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Journal of Molecular Catalysis A: Chemical 152 (2000) 187–200

JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL

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Heterogeneous liquid phase catalysis by metal (IV) phosphates of cyclic ether formation and a reverse Prins reaction

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Received 1 April 1999; received in revised form 14 June 1999; accepted 9 July 1999

Abstract

Catalysis of the formation of cyclic ethers from an unsaturated alcohol, 6-methylhept-5-en-2-ol, and of bicyclic ethers from 1,3-diols by metal (IV) phosphates has been investigated. Good yields were obtained. The diol, 1-(2-hydroxyethyl)cyclopentanol, was cyclised to form an oxetane ring, which is the intermediate in a reverse Prins reaction and provides an alternative to reaction through a cyclic five-membered ring. The reactivity of the metal (IV) phosphate catalysts can be contrasted to that of superacidic solvent systems containing fluorosulphuric acid.

Keywords: Catalysis; Diol; Dehydration; Cyclisation; Prins; Phosphates

1. Introduction

As part of current research into the specificity of metal (IV) phosphates for selective catalysis [1], their use as solid 'superacids' has been examined, specifically in the formation of mono- and bi-cyclic ethers from diols. The metal phosphates have been noted previously for their Brønsted and Lewis acid reactivity in simple acid-catalysed dehydration of monohydric alcohols. The reactions chosen for this investigation include some that were used earlier to probe carbocation behaviour in the superacidic medium of fluorosulphuric acid, in which there were only poorly nucleophilic counterions. Modern attempts to reduce the usage of solvents and environmentally adverse chemicals have seen a trend towards investigations into the use of heterogeneous catalysts as aids to liquid phase reactivity, the heterogeneous nature of the catalysts making them easy to remove and recover from reaction mixtures. It is shown in this work that some metal (IV) phosphates can be used as heterogeneous replacements for the liquid fluorosulphuric (super)acid and they also possess the extra advantage of

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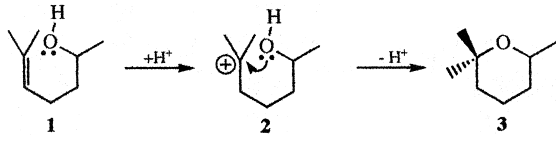
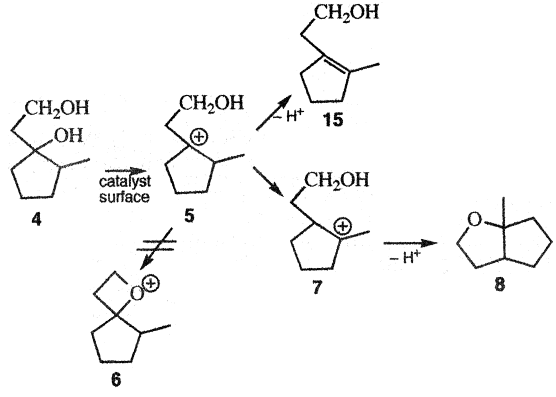
1381-1169/00/$ - see front matter
PII: S1381-1169(99)00296-4



Scheme 1.

the latter in having a poorly nucleophilic counterion. Further, the reactions considered here could be carried out conveniently in the absence of solvent and at modest temperatures.

One of the simplest methods of formation of a cyclic ether is to react a suitable unsaturated alcohol or diol with acid. Five- and six-membered rings are formed the most favourably during cyclisation; straightforward cyclisation to give larger and smaller rings is much less favourable and results in low or vanishingly small yields. The alcohols chosen for this study are known to form cyclic ethers. For an unsaturated alcohol, such as the heptenol **1** (Scheme 1), initial protonation of the double bond in superacid, followed by intramolecular nucleophilic attack on the resulting carbocation **2**, yields an ether **3**. Similarly, for a diol such as compound **4** (Scheme 2), protonation of one of the hydroxyl groups followed by its elimination as water leaves a carbocation **5**, which is difficult to attack by the second OH group because it would have to form a strained four-membered spiro ring system **6**. Instead, there is 1,2-rearrangement by transfer of hydrogen to give a new carbocation **7**, which can be intramolecularly attacked by the second hydroxyl so as to yield a five-membered ring ether **8**. The tertiary hydroxyl group is lost more readily than the primary. The poor nucleophilic nature of fluorosulphuric acid encourages cyclisation by not providing any alternative counterion for the carbocation centre shown in structures **2**, **5** and **7** (Schemes 1 and 2). In normal solution chemistry, tetrahydrofurans (five-membered ring ethers) are readily prepared from 1,4-diols in this manner [2] but, for most other 1,*n*-diols ($n = 3$, 5, 6, etc.), cyclisation to an ether proceeds only in low yields and consequently, the method is little used. In contrast, in superacidic media, cyclisation to ethers takes place much more readily and a wide range of mono- and bi-cyclic ethers has been prepared in this way [3]. However, this last reaction is of limited practical value because of technical difficulties in working with superacids. Since the metal (IV) phosphates have strongly acidic sites, it was considered possible that they could act as superacids by catalysing the formation of mono- and bi-cyclic ethers from acyclic precursors. Because such a cyclisation would be taking place on a solid catalyst surface rather than in the homogeneous medium used with the superacids, the reaction might be expected also



Scheme 2.

to be sensitive to the morphology of the surface and hence give greater selectivity than the previously investigated [3] solution phase reactions.

