = -168$]. A trace of the disubstitution product [$\delta(^{51}V) = -356$] is also detected. From the mixture the monosubstituted product can be isolated by treatment with hexane. The vanadium-carboxylate bond is unstable towards alcoholysis: Treatment with two equivalents of *i*BuOH leads to the formation of $VO(OiBu)Cl_2$ [$\delta(^{51}V) = -308$], $VO(OiBu)_2Cl$ and pimelic acid.



(4)

The reactions of $VO(OiBu)_2Cl$ with the monolithium salt of pimelic acid or pimelic acid itself in the presence of NH_3, which have proved appropriate routes for introducing long-chain, functionalized alcohols (see above), have been unsuccessful in this case, and only traces of $VO(OR)_2\{O_2C(CH_2)_5CO_2H\}$ are formed by re-esterification. However, if the monomethyl ester of pimelic acid is treated with $VO(OR)_3$ (R = *i*Pr, *i*Bu) in a molar ratio of 1:1, the mixed esters/anhydrides $VO(OR)_2\{O_2C(CH_2)_5C(O)OMe\}$ can be generated [eq. (5)] in high yields. Both the carbonyl bands of the ester group (1740 cm^{-1}) and the coordinated carboxylate residue (1658 cm^{-1}) are observed in the IR spectrum. The latter band is shifted towards lower wave numbers with respect to the free carboxylic acid function in the monoester (1710 cm^{-1}); this is indicative of the carboxylate binding in the η^2 (i.e. bidentate) mode [20], hence of a coordination number 5 of vanadium. The bidentate binding of carboxylate in a V(V) compound has been observed earlier in the heptacoordinate complex $VO(O_2CtBu)_3$ [21].



(5)

Conclusion and Prospects

We have shown that α,ω-difunctional molecules $HO(CH_2)_8OH$, $HO(CH_2)_6NHR$ (R = H, FMOC), *p*-HOC_6H_4X (X = NH_2, CN), and $HO_2C(CH_2)_5C(O)OMe$ can be attached to the $\{VO(OiBu)_2\}$ moiety via the hydroxyl and carboxyl functions, respectively, to form oxovanadium alkoxides of the composition $VO(OiBu)_2OR'$, with R' carrying a terminal function (a "handle") which is, in principle, available for attachment to a side-chain function of a protein. Linkage of an appropriate V(V) compound (a *hapten* in this context) to a carrier protein may well result in the ability of such a derivatized protein to promote the in vivo production of abzymes with phosphatase activities (kinases of run in reverse).

One of the compounds described in this work, the ester/anhydride $VO(OiBu)_2\{OC(O)(CH_2)_5C(O)OMe\}$, is a pentacoordinate complex (the carboxylate function coordinates in the bidentate mode) and hence may be considered a transition state analogue of phosphoester bond cleavage. But pure oxovanadium(V) esters have also been shown to be able to extend their coordination sphere *by association*, provided the substituents on vanadium are not too bulky. With the isobutyl group we have chosen a substituent compromising the accessibility of the vanadium centre to a fifth ligand on the one hand and steric stabilization of the functionalized ester on the other hand. Further work points into the direction of synthesizing five-coordinated esters (with the VO^{3+} core) exhibiting hapten properties.

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Experimental

IR: Perkin Elmer 1700 X FT. — ^{1}H NMR: Bruker WP 80. — $^{51}V\{^1H\}$ NMR: 94.73 MHz, Bruker AM 360, equipped with a multinuclear probe head. Samples, commonly with $c(V) = 10-100$ mmol, were filled into 10-mm diameter vials and measured at ambient temperatures [296(2) K]. Typical parameters: sweep width 125 kHz, time domain 8200 K, pulse angle 60°, no relaxation delay, line broadening factor 30 Hz, number of scans 10000–100000.

Preparation of Complexes

$VOCl_{3-n}(OR)_n$ with HOR = Monoalcohol: Preparative details of the compounds are listed in Table 3.

