The Four-centre Reactions of Alkanol–Alkoxide Negative Ions with Alkyl Ethers and Orthoacetates. An Ion Cyclotron Resonance Study

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Alkoxide–alkanol negative ions $[R^1O^- \cdots HOR^2]$ react with carbon ethers (*e.g.*, Me_3COR^3) by the four-centre reactions $[R^1O^- \cdots HOR^2] + Me_3COR^3 \longrightarrow [R^2O^- \cdots HOR^3] + Me_3COR^1$, and $[R^1O^- \cdots HOR^2] + Me_3COR^3 \longrightarrow [R^1O^- \cdots HOR^3] + Me_3COR^2$. The former reaction predominates when $R^1 < R^2$. In the case of di- and tri-ethers, the four-centre reaction can, in principle, compete with the alternative six-centre reaction. For example, for $Me_2C(OR^3)_2$, $[R^1O^- \cdots HOR^2] + Me_2C(OR^3)_2 \longrightarrow Me_2C{=}O + R^1OR^3 + [R^2O^- \cdots HOR^3]$. Evidence is presented which shows that the six-centre reaction does not occur.

Alkoxide–alkanol negative ions $[R^1O^- \cdots HOR^2]$ react with alkoxysilanes Me_3SiOR^3 in the gas phase in two ways. The stable ions $[M + R^1O^-]$ and $[M + R^2O^-]$ are formed and it is probable that these have trigonal bipyramidal geometry. In addition, an 'alkoxide exchange' reaction (1) is observed; the smaller alkoxide R^1O^- reacting at silicon, the larger alkanol R^2OH becoming part of the new alkanol–alkoxide ion.[1]

$$[R^1O^- \cdots HOR^2] + Me_3SiOR^3 \longrightarrow [R^2O^- \cdots HOR^3] + Me_3SiOR^1 \quad (1)$$

Dewar and Healy[2] have recently claimed that the difference in S_N2 reactivity at tetrahedral carbon and silicon can be rationalised solely by the sizes of the central atoms, *i.e.*, the trigonal bipyramidal structure formed during the reaction is a transition state for carbon and a reactive intermediate in silicon reactions. Our interest in this area[3] has led us to consider whether the reaction shown in (1) can be extended to carbon systems. The silicon reaction (1) is certainly aided by the ready formation of stable trigonal intermediates, and we believe the overall mechanism is as shown in Figure 1 (*cf.* ref. 3). In contrast, the corresponding trigonal bipyramidal species in any analogous carbon reaction will not be reactive intermediates; the transition state may perhaps be of higher energy than reactants in this case. A hypothetical mechanism, based partly on previous work with carbon systems,[4] is shown in Figure 2.

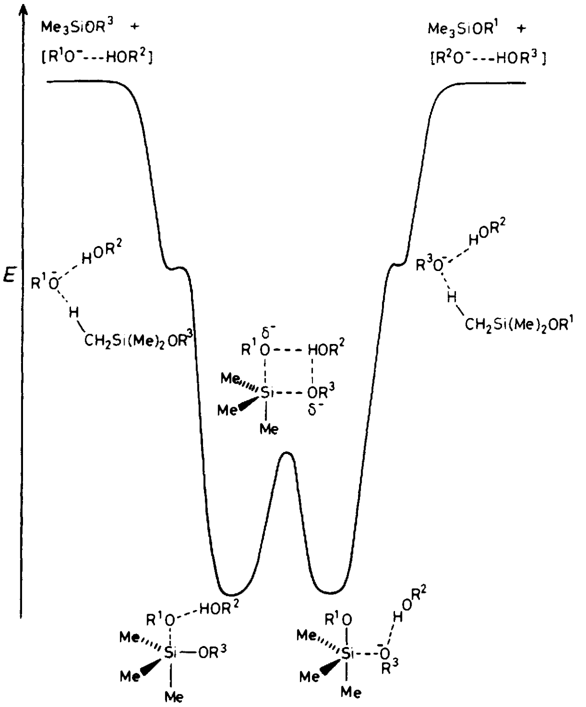


Figure 1. Suggested mechanistic pathway for the $[R^1O^- \cdots HOR^2]$–Me_3SiOR^3 reaction

In this paper we address the following questions. (*i*) Do reactions $[R^1O^- \cdots HOR^2] + Me_3COR^3 \longrightarrow Me_3COR^1 + [R^2O^- \cdots HOR^3]$ ($R^1 < R^2$) occur for carbon ether systems? (*ii*) If such reactions do occur, is the mechanism similar (in general terms) to that shown in Figure 2?