2. Experimental

^{1}H nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ on a Varian Gemini spectrometer at 300 MHz and ^{13}C spectra at 75 MHz, both with Me_4Si as internal standard. Infrared spectra were recorded on a Perkin Elmer 1320 instrument, solid samples in Nujol and liquid samples as neat films. GC analyses were carried out on a Dani 3800 chromatographic instrument with flame ionisation detection and a 25 mm × 0.03 mm capillary column coated with either OV351 or FFAP. Mass spectra were obtained on a Fisons Trio 1000 spectrometer, using 70 V electron ionization.

2.1. Preparation of metal (IV) phosphates — amorphous zirconium phosphate, ZrPA [4]

Phosphoric acid (23.3 g) in water (476 ml) was added with stirring to a solution of $ZrOCl_2 \cdot 8H_2O$ (22.5 g) in water (140 ml) at room temperature. The resulting gel was washed with large amounts of distilled water by decantation until the solution reached pH 3.5. The resulting material was filtered or, better, centrifuged and dried at 100°C for 18 h to give amorphous zirconium phosphate (21.3 g).

2.1.1. Amorphous titanium phosphate, TiPA [5]

Aqueous hydrochloric acid (2 M; 215 ml) containing titanium chloride (7.23 ml) was added slowly to phosphoric acid (1.25 M; 200 ml) with stirring at room temperature. After 24 h, the resulting precipitate was filtered off, washed with water to pH 3.5, and dried over P_2O_5 to give amorphous titanium phosphate (8 g).

2.1.2. Amorphous tin phosphate, SnPA

An aqueous solution of Na_2HPO_4 (0.6 M; 100 ml) was dropped over a period of 15 min into a stirred aqueous solution of $SnCl_4$ (0.3 M; 100 ml) at room temperature. The resulting gel was filtered off, washed with distilled water to pH 3.5 and then dried at 100°C for 18 h to yield amorphous tin phosphate (7.7 g).

2.2. Crystalline metal (IV) phosphates — ZrPC, TiPC, SnPC [6,7]

These were all prepared similarly by refluxing the first prepared amorphous phosphate in an excess of 10 M aqueous phosphoric acid for some time (weight of amorphous phosphate; volume of phosphoric acid solution; number of hours of reflux; yield): zirconium (10 g, 500 ml, 100 h, 9.2 g), titanium (8 g, 320 ml, 50 h, 7.5 g), tin (5.4 g, 250 ml, 100 h, 5.0 g). Each crystalline product was filtered off, washed with distilled water to pH 3–3.5 and then dried over P_2O_5. It was checked for crystallinity by X-ray diffraction.

2.3. Calcination of metal (IV) phosphates

Samples of the phosphates were heated in a muffle furnace in air for 8 h at 200°C, 300°C or 400°C, as indicated in the later tables. After cooling the samples to room temperature, they were stored over P_2O_5 in a desiccator (ZrPC300, ZrPC400, SnPC200, SnPC400).

2.4. Copper ion-exchanged zirconium phosphate — ZrPC / Cu

Crystalline zirconium phosphate (0.7 g) was heated to reflux temperature in a solution of copper acetate (0.56 M; 43 ml) for 16 h and was then filtered off, washed well with distilled water and dried in air at 100°C for 18 h.

2.5. Measurement of acidity

The total acidity and the acid strength distributions in the metal phosphates were determined by titration with butylamine [4,6,7]. Each sample was first dried for 18 h at 105°C. For the titration, the phosphate (0.2 g) was suspended in petroleum ether (bp 60/80°C, previously dried over KOH pellets and distilled; 2 ml) and titrated against butylamine (0.25 M) in petroleum ether (bp 60/80°C), using the following indicators: benzalacetophenone ($pK_a = -5.6$), dicinnamalacetone ($pK_a = -3.0$), 4-dimethylaminoazobenzene ($pK_a = +3.3$), methyl red ($pK_a = +4.8$). Results are listed in Table 1.

2.6. Synthesis of organic substrates

The alkenol, 6-methylhept-5-en-2-ol **1** and the diols, 2-methyl-1-(2-hydroxyethyl)cyclopentanol **4** and 2,2-dimethyl-1-(2-hydroxyethyl)cyclohexanol **9**, 1-(2-hydroxyethyl)cyclopentanol **10**, and 1-(2-hydroxyethyl)cyclohexanol **11** were prepared according to literature methods [3]. The alkenol, 1-(2-hydroxyethyl)cyclohexene **12**, was prepared by a published route [8]. All these compounds gave satisfactory elemental analyses, boiling points, ^{1}H NMR and mass spectra and showed single peaks on gas chromatography.

2.7. Cyclisation and dehydration of substrate alcohols by metal (IV) phosphates

Unless stated otherwise, reactions were carried out with a mixture consisting of the requisite metal (IV) phosphate (0.135 g), the requisite alkenol or 1,3-diol (5.5 mmol) which was heated to reflux for 15 min (and an internal standard, either dodecane or hexadecane (3.4 mmol) was used and the course of each reaction was monitored by removing small samples for GC).