Table 3. Preparation of $VOCl_{3-n}(OR)_n$, HOR = monoalcohol

R	n	Method[a]	Solvent/temp.	Recovery[b]	Characteristics
CPh_3	1[c]	Ia	benzene/room temp.	filt.	yellowish oil
*i*Pr	2	Ia	hexane/reflux	dist. i. v.	orange-yellow liquid
*i*Bu	2	Ia	hexane/reflux	dist. i. v.	orange-yellow liquid
tert-Pentyl	2	III	toluene/room temp.	rem. solv.	yellow oil
cyclo-C_5H_9	2	Ia	CCl_4/60°C	dist. i. v.	red oil/red crystals[d]
Octyl	2	Ia	hexane/40°C	rem. solv.	yellow oil
*i*Bu	3	II	isobutyl alcohol/reflux	rem. solv.	yellow liquid
3-Methylbutyl	3	II	3-methyl-1-butanol/reflux	rem. solv.[e]	yellow oil
$C_{12}H_{25}$	3	IV	benzene/reflux	filt.	yellow solid
cyclo-C_5H_9	3	Ib	hexane/room temp.	rem. solv.	colourl. oil/crystals[d]
*i*Pr	3	II	2-propanol/reflux	rem. solv.	colourless liquid
tert-Pentyl	3	II	1,1-dimethyl-1-propanol/reflux		colourless oil

[a] See text. — [b] dist. i. v. = distillation in vacuo after removal of solvent, rem. solv. = removal of solvent, filt. = filtration before removal of solvent. — [c] Small admixture of $VOCl(OCPh_3)_2$, a brown solid, which is only sparingly soluble in benzene. — [d] The oil solidifies at about −10°C. — [e] For a detailed description see text.

Method Ia: A solution of 8.66 g (4.7 ml; 0.05 mol) of $VOCl_3$ in 75–100 ml of an apt solvent was treated dropwise with the alcohol or a solution of the alcohol and heated for ca. 1 h. The product was recovered directly by removal of the solvent in vacuo at room temp. and, where appropriate (i.e. if substantial decomposition can be avoided), purified by vacuum distillation. In most cases, pure $VOCl(OR)_2$ was isolated by this method. with R = Ph_3C, a mixture of $VOCl_2(OCPh_3)$ and $VOCl(OCPh_3)_2$ was obtained. — *Method Ib:* The trisubstituted compounds were obtained, if NH_3 was passed over the reaction mixture until all ammonium chloride had precipitated. This was filtered off, and the filtrate processed as in Ia.

Method II: The triesters $VO(OR)_3$ (R = *i*Pr, *i*Bu, 3-methylbutyl, *tert*-pentyl) were obtained in higher yields (90% and more) according to the method described by Lachowicz and Höboldt[12] by refluxing ca. 5.5 g (20 mmol) of V_2O_5 in ca. 50 ml of HOR, followed by removal of the solvent alcohol and fractional distillation under high vacuum.

Method III: 15 mmol of triester $VO(OR)_3$ (see method II) dissolved in 150 ml of toluene was treated with 1.3 g (0.71 ml; 7.5 mmol) of $VOCl_3$ and stirred at room temp. for 24 h. The solvent was removed in vacuo to yield $VOCl(OR)_2$.