Results and Discussion

Alkanol–alkoxides used as primary reactant ions in this study were formed by the Riveros reaction $R^1O^- + HCO_2R^2 \longrightarrow [R^1O^- \cdots HOR^2] + CO$;[4–6] a three-centred transition state for this reaction is predicted by *ab initio* calculations.[7] The species $[MeO^- \cdots HOMe]$ is unsymmetrical in the ground state.[8,9] The barrier for the interconversion $[MeO^- \cdots$

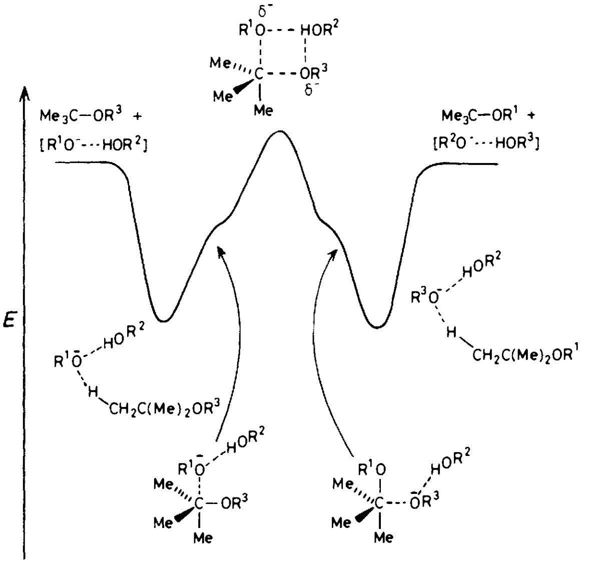


Figure 2. Suggested mechanistic pathway for the $[R^1O^- \cdots HOR^2]$–Me_3COR^3 reaction

Table 1. Reactions of $[R^1O^- \cdots HOR^2]$ with carbon ethers[a]

HCO–OR^1	R^{2}ONO	Substrate	$[R^2O^-]$	$[R^3O^-]$	$[R^1O^- \cdots HOR^2]$	$[R^2O^- \cdots HOR^3]$	$[R^1O^- \cdots HOR^3]$
Me	Pr	Me_3COEt	88		100	3	
Me	Pr	$MeCH(OEt)_2$	93		100	7	
Me	Pr	$Me_2C(OEt)_2$	80		100	6	
Et	Et	$MeC(OMe)_3$	100	27	14	1[b]	b
Pr	Pr	$MeC(OMe)_3$	100	7	97	4[b]	b
Pr^i	Pr^i	$MeC(OMe)_3$	100	24	30	5[b]	b
Me	Me	$MeC(OEt)_3$	100	2	85	80[b]	b
Me	Me	$CD_3C(OEt)_3$	100	5	80	72[b]	b
Me	Pr	$MeC(OCH{=}CH_2)_3$	100	7	84	3	
Et	Et	$MeC(OBu)_3$	100	8	39	5[b]	b
Et	Pr^i	$MeC(OBu)_3$	65	5	100	9	7
CD$_3$	Pr	$EtC(OEt)_3$	100	11	34	8	7
Pr	Pr	$Pr^iC(OMe)_3$	100	3	30	1[b]	b
Pr	Pr	$Bu^tC(OMe)_3$	100	5	67	2[b]	b

[a] We have also studied a large number of orthoformates. They give very similar results to those reported (above) for orthoacetates. However, orthoformates decompose (to a minor extent) to formates in the inlet system, and the occurrence of Riveros reactions with the formate complicates interpretation of the i.c.r. spectra. Orthoacetates also decompose slightly to acetates (see *e.g.* Figure 2) but the ion formed $[^-CH_2CO_2R^3]$ does not affect interpretation in these cases. [b] Since $R^1 = R^2$ in this case, $[R^2O^- \cdots HOR^3]$ is the same as $[R^1O^- \cdots HOR^3]$.