Table 1
Acidities of metal (IV) phosphates

Catalyst[a]	Acidity (mmol g^{-1})		
	$H_0 \leq 4.8$	$H_0 \leq 3.3$	$H_0 \leq -3.0$
ZrPC	5.8	1.8	0
TiPC	1.5	0.3	0
SnPC	6.0	5.8	0
ZrPC300	6.3	6.3	0
ZrPC400	7.6	7.6	0
ZrPC/Cu	0.1	0	0

[a] ZrPC = zirconium phosphate crystalline dried at 20°C over P_2O_5; TiPC, SnPC are the titanium and tin analogues; ZrPC300 and ZrPC400 are the same as ZrPC, but calcined at 300°C and 400°C, respectively; ZrPC/Cu is copper-exchanged ZrPC; all compounds are described in Section 2.

Table 2
Catalytic conversion of 6-methyl-5-hepten-2-ol **1** into ether **3**[a]

Catalyst[b]	Percentage conversion of compound **1** into products	Yield of ether **3** (%)	Selectivity to ether **3** (%)
H_3PO_4[c]	10	0	0
TiPC	15	5	33
ZrPC	86	58	67
SnPC	96	72	75
ZrPC/Cu	26	15	58

[a] The neat alcohol was refluxed for a standard 15 min — see Section 2.
[b] For descriptions of these catalysts, see Table 1 and Section 2.
[c] Phosphoric acid (85%, 14.6 M) was used, see Section 2.

2.8. Identification of products of reaction

Reaction mixtures were fractionally distilled or separated by preparative-scale gas chromatography. The individual products were identified by boiling point, gas chromatography/mass spectroscopy (GC/MS; 70 eV electron ionization), ^{1}H NMR spectroscopy ($CDCl_3$), and comparison with earlier described compounds [3]. Data are given in the following descriptions.

2.9. Individual reactions — cyclisation of 6-methylhept-5-en-ol *1*

The internal GC standard was dodecane. The major product of reaction, 2,2,6-trimethyltetrahydropyran **2**, was distilled, bp 123–125°C (literature [9], 126–127°C); MS, m/z 128 [$M^{+\cdot}$]; ^{1}H NMR, δ 1.13 (3H, d, Me), 1.20 (6H, s, $2\times$Me), 1.4–1.7 (6H, m, $3\times CH_2$), 3.6–3.7 (1H, m, CHO). Yields are shown in Tables 2 and 3.

2.10. Dehydration of 1-(2-hydroxyethyl)cyclopentanol *10*

The internal standard was dodecane. The product was distilled to give 1-hydroxyethylcyclopentene **13** as one of only two products: MS, m/z 112 [$M^{+\cdot}$]; ^{1}H NMR, δ 1.8–2.0 (4H, m, $2\times CH_2$), 2.2–2.4 (4H, m, $CH_2C=$), 3.7 (2H, t, CH_2O), 5.48 (1H, m, CH=C). The other product, cyclopentanone **14**, was identified by GC/MS and by comparison with an authentic sample. Yields are given in Table 4.

Table 3
Effect of calcination on activity of zirconium and tin catalysts for conversion of alcohol **1** into ether **3**[a]

Catalyst[b]	Percentage conversion of compound **1** into products	Yield of ether **3** (%)	Selectivity towards cyclic ether **3** (%)
ZrPC300	92	67	73
ZrPC400	95	69	73
SnPC200	100	86	86
SnPC400	100	84	84

[a] The neat alcohol was refluxed with the catalyst for a standard 15 min.
[b] For a description of each catalyst, see Table 1.

Table 4
Products of catalytic dehydration of 1-(2-hydroxyethyl)cyclopentanol **10**

Catalyst[a]	Percentage conversion of **10** into products	Percentage composition of products of dehydration	
		Cyclopentanone **14**	Cyclopentenol **13**[b]
H_3PO_4 (85%)	26	100	–
TiPC	61	34	66
ZrPC	63	10	90
SnPC	70	78	22
ZrPC/Cu	91	12	88
ZrPC300	83	30	70
ZrPC400	82	38	62

[a] For a description of these catalysts, see Table 1 and Section 2.
[b] 1-(2-Hydroxyethyl)cyclopentene.

2.11. Cyclisation of 1-(2-hydroxyethyl)cyclohexanol *11*

The internal standard was dodecane. The major product of the reaction, 1-(2-hydroxyethyl)cyclohexene **12**, was identified by comparison with an authentic sample synthesised as described above. It had m/z 126 (6% relative abundance; M^+), 95 (27), 81 (32), 79 (100), 67 (46), 41 (42). The other product, cyclohexanone **15**, was identified by GC/MS and by comparison of its relative retention time with that of an authentic specimen. Yields are given in Table 5.

2.12. Cyclisation of 2-methyl-1-(2-hydroxyethyl)cyclopentanol *4*

The internal standard was dodecane. The cyclic ether, 3-methyloxabicyclo[3.3.0]nonane **8**, had m/z 126 (34% relative abundance; M^+), 95 (87), 93 (100), 81 (52), 79 (83), 67 (59). The unsaturated alcohol, 2-methyl-1-(2-hydroxyethyl)cyclopentene **15**, had m/z 126 (42%; M^+), 95 (100), 79 (45), 67 (39). Yields are given in Table 6.