Method IV: Re-esterification may be employed to replace small groups R (such as Et) by large ones [such as dodecyl; cf. (d)] or to produce mixed esters $VO(OR)_{3-n}(OR')_n$. A triester or a mixed ester/chloride can be the starting material: (a) 1.11 g (2.8 mmol) of $VOCl_2(OCPh_3)$ was treated with 100 ml of hexane to yield an orange-yellow suspension. This was warmed to 50°C, and 2.34 g (3.0 ml; 39 mmol) of 2-propanol was added. The solution immediately became clear and colourless, and HCl evolved. The ^{51}V-NMR spectrum (hexane) showed four species in the ratio of 16:1:3:3; δ = −311 [$VOCl_2(OiPr)$], −327 [$VOCl_2(OCPh_3)$], −507 [$VOCl(OiPr)_2$], −531 [$VO(OiPr)(OCPh_3)$]. — (b) 1.65 g (4.2 mmol) of $VOCl_2(OCPh_3)$ was dissolved in 50 ml of toluene and treated with 0.68 g (5 mmol) of 1-octanol dissolved in 30 ml of toluene. The originally orange solution turned yellow and HCl evolved, which was removed by passing N_2 through the solution for 2 h. Two species in a ratio of 1:3 were detected by ^{51}V-NMR spectroscopy (toluene): δ = −292 [$VOCl_2(OC_8H_{17})$], −481 [$VOCl(OC_8H_{17})_2$]. — (c) 1.2 g (4.9 mmol) of $VOCl(OiBu)_2$ and 1.28 g (4.9 mmol) of triphenylmethanol were dissolved in 50 ml of THF, and NH_3 was passed over the solution, which turned brown and became turbid. After 3 h, the THF was removed in vacuo. Extraction of the dark grey, pasty residue with hexane gave a yellow solution (the remaining residue was unreacted Ph_3COH), from which 320 mg of a yellowish solid [mainly $VO(OiBu)(OCPh_3)_2$] precipitated after standing in the fridge for 1 d. ^{51}V NMR ($CDCl_3$): δ = −670. — IR (KBr): $\tilde{\nu}$ = 1006 cm^{-1} (V=O). — ^1H NMR ($CDCl_3$): δ = 0.87 (m, 6H, CH_3), 1.81 (sparsely structured, br. m, 1H, CH), 4.70 (m, 2H, CH_2), 7.29 (m, 26H, Ph). As evidenced by ^{51}V-NMR spectroscopy, the product contained ca. 10% of $V(OiBu)_2OCPh_3$ (δ = −624). The main product in the supernatant hexane solution was $VO(OiBu)_3$ (δ = −604 in hexane). — (d) 2.80 g (15 mmol) of 1-dodecanol was dissolved in 50 ml of benzene and the solution heated to the boiling point. 10 ml of this solution was distilled off in order to remove azeotropically residual amounts of water. 1.01 g (5 mmol) of $VO(OEt)_3$, dissolved in 10 ml of benzene, was then added and the reaction mixture refluxed for 8 h. The solvent was removed in vacuo. The remaining solid was washed twice with 5 ml of hexane to yield a light yellow, crystalline powder of $VO(OC_{12}H_{25})_3$. Yield 2.90 g (93%).

$C_{36}H_{75}O_4V$ (622.9) Calcd. C 69.41 H 12.14 V 8.18
Found C 69.33 H 12.12 V 8.19

Esters with Functionalized Alcohols

$VO(OiBu)_2O(CH_2)_8OH$: 14.62 g (0.1 mol) of 1,8-octanediol dissolved in 300 ml of THF was treated with 20 ml of a 2.5 M hexane solution of butyllithium (3.2 g LiBu; 0.1 mol). After stirring the mixture overnight the white monolithium salt of octanediol was filtered off, washed with hexane, and dried. Yield 11.45 g (74%). IR (KBr): $\tilde{\nu}$ = 3333 cm^{-1} (OH). 670 mg (4.4 mmol) of $LiO(CH_2)_8OH$ was dissolved in 50 ml of CH_2Cl_2 and treated dropwise with a solution of 1.094 g (4.4 mmol) of $VO(OiBu)_2Cl$ in 20 ml of CH_2Cl_2. After stirring for 20 h and separation of small amounts of decomposition products by filtration, the solvent was removed in vacuo to yield a viscous, yellow oil which solidified at 2°C and remained solid when again warmed to room temp. Yield 1.34 g (3.8 mmol; 85%). — IR (KBr): $\tilde{\nu}$ = 3335 cm^{-1} (OH), 1007 (V=O).

