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Acyclic O- and N-substituted Pentadienyl Cations: Structural Characterisation, Cyclisation and Computational Results

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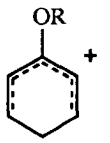
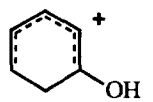
Abstract: A number of 1- and 3-hydroxy and 1-amino substituted acyclic pentadienyl cations have been characterised by NMR spectroscopy *in situ* at low temperature. Some of the 3-hydroxy cations undergo cyclisation to give 1-hydroxycyclopentenyl cations which on deprotonation give substituted cyclopentenones.

INTRODUCTION

Cyclic and acyclic pentadienyl cations have been postulated as intermediates in several important organic reaction pathways, and may indeed be generated and studied at low temperature in strong or superacid media by protonation of arenes or, in the acyclic series, by protonation of suitable triene or dienol precursors.[1a,b] Such studies have concentrated mainly on alkyl substituted derivatives,[2a-c] though cyclic hydroxy- and alkoxy-substituted cations such as (1) and (2) may be generated from protonation of phenol and anisole[3a-e] or appropriate 2,5- or 2,4-cyclohexadienones.[4a,b] We are unaware of the full *in situ* characterisation of any acyclic heteroatom substituted pentadienyl cation, despite recent theoretical interest[5a-e] and the importance of the 3-hydroxypentadienyl cation as an intermediate in the synthetically useful Nazarov cyclisation.[6]



(1) R = H, Me

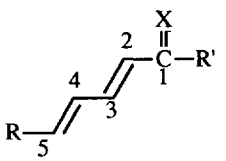


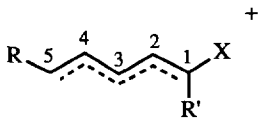
(2)

Our work on the synthesis of alkoxy and acyloxy substituted [(pentadienyl)$Fe(CO)_3$]X salts[7] has led us to investigate the possibility of *in situ* generation of free O- and N-substituted pentadienyl cations.

RESULTS AND DISCUSSION

Cations (7) to (10) were generated *in situ* by addition of HSO_3F to CD_2Cl_2 solutions of the aldehyde, ketone or imine precursors (3) to (6) at -80 °C, followed by equilibration at -20 °C in the NMR spectrometer.





(3) R=R'=H, X=O

(4) R=Me, R'=H, X=O

(5) R=R'=Me, X=O

(6) R=Me, R'=H, X=NBu^n

(7) R=R'=H, X=OH

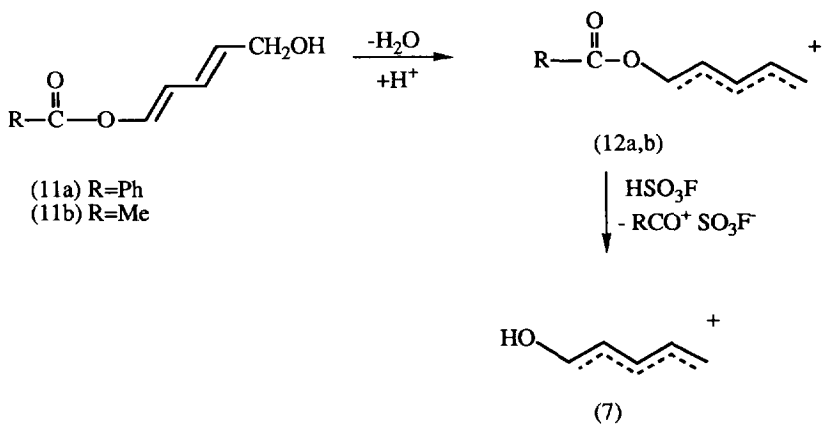
(8) R=Me, R'=H, X=OH

(9a) R=Me, R'=OH, X=Me

(9b) R=R'=Me, X=OH

(10) R=Me, R'=H, X=NHBu^n

Attempts to generate acyloxy cations (X=OCOR) by protonation of alcohols (11a,b) led only to spectra which were identical in the pentadienyl region with that of (7). These results imply that an initial formation of the acyloxy cation (12a,b) is followed by rapid solvolysis with elimination of acylium ion to generate (7).