2.13. Cyclisation of 2,2-dimethyl-1-(2′-hydroxyethyl)cyclohexanol *9*

The internal GC standard was hexadecane. After reaction and distillation, a mixture of *cis*- and *trans*-3,8-dimethyloxabicyclo[4.3.0]nonane **16** and **17** was obtained; this was separated into its components by preparative scale GC on a packed column of OV1 with a temperature programme starting at 40°C (for 0.5 min) followed by an increase at 10°/min to 250°C; the pure *cis*-isomer **16** emerged in 7.4 min and the *trans* **17** in 7.7 min (the retention times for the isomers *relative* to the retention time for the monodehydrated ene-ol **18** were $R_v(cis) = 0.74$ and $R_v(trans) = 0.77$). The

Table 5
Products of catalytic dehydration of 1-(2-hydroxyethyl)cyclohexanol **11**

Catalyst[a]	Percentage conversion of **11** into products	Percentage composition of products of dehydration	
		Cyclohexanone **15**	1-(2-Hydroxyethyl)cyclohexene **12**
TiP	39	10	28
ZrP	65	7	54
SnP	70	13	56
ZrP/Cu^{2+}	91	10	80

[a] For designation of catalysts, see text.

Table 6
Products of catalytic dehydration of 2-methyl-1-(2-hydroxyethyl)cyclopentanol **4**

Catalyst[a]	Percentage conversion of **4** into products	Percentage composition of products of dehydration	
		8[b]	**15**[c]
ZrPA	82	23	20
TiPA	85	12	42
SnPA	90	64	3

[a] See text for nomenclature of catalysts.
[b] 3-Methyloxabicyclo[3.3.0]nonane.
[c] 2-Methyl-1-(2-hydroxyethyl)cyclopentene.
[d] For each catalyst, the remainder of the product mixture consisted of a material previously identified as 2-methyl-1-(ethenyl)cyclopentene.

isomers could be differentiated by ^{1}H nuclear Overhauser spectroscopy; irradiation of the methyl signal at δ 0.99 in the first eluting isomer caused a 17.5% increase in its companion methyl signal at δ 1.05, showing that the two methyls must be on the same side of the ring junction and that the compound was indeed the *cis*-isomer. No such enhancement was observed for the second eluting isomer, showing that the two methyls must be on opposite sides of the ring junction and that this was the *trans*-isomer. MS (*cis*), EI, *m/z* (% relative abundance): 139 (28), 96 (35), 68 (11), 67 (100), no molecular ion; ^{1}H NMR, δ: 0.99 (3H, s), 1.05 (3H, s), 1.17–1.6 (8H, m), 1.82 (1H, d, *J* 7.6 Hz), 2.55 (1H, t, *J* 7.6 Hz), 3.97, t, *J* 7.6 Hz); MS (*trans*), EI, *m/z* (% relative abundance): 139 (22), 96 (85), 68 (100), 52 (45), no molecular ion.

This preparative GC purification gave also pure samples of the conjugated diene **19** (retention time relative to the ene-ol **18** = 0.51), resulting from two dehydrations: MS, *m/z* 136 [$M^{+\cdot}$]; ^{1}H NMR δ 1.05 (6H, s, 2 × CH_3), 1.45–1.56 (4H, m, 2 × ring CH_2), 2.03 (2H, m, ring CH_2), 4.88–4.94 (1H, m, =CH), 5.22–5.3 (1H, m, =CH), 5.77 (1H, s, =CH), 6.3 (1H, m, =CH) and the ene-ol **18** (R^1, R^2=CH_3), the product of single dehydration, MS, *m/z* 154 [$M^{+\cdot}$], 139 [M-15]$^+$; ^{1}H NMR δ 1.05 (6H, s, 2 × CH_3), 1.45–1.56 (5H, m, ring CH_2 and OH), 2.0 (2H, m, ring CH_2), 2.8 (2H, m, CH_2), 3.7 (2H, m, CH_2O), 5.4 (1H, m, =CH). A small amount of a third product was identified by GC/MS as compound **20**, also reported in earlier work [3], MS, *m/z* 140 (8.6%) [$M^{+\cdot}$], 125 (41.1), 97 (100), 55 (27.9), 43 (50.7). Yields are given in Table 7.

Table 7
Composition of cyclic ether mixture arising from catalysed reactions of 1-(2-hydroxy-ethyl)-2,2′-dimethylcyclohexanol **9**

Catalyst[a]	Percentage conversion of **9** into products	Percentage composition of reaction product mixture (%)			
		16+**17**[c]	**18**[c]	**19**[c]	**20**[c]
H_3PO_4 (85%)	29	11	–	18	–
TiPC	82	12	42	24	4
ZrPC	88	21	23	22	22
SnPC	91	68	2	19	2
ZrPC300	93	42	28	18	5
ZrPC400	82	48	9	20	5
SnPC200	82	57	11	14	4
SnPC400	100	66	21	13	–
ZrPC/Cu	88	27	30	22	9

[a] Descriptions of catalysts appear in Table 1 and Section 2.
[b] This was a mixture of *cis*- and *trans*-isomers, as described in Section 2.
[c] **16**, **17** are the *cis*-, *trans*-isomers of 3,8-dimethyloxabicyclo[4.3.0]nonane; **18** is 2,2-dimethyl-1-(2-hydroxyethyl)cyclohexene; **19** is 2,2-dimethyl-1-(ethenyl)cyclohexene; **20** is 3-methyloxabicyclo[4.3.0]nonane.