$C_{16}H_{35}O_5V$ (358.4) Calcd. C 53.62 H 9.84 V 14.21
Found C 53.20 H 9.84 V 14.31

With [D_4]methanol, complete conversion to the trimethyl ester $VO(OCD_3)_3$ occurs. — ^{51}V NMR ([D_4]methanol): δ = −552.

$VO(OiBu)_2O(CH_2)_6NH(FMOC)$ (FMOC = 9-fluorenylmethyleneoxycarbonyl)

Method I: 1.0 g (8.5 mmol) of 6-amino-1-hexanol dissolved in 50 ml of water was added dropwise within 60 min to a solution of 2.4 g (9.2 mmol) of FMOC–Cl in 100 ml of dioxane. After stirring

for an additional hour, the dioxane was removed in vacuo. White (FMOC)NH$(CH_2)_6$OH precipitated which was filtered off, washed several times with H_2O and hexane, and dried under vacuum. The correct product composition was confirmed by IR spectroscopy (KBr): $\tilde{\nu}$ = 1689 cm^{-1} [C=O (amide I); compare ν(C=O) = 1768 in FMOC—Cl], 1528 [C=O (amide II)], 1063 (C—O).

0.70 g (2.07 mmol) of *N*-protected aminohexanol was dissolved in 50 ml of THF and treated with 0.506 g (2.07 mmol) of VO(O*i*Bu)$_2$Cl. A red solution formed, which became yellow when NH_3 was passed over the reaction mixture. At the same time, a white precipitate of $[NH_4]Cl$ (by IR) formed. The bands for amide I and II were still present, confirming that the amino group was still protected. Removal of THF yielded the ester as a uniform, yellow powder. Yield 1.07 g (95%). — IR (KBr): $\tilde{\nu}$ = 3325 cm^{-1} (NH), 1690 (amide I), 1541 (amide II), 1007 (V=O).

$C_{29}H_{42}NO_6V$ (551.6) Calcd. C 63.14 H 7.68 N 2.54 V 9.24
Found C 63.07 H 7.75 N 2.55 V 9.20

Method II: A solution of 0.72 g (2.51 mmol) of VO(O*i*Bu)$_3$ in 40 ml of THF was heated to reflux. To this boiling solution a THF solution containing 0.85 g (2.51 mmol) of FMOC-protected aminohexanol was added within 1 h. After 3 h, the dark yellow solution was allowed to stand at 0°C overnight. Removal of the organic solvents in vacuo yielded a dark, yellow oil which solidified on treatment with hexane. The yellow solid was filtered off, washed several times with hexane to remove unreacted triisobutyl ester, and dried under vacuum. A product with the same spectral properties and very similar analytical results as noted in method I was obtained. Yield: 0.28 g (25%).

VO(OiBu)$_2$(CH$_2$)$_6$NH$_2$: 240 mg (0.44 mmol) of VO(OiBu)$_2$O(CH$_2$)$_6$NH(FMOC), dissolved in 20 ml of THF, was treated with 37 mg (43 µl; 0.44 mmol) of piperidine. The solution, which immediately turned brown, contained the desired product with the amino group deblocked [$\delta(^{51}V)$ = −569] and a byproduct (−491) in a ratio of 5:1. After stirring for 10 min, the THF was evaporated. From the pasty, brown residue, organic products formed according to eq. (3) (see above) and the byproduct were extracted with hexane by stirring at room temp. for 10 h, leaving a light brown powder of VO(O*i*Bu)$_2$O(CH$_2$)$_6$NH$_2$. — ^{51}V NMR ($CDCl_3$): δ = −556. — IR (KBr): $\tilde{\nu}$ = 3400 cm^{-1} (NH_2), 1058 (CO), ca. 1020 (sh, V=O); δ = 1539 cm^{-1} (NH_2).