HOMe] $\longrightarrow$ $[MeOH \cdots {}^-OMe]$ is computed to be of the order of 2 kJ mol^{-1}, a value consistent with the experimental observation that $[CD_3O^- \cdots HOMe]$ reacts as a 'symmetrical' reagent.[9] For purely logistic purposes in this paper we will represent unsymmetrical alkanol–alkoxides as $[R^nO^- \cdots HOR^m]$ where $n < m$.

Ion cyclotron resonance (i.c.r.) spectra were measured routinely with a Dynaspec ICR 9 spectrometer equipped with a three-section cell. In particular cases (indicated in the text) spectra were determined with a trapped-ion i.c.r. spectrometer. Full details are given in the Experimental section.

The data in Table 1 show that the 'alkoxide exchange' reaction does occur for carbon ethers. The reaction is much less pronounced than that observed for the corresponding silanes.[1] The reaction is minor for mono- and di-ethers but becomes pronounced for certain orthoacetates. For example, in the $[MeO^- \cdots HOMe]$–$MeC(OEt)_3$ system, the reactant $[MeO^- \cdots HOMe]$ and product $[MeO^- \cdots HOEt]$ ions are of comparable abundance. With elaboration of the substituents on either the alkanol–alkoxide or substrate, the abundance of the product peak decreases dramatically. The steric and kinetically favoured product $[R^2O^- \cdots HOR^3]$ is formed exclusively from unsymmetrical alkanol–alkoxides $[R^1O^- \cdots HOR^2]$ ($R^1 < R^2$) in some systems, in others both products, $[R^2O^- \cdots HOR^3]$ and $[R^1O^- \cdots HOR^3]$, are formed, with the former predominating. This feature is illustrated in Figures 3 and 4 for the $[CD_3O^- \cdots HOPr]$–$CD_3C(OEt)_3$ system.

There is now an important problem to be resolved. In the case of $[R^1O^- \cdots HOR^2]$–Me_3SiOR^3 systems there is no doubt that the reaction ultimately involves a four-centred transition state although there could be debate concerning the details of the mechanism shown in Figure 1. In the case of the carbon di- and tri-ethers two possibilities exist, *viz.*, a four-centre mechanism based on that shown in Figure 2, or the six-centre mechanism shown in sequence (2).

Our approach to this problem was to investigate substrate molecules which (in our view) had a reasonable probability of reacting *via* a six-centre mechanism, and secondly, substrate molecules which are restricted to the four-centre mechanism. The clue to how this problem could be solved lies in a result obtained in our earlier silicon work. Sequence (3) operates when alkanol–alkoxides react with cyclic silyl diethers; the smaller alkoxide reacts at silicon, the larger alkanol solvates the resulting alkoxide in an intramolecular reaction.[1] This reaction should be capable of extension to carbon systems. For example, the six-centre reaction shown in sequence (4) should be most

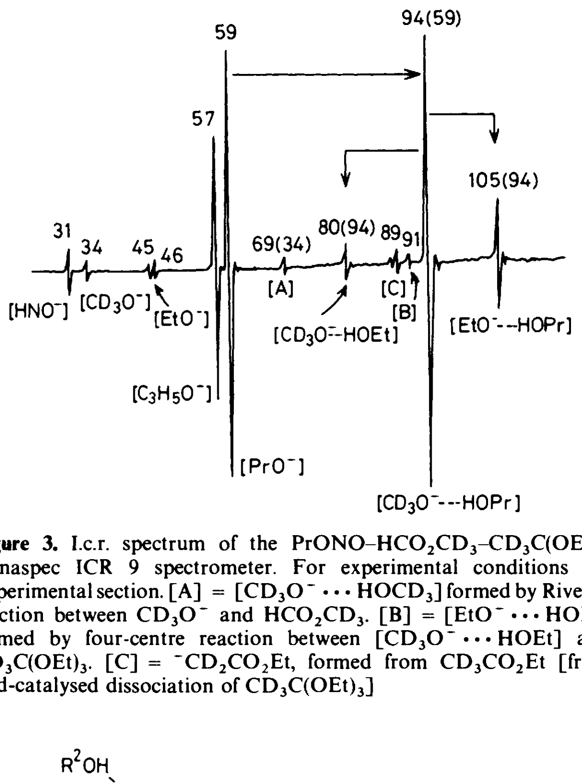
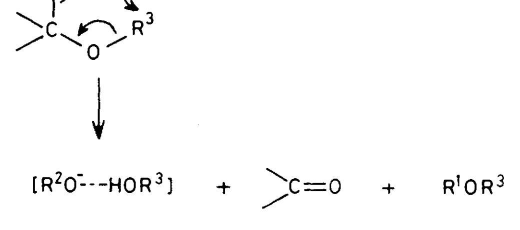