2.14. Reaction of nopol with aluminium chloride

Nopol (**21**; 2 g) was reacted with $AlCl_3$ (1 g) in DCM (20 ml) for 15 min at room temperature. The mixture was poured into water (100 ml) and the DCM layer was separated off. Removal of the solvent gave an oily residue, which was shown by GC to consist of three components. Separation of the mixture by chromatography on a column of alumina (Brockman type 1, weakly acidic; 15 cm × 2 cm), using petroleum ether (bp 40–60°C) and DCM in a in a ratio of 30:70 (v/v) as eluant gave the cyclic ether **22**, for which the ^{13}C NMR spectrum showed δ ($CDCl_3$) 66.6 (d, C-2), 59.6 (t, C-11), 52.1 (s, C-1)*, 49.3 (s, C-7)*, 44.7 (d, C-4), 40.8 (t, C-3), 33.4 (t, C-10), 27.8 (t, C-5), 26.1 (t, C-6), 20.7 (q, C-8) and 18.8 (q, C-9). Assignments marked with an asterisk might be interchanged.

3. Results and discussion

In superacidic solution, reaction of the diols to give cyclic ethers proceeds by protonation of the tertiary hydroxyl group, followed by loss of water to leave a carbocation. Subsequent 1,2-shift of the carbocationic centre permits formation of a stable cyclic ether. However, dehydration of tertiary alcohols in the gas phase over metal (IV) phosphates appears to follow a different route [10]. The catalyst bonds to the hydroxyl group and water is eliminated in a synchronous reaction, which involves loss of a neighbouring proton, and a carbocation is not involved. If the formation of cyclic ethers described in this present work does not involve carbocations, then the observed cyclisation of the primary hydroxyl group onto the site of the (departing) tertiary hydroxyl must occur while the tertiary hydroxyl is still bonded to the surface, as shown in Fig. 1.

Alternatively, cyclisation to carbon other than the site of the departing tertiary hydroxyl group could proceed only with a concomitant shift of an alkyl or hydride from the site of cyclisation, as illustrated in Fig. 2. This process could be synchronous or it could involve initial formation of a carbocation.

In superacidic media, 6-methyl-5-hepten-2-ol **1** (Scheme 1) cyclises to 2,2,6 trimethyltetrahydropyran **3** in 50% yield. On refluxing this same alkenol **1** with metal (IV) phosphates, the cyclic ether **3** was isolated as the major product, together with small amounts of other unidentified materials (Table 2). Percentage conversions of the heptenol **1** range from 0 to 96%, with a similar trend in selectivity towards formation of the cyclic ether; the better the conversion, the better the selectivity, reaching a maximum for the very acidic tin phosphate (Table 2). Remarkably, in a homogenous system of phosphoric acid, which has a greater H_0 value than any of the metal phosphate catalysts, no cyclic ether was formed. Also, for two of the crystalline phosphates (SnPC, ZrPC), the yields of cyclic ether were better than those obtained in superacidic media. It might be noted that, for purposes of comparison in this work, all the reactions with the heterogeneous phosphate catalysts were stopped

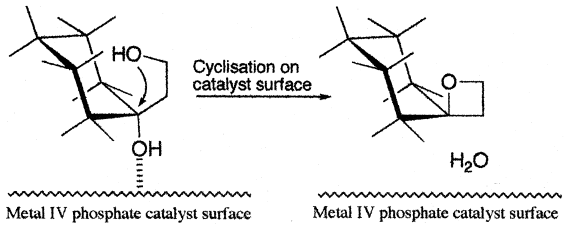


Fig. 1.

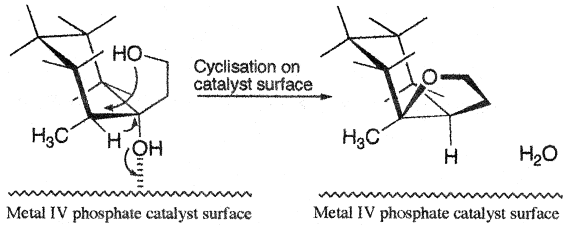
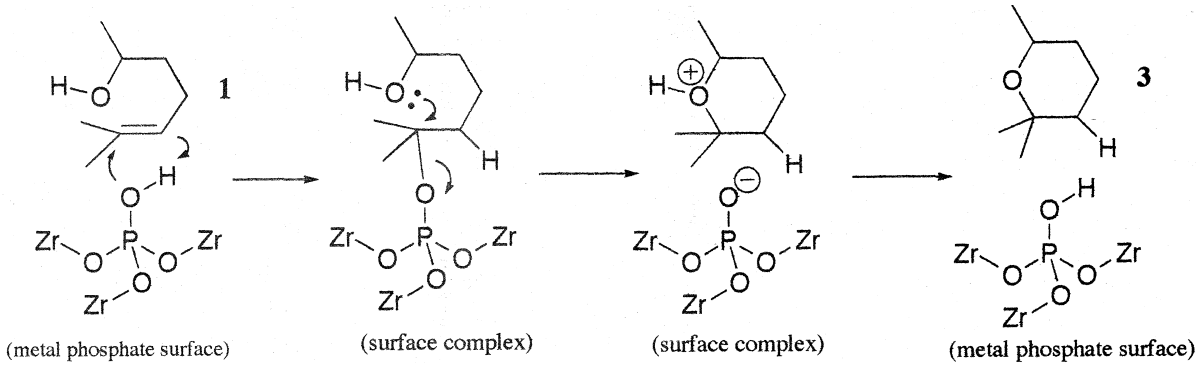