$C_{14}H_{32}NO_4V$ (329.35) Calcd. C 51.06 H 9.79 N 4.25 V 15.47
Found C 52.0 H 10.1 N 4.0 V 14.8

Reactions with HO—C$_6$H$_4$—X, X = 4-CN and 4-NH(FMOC): Treatment of an equimolar mixture of 4-hydroxybenzonitril and VO(O*i*Bu)$_2$Cl in THF with NH_3 gave a solution from which, after filtration, a brown pasty product was recovered. Extraction with hexane yielded a dark red solution and, after removal of the hexane, a red brown oil with the characteristics of VO(O*i*Bu)$_2$OC$_6$H$_4$CN. — IR (hexane): $\tilde{\nu}$ = 2234 cm^{-1} (CN), 1014 (V=O), no ν(OH). — ^{1}H NMR ($CDCl_3$): δ = 0.93 and 1.01 (12H, CH_3), 2.03 (nonet, J = 7 Hz, 2H, CH), 4.83 and 4.91 (4H, CH_2), 7.15, 7.26, 7.50 and 7.61 (t indicated, 4H, aromatic protons). — The same product was also obtained from a re-esterification between VO(O*i*Bu)$_3$ and HOC$_6$H$_4$CN.

The reaction of 1.19 g (3.6 mmol) of FMOC-protected 4-aminophenol [prepared from 2.58 g (0.01 mol) of FMOC—Cl and 1.09 g (0.01 mol) of aminophenol in 50 ml of dioxane] with 0.89 g (3.6 mmol) of VO(O*i*Bu)$_2$Cl in THF yielded, after treatment with NH_3, filtration, and evaporation of the solvent, a brown solid, consisting of two components with $\delta(^{51}V)$ = −597 (main product) and −578. Extraction with $CHCl_3$ led to an enrichment of the main product, which showed the characteristics of VO(O*i*Bu)$_2$OC$_6$H$_4$NH$_2$. — IR (KBr): $\tilde{\nu}$ = 3342 and 3282 cm^{-1} (NH_2), 982 (V=O). = ^{1}H NMR ($CDCl_3$): δ = 0.97 and 1.05 (14H, CH_3), 2.06 (nonet, J = 6.5 Hz, 2H, CH), 4.80 and 4.88 (5H, CH_2), 6.09 (2H, NH_2), m$_c$ 7.39 and 7.70 (5H, aromatic).

VOCl$_2${O$_2$C(CH$_2$)$_5$CO$_2$H}: 1.60 g (10 mmol) of pimelic acid (1,7-heptanedioic acid) was dissolved in 50 ml of CH_2Cl_2. 1.73 g (0.942 ml; 10 mmol) of $VOCl_3$ was added dropwise and with stirring, and the solution was refluxed for 3 h. To remove HCl, N_2 was passed through the reaction mixture. The solvent was evaporated in vacuo and unreacted $VOCl_3$ extracted with hexane. The residue, consisting of VOCl$_2${O$_2$C(CH$_2$)$_5$CO$_2$H} and unreacted pimelic acid, was dissolved in 10 ml of THF. Addition of 1 ml of hexane and standing in the refrigerator for 3 d resulted in a practically complete precipitation of the acid. An almost pure product was obtained by evaporation of the solution to dryness. Yield 0.90 g (33%). — IR (KBr): $\tilde{\nu}$ = 1701 (sh at ca. 1650) cm^{-1} (C=O), 993 (V=O).