Figure 3. I.c.r. spectrum of the PrONO–HCO_2CD_3–$CD_3C(OEt)_3$. Dynaspec ICR 9 spectrometer. For experimental conditions see Experimental section. [A] = $[CD_3O^- \cdots HOCD_3]$ formed by Riveros reaction between CD_3O^- and HCO_2CD_3. [B] = $[EtO^- \cdots HOEt]$ formed by four-centre reaction between $[CD_3O^- \cdots HOEt]$ and $CD_3C(OEt)_3$. [C] = $^-CD_2CO_2Et$, formed from CD_3CO_2Et [from acid-catalysed dissociation of $CD_3C(OEt)_3$]



(2)

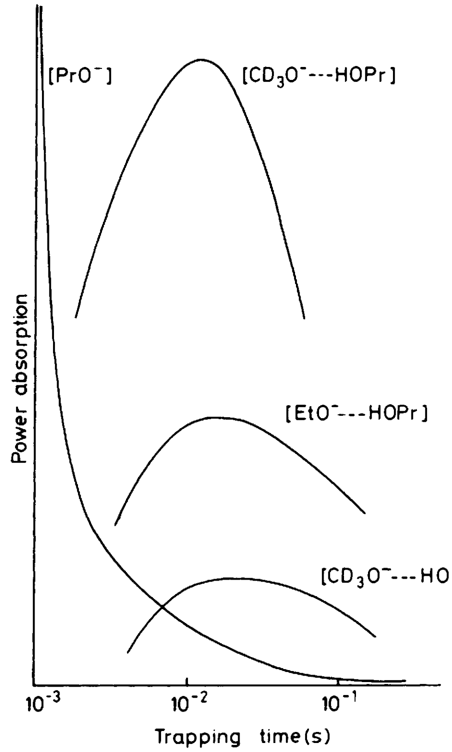
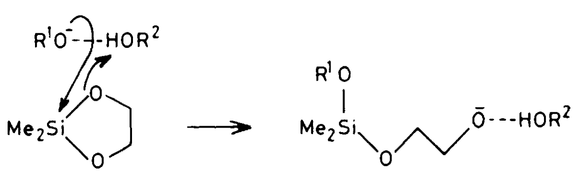
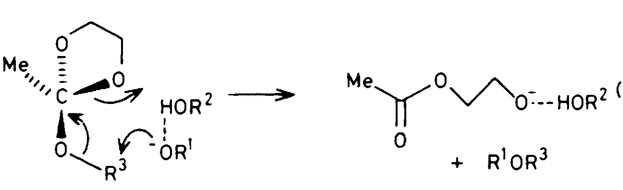


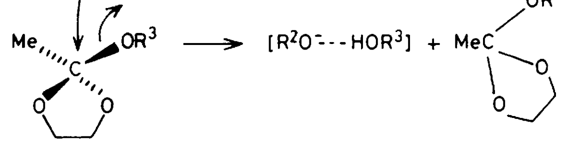
Figure 4. Relative power absorptions of the ions [PrO⁻], [CD_3O^- ··· HOPr], [EtO^- ··· HOPr], and [CD_3O^- ··· HOEt] as a function of trapping time for the system PrONO–HCO_2CD_3–$CD_3C(OEt)_3$ (*cf.* Figure 3). Trapped-ion spectrometer. For experimental conditions see Experimental section

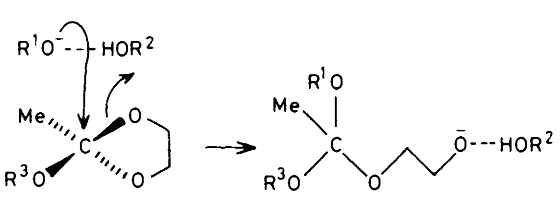

(3)

favourable when R^3 is particularly electrophilic (*e.g.*, for R^3 = CH_2CF_3 or CH_2-cyclo-C_3H_5). In contrast, sequence (4) should not occur when R^3 is $CH{=}CH_2$.[10] In this case, one or both of the four-centre reactions shown in sequences (5) and (6) should occur. The i.c.r. spectra of appropriate systems are listed in Table 2.