Fig. 2.

after only 15 min and, given more time, there is no reason why each of them should not give higher conversions and yields. Reduction in acidity of the phosphates by replacing protons with copper ions dramatically reduced the yield of the cyclic ether but not the selectivity. The reactions were repeated after increasing the acidity of the ZrPC and SnPC catalysts by calcination. As shown in Table 1, this simple heat treatment boosted the acidity of the zirconium catalyst to an extent that it became very comparable with that of the most effective tin phosphate. The tin phosphates were similarly calcined. Table 3 reveals that the calcined catalysts were even more efficient than before calcination, with conversions reaching between 92% and 100% within the 15-min standard reaction time. However, although the catalysts became almost equal in efficiency towards conversion of the heptenol into the cyclic ether, the selectivites towards this conversion were significantly different, being 73% for the zirconium compound and 85% for the tin. Thus, the phosphates catalyse cyclic ether formation like the fluorosulphuric (super)acid medium and, for some of them, with greater selectivity and conversion efficiency. For example, SnPC (Table 2) converts the alcohol **1** into the cyclic ether **3** in 72% yield with 75% selectivity (Table 2) and, after calcination, in 86% yield and selectivity (Table 3).

Because exchange of protons in ZrPC by copper ions gives a catalyst (ZrPC/Cu) that slows but does not stop the cyclisation reaction and has only a small effect on selectivity (Table 2), it appears that the catalytic effect of the phosphate catalysts is not due only to Brønsted acidity but that Lewis acidity is also significant. Allied to the experience with the homogeneous phosphoric acid system, which gave no cyclic ether **3**, and with superacid, which gave only a 67% yield of the ether, the selectivity towards formation of cyclic products by the phosphates suggests that surface features of these catalysts are important. Possibly, bonding from the double bond to the phosphate surface occurs in such a way as to facilitate intramolecular cyclisation (Scheme 3). A similar conclusion was reached in a comparison of the cyclisation of the *cis*- and *trans*-isomers, nerol and geraniol, which were found to cyclise to a much greater extent for the *cis*- as against the *trans*-isomer [11]. The point is reinforced by reference to homogeneous superacidic media, for which neither yield nor selectivity is anywhere near as good as for the *calcined* heterogeneous zirconium and tin phosphates (Table 3). For the cyclisation of the en-ol **1**, the calcined tin and zirconium phosphates were more efficient than the superacidic fluorosulphuric acid. This enhancement of cyclisation was examined in more detail with other, more complex systems (diols) which had the potential for dehydration and/or intramolecular cyclic ether formation. In these more complicated systems, cyclisation was made more difficult because the most direct intramolecular cyclisation would lead to an unstable four-membered ring oxetane; more stable five- or six-membered cyclic ethers could be formed only following 1,2-shifts of hydrogen or carbon after initial production of a carbocation centre.

The reactions of the diols are considerably more complex than those of the simple unsaturated alcohol **1**. All of the alcohols are 1,3-diols and cyclisation without rearrangement would give only an oxetane ring. To obtain a stable product, a shift of the reaction centre appears to be necessary. Diol **4** (2-methyl-1-(2-hydroxyethyl)cyclopentanol) undergoes the most straightforward reaction (Scheme 2).

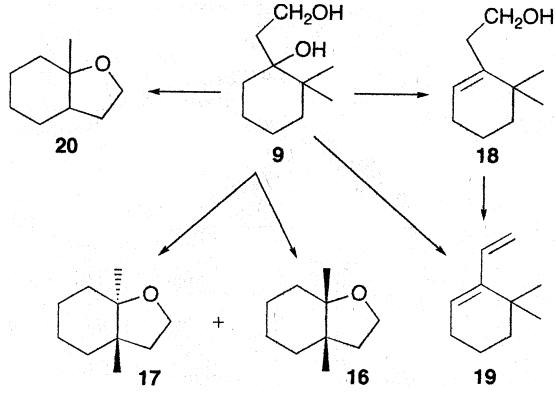


Scheme 3.

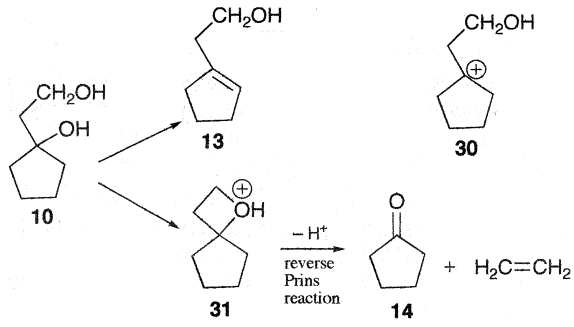
The first step is almost certainly loss of the tertiary hydroxyl group since all of the unsaturated alcohols isolated in this work have been primary. Elimination of a tertiary OH leads to formation of the unsaturated alcohol **15** and a cyclic ether by shift of the reaction centre to the ring/methyl junction, followed by ring closure to give 3-methyloxabicyclo[4.3.0]nonane **8**. Yields are shown in Table 6.