(11a) R=Ph
(11b) R=Me

(12a,b)

Attempts to generate simple alkyl substituted cations, for example by the protonation of (E,E)- 2,4-heptadien-1-ol, resulted only in polymerisation.

Spectra and spectral data for cations (7) to (10) are given in Figure 1 and in the Experimental section. Chemical shifts and multiplicities clearly differ from spectra of the precursors (3) to (6) in CD_2Cl_2. The coupling of the N-H proton in (10) to both H1 and the ∝-CH_2 of the Bu^n group may be noted, and indeed stable salts of cation (10) may be isolated.[8] Coupling of the OH proton in (7) to (9) is not observed, presumably due to faster rate of exchange with solvent.

The magnitude of the coupling constants (12-15 Hz) is clearly indicative of the "W" conformation previously found by experiment to be the lowest energy conformation of alkyl substituted pentadienyl cations.[2a-c] The large $J_{1\text{-}2}$ and $J_{4\text{-}5}$ values also indicate trans configurations of the substituents at the C1-C2 and C4-C5 bonds.

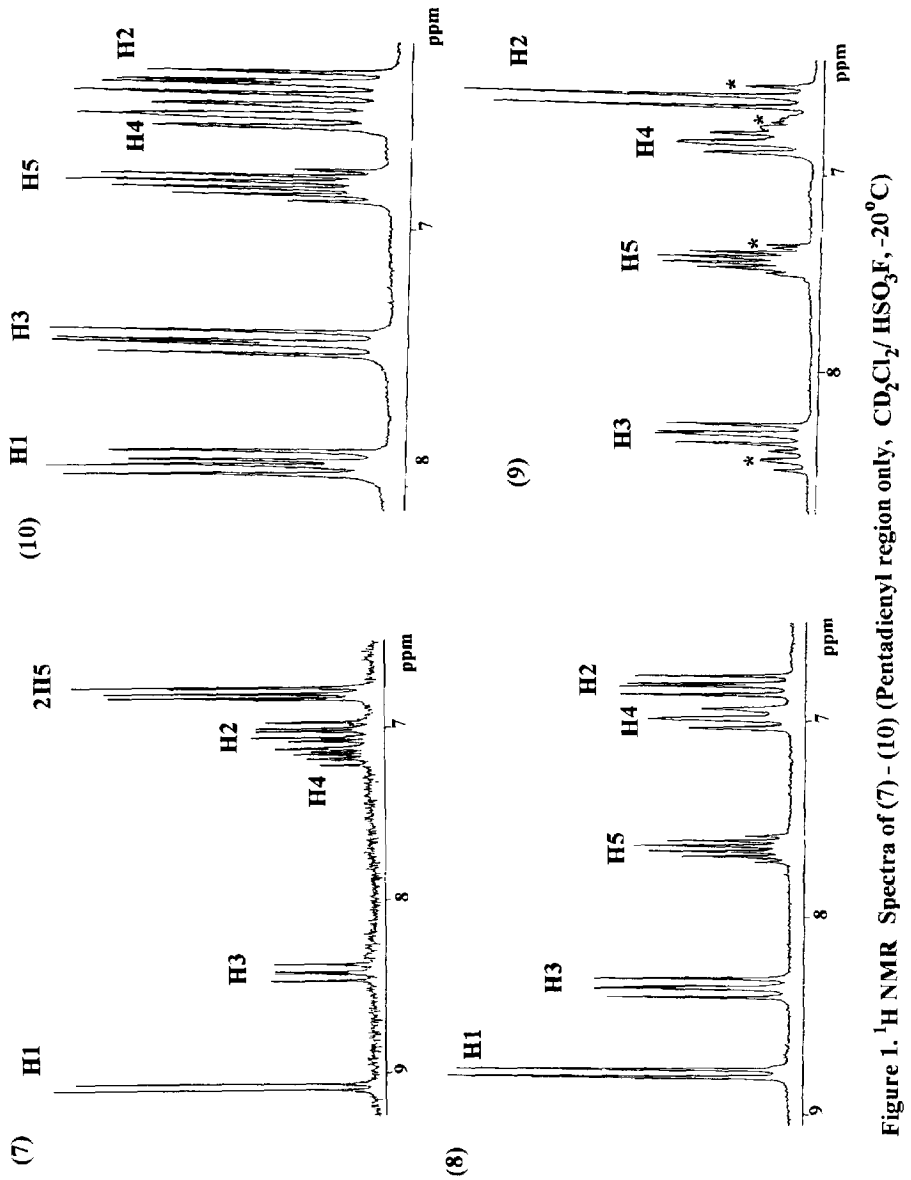


Figure 1. ^{1}H NMR Spectra of (7) - (10) (Pentadienyl region only, CD_2Cl_2/ HSO_3F, -20°C)

These experimental observations are consistent with AM1 computational results on (7) (Table 1) which shows the all-trans structure (7a) to be more stable than the cis-1,2 "W" conformation (7b) or the alternative "sickle" conformations (7c)-(7f) or the "U" conformations (7g) and (7h). Calculations on the unsubstituted pentadienyl cation (12)[9] and the 1-amino cation (11) also support these conclusions. Methyl substitution at C5 [as in (8) or (10)] does not alter the relative stability of the "W", "sickle" and "U" conformations, and is most stable in a trans-C4-C5 configuration.