(4)

The data contained in Table 2 show that the six-centre reaction (4) does not occur even in favourable cases (*i.e.*, for R^3 = CH_2CF_3 or CH_2-cyclo-C_3H_5). We have additionally examined these systems in the trapped-ion i.c.r. instrument using ion-trapping times of up to 0.5 s. No six-centre reactions were detected, but reaction (5) was observed in all cases. In this context it is of interest to note that MeO^- reacts as shown in sequence (7); even in this case there is no detectable S_N2 attack at the methylene group to form $MeCO_2(CH_2)_2O^-$. At this stage it was probably unnecessary to investigate systems that we designed in such a way that the six-centre reaction cannot occur. Nevertheless, we studied the possibility of the occurrence of reactions (4)—(6) when R^3 = vinyl. As expected, only reaction (5) was noted (Table 2). Thus in all cases studied, four-centre reaction (5) occurs to the exclusion of four-centre reaction (6). Even so, the reaction is not normally specific as shown in (5); the major product does correspond to [R^2O^- ··· HOR^3], but the reactant alkanol–alkoxide may also add in the opposite sense to form [R^1O^- ··· HOR^3] as the minor product.


(5)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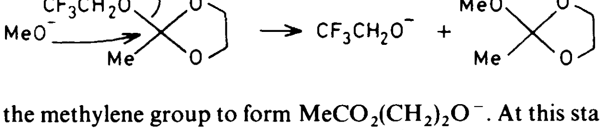

(7)

Thus we believe that the reactions described in this paper proceed through a four-membered transition state, but is the intimate mechanism of the reaction that shown in Figure 2? In our studies of [RO^- ··· DOR]–>CH–CO– systems we were able to demonstrate, experimentally, attachment of the nucleophile at hydrogen because of H–D equilibration which we rationalised (using *ab initio* calculations) by the intermediacy of symmetrical disolvated species.[9,11] In principle, similar intermediates could be formed in carbon ether systems. If we could observe H–D equilibration [*e.g.*, (**i**)$\rightleftharpoons$(**ii**)$\rightleftharpoons$(**iii**)] for the reaction between [MeO^- ··· HOMe] and $CD_3C(OEt)_3$, this would support initial attachment of the nucleophile to hydrogen (as shown in Figure 2). However, (**ii**) will be more stable than (**i**) and the reaction may not be an equilibrium. If so, this may preclude the channel to the four-centre reaction. In the event, no H–D equilibration occurs for the [MeO^- ··· HOMe]–

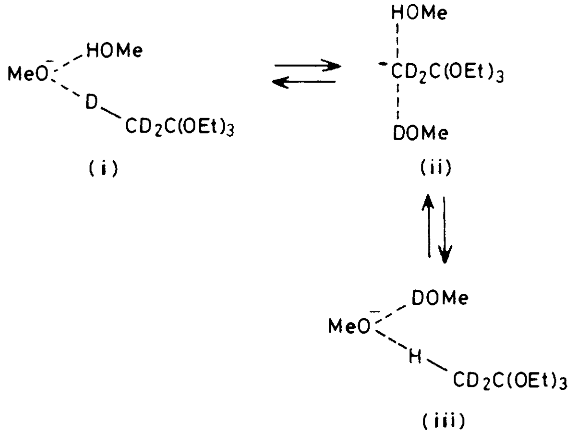
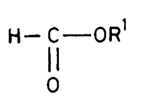
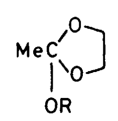


Table 2. Reactions of $[R^1O^- \cdots HOR^2]$ with alkoxymethyl-1,3-dioxolanes

 $HC(=O)OR^1$	R^2ONO		$[R^2O^-]$	$[R^3O^-]$	$[R^1O^- \cdots HOR^2]$	$[R^2O^- \cdots HOR^3]$	$[R^1O^- \cdots HOR^3]$
CD_3	Pr	Me	100	28	25	8	7[a]
Me	Me	CH_2CF_3	21	100	39	21[b,c]	c
Me	Pr	CH_2CF_3	68	100	23	2	3[d]
Me	Et	CH_2-cyclo-C_3H_5	100	51	52	10	15[e]
Pr	Pr	$-CH{=}CH_2$	100	8	60	19[c]	c
Et	Pr	$-CH{=}CH_2$	100	25	30	9	