The reactivities of the cyclic diols do not correlate with acidity as easily as do those of the acyclic unsaturated alcohol. For 1-(2-hydroxyethyl)cyclopentanol **10**, phosphoric acid is the least effective catalyst, with the three crystalline metal phosphates being similar. However, zirconium phosphate becomes more effective after calcination and the copper-exchanged zirconium phosphate is the most effective although having the lowest acidity. This general pattern of reactivity is repeated with the other diols and it is possibly accounted for by Lewis rather than Brønsted acidity, particularly in view of the result with copper exchange, which has been shown to remove or seriously reduce the concentration of Brønsted acid sites (Table 1). It is worth noting that, for these complex systems reacting on the surface of a catalyst, it is not even certain that the overall rate determining step remains the same throughout the reaction series.

The reaction of the dimethyl diol, 2,2-dimethyl-1-(2-hydroxyethyl)cyclohexanol **9**, proceeds along a slightly more complex path, which is outlined in Scheme 4. The unsaturated alcohol **18** and the diene **19** can be formed by dehydration but a 1,2 methyl shift is then needed to give a five-membered ring ether; this ether is observed as a mixture of *cis*- and *trans*-isomers **16**, **17**. However, as was also



Scheme 4.



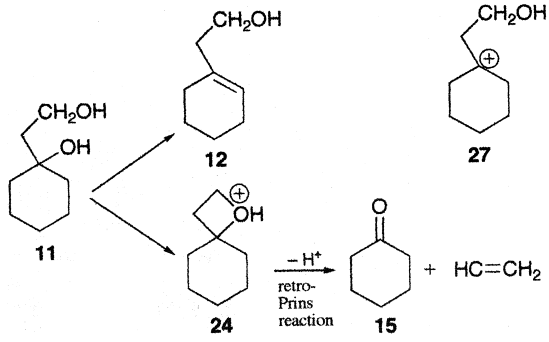
Scheme 5.

observed when this cyclisation was originally carried out in a superacid, fluorosulphuric acid [3], there was a complete loss of a methyl group, which occurred at the same time as the 1,2-shift. In fluorosulphuric acid, the methyl was believed to form methyl fluorosulphonate [12], but in the present system over metal (IV) phosphates, the fate of the methyl is unknown although it is possible that it is transferred to an oxygen on the catalyst surface. It is interesting to observe that the metal phosphates behave similarly to superacids in the liquid phase. Thus, reaction of diol **9** yields three ethers since the 1,2-shift of methyl gives rise to *cis*- and *trans* (1,2 dimethyl)- isomers in almost equal amounts (Table 7).

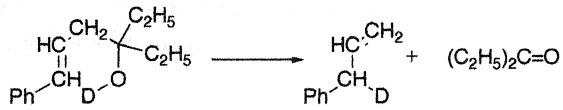
In the cases of diols that do not have methyl substituents on the carbon atom next to that bearing the tertiary hydroxyl group **10**, **11**, the formation of cyclic ethers is no longer observed [13]. This result is in marked contrast to the effect found in superacidic media, in which a tertiary to secondary carbocation rearrangement occurs, aided by stabilisation of the carbocation by the fluorosulphonate counterion. In the present work, both diols yield a cyclic ene-ol **12**, **13** by simple dehydration at the tertiary hydroxyl group. At the same time, the cyclic ketones **14**, **15** are formed via a *retro*-Prins reaction (Schemes 5 and 6; Tables 5 and 6).

A *retro*-Prins reaction is known to take place at 500°C in an uncatalysed reaction [14], which has been shown by deuterium labelling to proceed through a six-membered cyclic transition state (Scheme 7).

The reaction of 1-(2-hydroxyethyl)cyclohexanol **11** was examined in more detail. First, the unsaturated alcohol **12** was prepared independently; on refluxing this alcohol with zirconium phosphate catalyst, it did not produce cyclohexanone **15**. When the more acidic $AlCl_3$ was used with the unsaturated alcohol **12**, a complex product mixture resulted but it contained no cyclohexanone. It



Scheme 6.



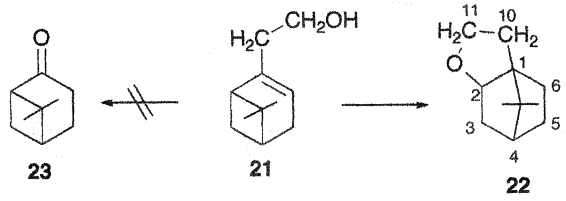
Scheme 7.

seems clear that the alcohol **12** is not an intermediate in the formation of cyclohexanone. However, it appeared possible that reaction of the Lewis acid at the primary alcohol site of **12** might be enough to inhibit the *retro*-Prins reaction to give cyclohexanone. Accordingly, an attempt was made to prepare nopinone **23** via a *retro*-Prins reaction of nopol **21**, an analogue of the alcohol **12**. With $AlCl_3$ in dichloromethane, nopol reacted in 30 min at room temperature to give the cyclic ether **22** (Scheme 8), which has been reported previously as a product of the condensation of camphene with paraformaldehyde [15,16]. No nopinone **23** was observed. The rearrangement of nopol, a pinane derivative, to a bornane compound indicates that the reaction must have proceeded through a carbocation generated at C-2 by reaction of acid with the double bond in nopol (Scheme 8).