All spectra except those of (9) indicate that a single isomer is present in solution. A second minor isomer (ratio 2.5:1) is observed in the spectrum of (9) (asterisked resonances in Figure 1); although there is some spectral overlap, decoupling of the common methyl(R) resonance at 2.25 ppm shows clearly that the trans-H4-H5 geometry is maintained. The isomers are thus assigned as (9a)/(9b), with computational results suggesting a greater stability of (9b) relative to (9a) (Table 1) of approximately 1.2 kcal. This is in contrast to results on cation (8), where calculations indicate (8a) to be more stable than (8b) by approximately 1.7 kcal. Interconversion of (9a)/(9b) on the NMR timescale is obvious in the reversible temperature broadening of the resonances. Line shape analysis of the Me(R') resonance yields a value of $\Delta G^{\ddagger}_{273} = 13.8 \pm 0.2$ kcal for the C1-C2 rotational process. The rate of C1-C2 rotation observed for (9a)/(9b) interconversion is approximately 10^2 times that postulated for methyl substituted pentadienyl cations (based on indirect evidence from cyclisation studies),[2a,c,10] but appears similar to that observed for analogous rotation in protonated 3-buten-2-one.[11]

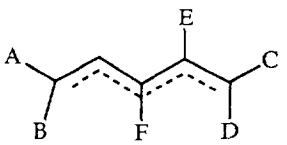
Though spectral quality degrades with time, particularly on warming, we find no evidence for isomerisation to 2- or 3-hydroxy cations or cyclisation to cyclopentenyl cations. 1,3-Isomerisation has been observed in the case of a cyclic 1-hydroxypentadienyl cation,[4b] while a facile, allowed conrotatory thermal ring closure has been observed for many alkyl substituted pentadienyl cations, and forms the driving force in the Nazarov cyclisation involving 3-hydroxypentadienyl cations as presumed intermediates.[5c,6]

Lack of isomerisation is also consistent with computational results (Table 1) which show the ordering of stability to be 1-hydroxy (7) > 3-hydroxy (14) >> 2-hydroxy (13) in all conformations, though the energy difference between the "U" conformations in 1-hydroxy (7g) and 3-hydroxy (14c) (required for a cyclic pentadienyl system) is sufficiently small that the ordering may be potentially sensitive to the substitution pattern of the cation.