[a] Cyclotron ejection experiments show that this ion is formed exclusively by the Riveros reaction $MeO^- + HCO_2CD_3 \longrightarrow [MeO^- \cdots HOCD_3] + CO$. [b] This ion is produced mainly by the Riveros reaction $CF_3CH_2O^- + HCO_2Me \longrightarrow [MeO^- \cdots HOCH_2CF_3] + CO$; it is also formed from $[MeO^- \cdots HOMe]$ by the four-centre reaction [*cf.* sequence (5)]. [c] In this case $R^1 = R^2$. [d] This ion is *mainly* formed by the Riveros reaction between $CF_3CH_2O^-$ and HCO_2Me. It is also formed by the *minor* four-centre reaction $[MeO^- \cdots HOPr] \longrightarrow [MeO^- \cdots HOCH_2CF_3]$. [e] This ion is *mainly* formed by the Riveros reaction between cyclo-$C_3H_5CH_2O^-$ and HCO_2Me. It is also formed by the *minor* four-centre reaction $[MeO^- \cdots HOEt] \longrightarrow [MeO^- \cdots HOCH_2$-cyclo-$C_3H_5]$.

$CD_3C(OEt)_3$ reaction (see Table 1 and *cf.* Figure 3), only $[MeO^- \cdots HOEt]$ is formed. Thus we have no experimental evidence to confirm or refute the intermediacy of the H-bonded species shown in Figure 2. We believe that in the general case, nucleophilic attack at carbon is preceded by initial attachment at an 'acidic' hydrogen when the carbon in question bears an electronegative substituent.

Finally, the non-specificity (in most cases) of the reaction is explicable in terms of the relative barrier heights of the competing reactions. The major product $[R^2O^- \cdots HOR^3]$ (see Figure 2) is formed by reaction of the smaller alkoxide at the crowded carbon centre. Consequently, the barrier height for this reaction should be marginally smaller than that for addition in the reverse sense to form $[R^1O^- \cdots HOR^3]$.

Experimental

The i.c.r. spectra shown in Figure 3 and listed in Tables 1 and 2 were measured with a Dynaspec ICR 9 spectrometer equipped with a three-section cell. Spectra were obtained at 70 eV (primary negative ions formed by dissociative secondary electron capture). Other reaction conditions: $\omega_c/2\pi = 125.0$ kHz, total pressure of reactants in cell $= 2 \times 10^{-5}$ Torr ($R^2ONO = 5 \times 10^{-6}$ Torr, $HCO_2R^1 = 5 \times 10^{-6}$ Torr, carbon ether $= 1 \times 10^{-5}$ Torr), ion current in 10^{-10} A range, emission current 0.2 μA, and ion transit time 1×10^{-3} s. Precursor ions in reaction sequences were determined by the cyclotron ejection technique.

The trapped-ion spectrometer was built by R. L. Paltridge. The cell is based on a design originally developed by McIver[12] and is made of 316 polished stainless-steel plate (20 p.w.g.). Internal dimensions 2.5 × 2.5 × 9.0 cm; plates supported with 'Macor' machineable ceramic spacers. The filament mounting block is made of the same material. A grid of 316 stainless steel (40 mesh per inch) is mounted inside the filament-mounting block (1.0 mm from the filament and 1.5 mm from the filament side-plate). The cell was mounted in the vacuum chamber of a vacuum and magnet system based on the original design of the Dynaspec ICR 9 spectrometer. Signals were detected using a capacitance-bridge detector of a type originally due to McIver *et al.*[13] The observing frequencies are supplied by a Hewlett-Packard 3325A synthesizer.

Acetaldehyde diethyl acetal, 2,2-diethoxy propane, ethyl 2-methyl-2-propyl ether, trimethyl orthoacetate, triethyl orthoacetate, and triethyl orthopropionate are available commercially and were purified by distillation prior to use. Tributyl orthoacetate was prepared from trimethyl orthoacetate by butanol exchange.[14] 2-Methoxy-2-methyl-1,3-dioxolane was prepared by the method of Altona and van der Veek.[15] Trimethyl orthoisobutyrate and trimethyl orthopivalate were prepared by methanolysis of the appropriate nitrile.[16] All products were distilled using a 10 cm Vigreux column. Microanalyses were performed by the Australian Microanalytical Service, Melbourne.