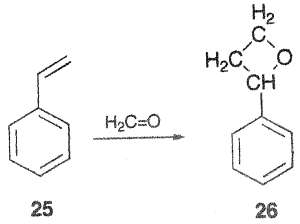
Thus, these results confirm that the *retro*-Prins reaction observed with the metal (IV) phosphates does not proceed along the route outlined in Scheme 7 and that the unsaturated alcohol **12** is not an intermediate in the formation of cyclohexanone. In which case, the ketone must be formed directly from the substrate diol **11**. If the reasonable assumption is made, that the tertiary hydroxyl group departs rather than the primary, then the oxygen that appears in the cyclohexanone must arise from the primary hydroxyl, with initial formation of an oxetane. A plausible mechanism is outlined in Scheme 6, in which the oxetane **24** is the source of the ketone **15** formed by the *retro*-Prins reaction. This type of mechanism is well-established for the forward Prins reaction [17], but has not been reported for the reverse process. Studies on the reaction of styrene **25** with formaldehyde have revealed that the forward Prins reaction proceeds through an oxetane **26** (Scheme 9) [17]. It is not clear from these data whether or not the oxetane **24** is formed by reaction of a carbocation **27** or from the diol **11**.

Next, reaction of 1-(2-hydroxyethyl)cyclopentanol **10** with metal (IV) phosphates was examined. Here, much better yields of ketone **14** were obtained than was the case discussed above for the formation of cyclohexanone. The greatest unoptimised yield of cyclohexanone **15** was 13% but yields as high as 78% were observed for cyclopentanone (Table 7) when the diol **10** was reacted with crystalline tin (IV) phosphate; this ketone was the sole product of reaction with phosphoric acid itself.

Examination of molecular models of the diols **10**, **11** provides some explanation of the disparity in rates of oxetane formation. For the cyclohexane diol **11**, its preferred conformation (structure **28**) will be one in which the side-chain lies in the equatorial position. Formation of an oxetane will be impeded by the axial hydrogens at C-2 and C-6 if the side-chain approaches from below and by the axial hydrogens at C-3 and C-5 if the approach is from above. Formation of a carbocation at C-1 would make only a slight improvement in the ease of approach. If it is considered that the tertiary



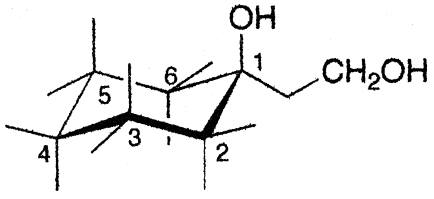
Scheme 8.



25 26

Scheme 9.

hydroxyl is bonded to the catalyst surface, then this will cause the cyclohexane ring to flip so as to place the side-chain in an axial position so that it can then approach from behind the carbon holding the bonded tertiary hydroxyl, leading to its displacement and formation of an oxetane **24** without formation of a carbocation (Fig. 1). In contrast, when the unsaturated alcohol **12** reacts with the catalyst surface, the side-chain CH_2OH group can remain in the plane of the double bond and does not cyclise.



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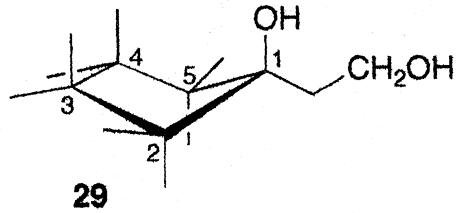

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In contrast to the behaviour of the six-membered ring, the conformation (structure **29**) of the five-membered ring diol **10** permits the side-chain CH_2OH group to approach from an equatorial or an axial position so as to displace the surface-bound tertiary hydroxyl from either side of the ring (a flexible 'envelope' shape). Thus, reaction takes place in phosphoric acid alone or on the metal (IV) phosphate surface.

Estimation of the enthalpies of formation and of transition states confirms these deductions [18]. Proceeding from carbocation **30** to the oxetane **31** requires only a small increase of about 2.5 kJ mol^{-1} in their relative enthalpies of formation. Similarly, the transition state energy in going from structure **30** to **31** is similar to the difference in enthalpies of formation, suggesting that the change from one ion to the other proceeds very readily. Ion **31** then undergoes the reverse Prins reaction to form cyclopentanone. In contrast, the cyclohexyl carbocation **27** must surmount an activation energy barrier of about 210 kJ mol^{-1} to reach structure **24**. Additionally, formation of the oxetane **24** is accompanied by an increase in the relative enthalpy of formation of some 42 kJ mol^{-1}. Such energy barriers confirm the deductions made from consideration of molecular models, as discussed above.

Although the reactions reported here could proceed through either a carbocation or a synchronous elimination of water on a catalyst surface, the observation of *retro*-Prins reactions is only consistent with a synchronous reaction and not with a carbocation mechanism. In all of the reactions, formation of a five-membered ring cyclic ether is preferred and an oxetane is only produced when the cyclisation to an ether is unfavourable. The results indicate that a hydroxyl group bonded to a metal (IV) phosphate surface can be displaced by shift of hydrogen or an alkyl group or by internal nucleophilic attack from the side-chain, with ring formation.

It may be supposed that all of the diol reactions catalysed by metal (IV) phosphates proceed through synchronous elimination of water from the diol, accompanied by a hydrogen or alkyl shift to accommodate formation of a 5-membered ring ether. When this route is energetically difficult, an oxetane can be formed and decomposes rapidly to give a ketone.

Acknowledgements

The authors gratefully acknowledge the CVCP for ORS awards (J.-Y. Liu, LL), the government of Kuwait for financial support (F.A.H. Al-Q), and the Eschenmoser Trust UK (L.F.H., LL).

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