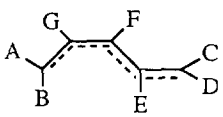
Lack of cyclisation of the 1-OH and 1-NHBu^t substituted cations is also consistent with computational results of the stabilities of the cyclopentenyl cation (15) relative to the precursor "U" conformations (7g,h) (11c,d) and (12) (Table 2). Computed barriers to cyclisation increase in the order X=H (10.4 kcal) < X=OH (18.5 kcal) < X=NH_2 (36.0 kcal). Lack of cyclisation is likely to be thermodynamic in origin, since the 3-hydroxy-1,5-dimethyl cation undergoes facile cyclisation (*vide infra*), though the computed barrier (24.3 kcal) is larger than that of the 1-hydroxy cation.

Protonation of (E,E)-2,5-heptadien-4-one (16) at -20 °C under the same conditions yields the 3-hydroxy cation (17) [Figure 2]. The symmetry of the spectrum is consistent with either the "W" or "U" conformations (17a) or (17c) (Table 1) or with a "sickle" conformation (17b) in which the methyl groups are exchanged by rapid C-C rotation on the NMR timescale. This latter possibility seems unlikely in view of the barrier measured for (9). AM1 calculations on both (17) and the unsubstituted cation (14) indicate a slightly greater stability of the "sickle" conformation. More sophisticated calculations on (14)[5c] reduce the energy gap between the "sickle" and "W" conformations, and even suggest that the "U" conformation may in fact be the ground state. A definitive assignment of structure in this and other 3-hydroxy cations is thus problematical.

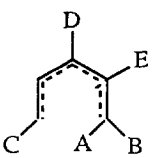
Table 1 Calculated Energies of Pentadienyl Cations



	A	B	C	D	E	F	ΔH_f[a]
(7a)	H	H	OH	H	H	H	160.7
(7b)	H	H	H	OH	H	H	162.4
(8a)	Me	H	OH	H	H	H	146.2
(8b)	Me	H	H	OH	H	H	147.9
(8c)	H	Me	OH	H	H	H	147.6
(8d)	H	Me	H	OH	H	H	149.2
(9a)	Me	H	OH	Me	H	H	137.0
(9b)	Me	H	Me	OH	H	H	135.8
(9c)	H	Me	OH	Me	H	H	138.4
(9d)	H	Me	Me	OH	H	H	137.1
(10a)	Me	H	NH_2	H	H	H	174.8
(10b)	Me	H	H	NH_2	H	H	176.1
(11a)	H	H	NH_2	H	H	H	187.9
(11b)	H	H	H	NH_2	H	H	189.3
(12a)	H	H	H	H	H	H	222.6
(13a)	H	H	H	H	OH	H	183.1
(14a)	H	H	H	H	H	OH	167.2
(17a)	Me	H	Me	H	H	OH	138.2



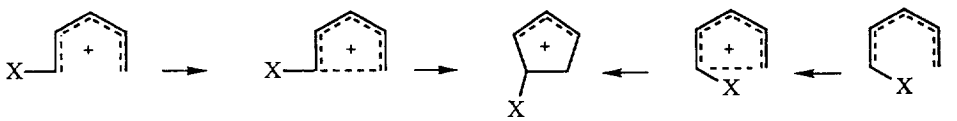
	A	B	C	D	E	F	G	ΔH_f[a]
(7c)	H	H	OH	H	H	H	H	162.1
(7d)	H	H	H	OH	H	H	H	163.8
(7e)	OH	H	H	H	H	H	H	161.7
(7f)	H	OH	H	H	H	H	H	163.8
(12b)	H	H	H	H	H	H	H	223.8
(13b)	H	H	H	H	OH	H	H	183.0
(13c)	H	H	H	H	H	H	OH	184.1
(14b)	H	H	H	H	H	OH	H	166.1
(17b)	Me	H	H	Me	H	OH	H	137.0



	A	B	C	D	E	ΔH_f[a]
(7g)	H	OH	H	H	H	165.5
(7h)	OH	H	H	H	H	168.5
(11c)	H	NH_2	H	H	H	191.8
(11d)	NH_2	H	H	H	H	192.8
(12c)	H	H	H	H	H	227.5
(13d)	H	H	H	H	OH	188.2
(14c)	H	H	H	OH	H	169.3
(17c)	H	Me	Me	OH	H	141.2

[a] ΔH_f values in kcal.