VO(OiBu)$_2${O$_2$C(CH$_2$)$_5$C(O)OMe}: 16.01 g (0.10 mol) of pimelic acid, 3.2 g (0.1 mol) of methanol, and 1 ml of concd. H_2SO_4 in 75 ml of CCl_4 was refluxed for 10 h. Removal of the solvent yielded a colourless liquid, which was distilled under high vacuum (b.p. 95—98°C). Yield 6.1 g (35%) of the monomethyl ester of pimelic acid. 0.50 g (2.8 mmol) of the ester was dissolved in 40 ml of THF. 0.70 g (2.8 mmol) of VO(O*i*Bu)$_2$Cl was added and the mixture treated with NH_3, whereupon the originally dark red solution turned yellow and $[NH_4]Cl$ precipitated. To complete the separation of ammonium chloride, the mixture was allowed to stand in the fridge for 2 h. Filtration and removal of the solvent afforded a viscous, red brown oil which dissolved in hexane (yellow) and THF (dark brown). — IR (neat film): $\tilde{\nu}$ = 1740 cm^{-1} [MeO*CO*], 1658 (coord. −CO_2), 1007/993 (V=O).

$C_{16}H_{31}O_7V$ (386.35) Calcd. C 49.74 H 8.09 V 13.18
Found C 49.90 H 8.22 V 12.98

The corresponding isopropyl compound VO(O*i*Pr)$_2${O$_2$C(CH$_2$)$_5$C(O)Me} [$\delta(^{51}V)$ = −621] was prepared by refluxing 1.55 g (8.91 mmol) of pimelic acid monomethyl ester and 2.17 g (8.91 mmol) of VO(O*i*Pr)$_3$ in 25 ml of CH_2Cl_2 for 20 h. The compound was obtained in a mixture with VO(O*i*Pr)$_3$ [$\delta(^{51}V)$ = −631; product:starting compound = 7:1]; no attempts were undertaken to separate the two components.

CAS Registry Numbers

$VOCl_3$: 7727-18-6 / V_2O_5: 1314-62-1 / VOCl$_2$(O*i*Pr): 1636-01-7 / VO(O*i*Pr)(OCPh$_3$): 134939-05-2 / VOCl$_2$(OC$_8$H$_{17}$): 89932-59-2 / VO(O*i*Bu)(OCPh$_3$)$_2$: 134939-20-1 / VO(O*i*Bu)$_2$OCPh$_3$: 134967-14-9 / VO(OEt)$_3$: 1686-22-2 / VO(O*i*Bu)$_2$O(CH$_2$)$_8$OH: 134939-06-3 / VO(OCD$_3$)$_3$: 134939-07-4 / VO(O*i*Bu)$_2$OC$_6$H$_4$NH$_2$: 134939-08-5 / VO(O*i*Bu)$_2$O(CH$_2$)$_6$NH(FMOC): 134939-09-6 / VO(O*i*Bu)$_2$O(CH$_2$)$_6$NH$_2$: 134939-10-9 / VO(O*i*Bu)$_2$OC$_6$H$_4$CN: 134939-11-0 / VOCl$_2${O$_2$C(CH$_2$)$_5$CO$_2$H}: 134939-19-8 / VO(O*i*Bu)$_2${O$_2$C(CH$_2$)$_5$C(O)OMe}: 134939-12-1 / VO(O*i*Pr)$_2${O$_2$C(CH$_2$)$_5$C(O)}: 134939-13-2 / VOCl$_2$(OCPh$_3$): 134939-14-3 / VOCl(O*i*Pr)$_2$: 1636-00-6 / VOCl(O*i*Bu)$_2$: 68114-30-7 / VOCl(*tert*-pentyloxy)$_2$: 134939-15-4 / VOCl(O-*cyclo*-C$_5$H$_9$)$_2$: 134939-16-5 / VOCl(OC$_8$H$_{17}$)$_2$: 60951-07-7 / VO(O*i*Bu)$_3$: 19120-62-8 / VO(3-methylbutyloxy)$_3$: 26496-12-8 / VO(OC$_{12}$H$_{25}$)$_3$: 134939-17-6 / VO(O-*cyclo*-C$_5$H$_9$)$_3$: 134939-18-7 / VO(O*i*Pr)$_3$: 5588-84-1 / VO(*tert*-pentyloxy)$_3$: 25611-91-0

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