$[1,1,1\text{-}^2H_3]$*Triethyl Orthoacetate*.—A mixture of ethyl-acetimino-$[^2H_3]$-ester hydrochloride[17] (2 g) and anhydrous ethanol (10 ml) was stirred under N_2 until the salt had dissolved. Anhydrous diethyl ether (20 ml) was then added, the solution was heated under reflux for 6 h, the suspension cooled to 0 °C, and filtered to remove ammonium chloride. The solid was washed with anhydrous diethyl ether (2 × 10 ml), and the combined filtrate was distilled to yield triethyl $1,1,1\text{-}[^2H_3]$-orthoacetate, b.p. 144—146 °C (1.95 g, 73% yield); $^2H_3 = 99\%$.

Trivinyl Orthoacetate.—1. *Tris-*(2-*chloroethyl*) *orthoacetate*. A mixture of 2-chloroethanol (15 g), trimethyl orthoacetate (7.6 g), and trifluoroacetic acid (1 ml) was heated under reflux at reduced pressure (5 cmHg) for 3 h. During this period, methanol (6 g) distilled from the reaction mixture. Sodium methoxide (0.5 g) in methanol (10 cm^3) was added, and fractional distillation of the mixture yielded tris-(2-chloroethyl) orthoformate, b.p. 155—156 °C at 13 mmHg[18] (14.5 g, 87% yield).

2. *Trivinyl orthoacetate*. To a suspension of sodium hydride [3.5 g (85% suspension in oil)] in anhydrous dimethoxyethane (10 ml) was added t-butanol (0.5 g) dropwise with stirring. Tris-(2-chloroethyl) orthoacetate (10 g) was added dropwise to the suspension with stirring over 0.5 h. The reaction mixture was heated under reflux for 2 h, excess of dimethoxyethane removed *in vacuo* (20 °C at 15 mmHg), diethyl ether (20 ml) and water (10 ml) were added cautiously and the two phases separated. The organic phase was washed with water (2 × 10 ml), dried (Na_2SO_4), excess of solvent removed *in vacuo* (15 °C at 15 mmHg) after some hydroquinone (50 mg) was added to reduce polymerisation. Distillation of the residue yielded trivinyl orthoacetate, b.p. 145—146 °C[19] (3.8 g, 64% yield).

2-*Vinyloxy*-2-*methyl*-1,3-*dioxolane*.—2-Vinyloxy-2-methyl-1,3-dioxolane was prepared from trivinyl orthoacetate by exchange with ethylene glycol.[20]

2-(2,2,2-*Trifluoroethoxy*)-2-*methyl*-1,3-*dioxolane*.—A mixture of 2-methoxy-2-methyl-1,3-dioxolane (1.5 g), 2,2,2-trifluoroethanol (2 g), and toluene-*p*-sulphonic acid (1 mg) was heated under reduced pressure (40 mmHg) with stirring for 3 h. Methanol (0.4 g) distilled from the reaction mixture. 2-(2,2,2-Trifluoroethoxy)-2-methyl-1,3-dioxolane (1.8 g, 76% yield) was obtained by fractional distillation, b.p. 138—139 °C (Found: C, 38.5; H, 5.1. $C_6H_9F_3O_3$ requires C, 38.7; H, 4.9%).

2-(2-*Cyclopropylmethoxy*)-2-methyl-1,3-*dioxolane*.—A mixture of 2-methoxy-1,3-dioxolane (8.5 g), 2-cyclopropylmethanol (5.2 g), and toluene-*p*-sulphonic acid (5 mg) was heated under reflux at reduced pressure (7 cmHg). Methanol (2.2 g) distilled from the reaction mixture. The residue was neutralised with methanolic sodium methoxide (2N), then distilled to yield 2-(2-cyclopropylmethoxy)-2-methyl-1,3-dioxolane, b.p. 104—105 °C at 25 mmHg. This compound decomposes on standing and gives unsatisfactory analytical results. When freshly distilled the compound is spectroscopically pure. ^{13}C N.m.r. (Bruker WP 80 instrument) δ($CDCl_3$) 121.6 (quaternary C), 67.2 (-O-$\mathit{C}H_2$-C_3H_5), 64.7 [-O-($\mathit{C}H_2)_2$-O-], 21.9 (CH_3), 10.7 (CH), and 2.95 p.p.m. [CH($\mathit{C}H_2)_2$].

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