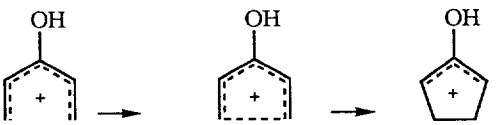
Table 2 Computational Results on Cyclisation



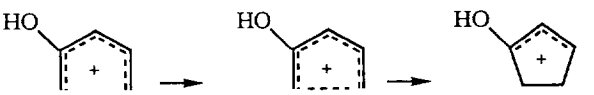
(15)

Energy (kcal)

X=H	227.5	238.0	205.8	238.0	227.5
	21.8	32.2 (2.27)[b]	0[a]	32.2 (2.27)	21.8
X=OH	165.5	184.0	168.7	194.8	168.5
	-3.2	15.3 (2.75)[b]	0[a]	26.2 (2.14)	-0.2
X=NH_2	191.8	227.8	212.4	230.7	192.9
	-20.6	15.4 (2.21)[b]	0[a]	18.3 (3.26)	-19.6



169.3	193.6	166.8
2.5	26.8 (2.03)[b]	0[a]



188.2	195.3	146.6
41.5	48.7 (2.46)[b]	0[a]

[a] cyclopentenyl cation assigned as arbitrary zero.
[b] value in parenthesis is the C1-C5 distance in Å at the transition state.

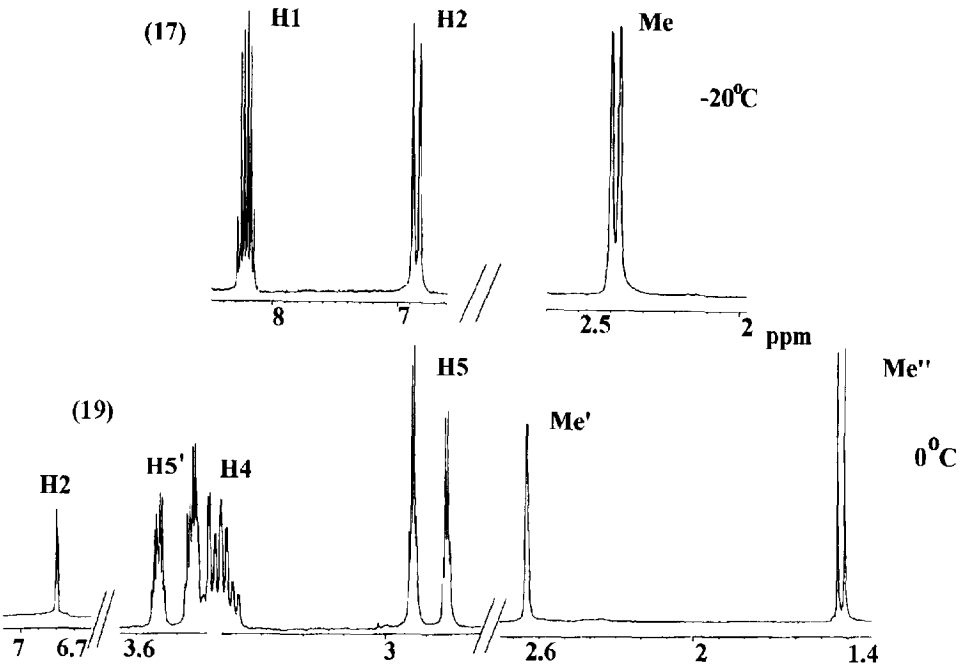


Figure 2. ^{1}H NMR Spectra of (17) & (19) (CD_2Cl_2/HSO_3F)

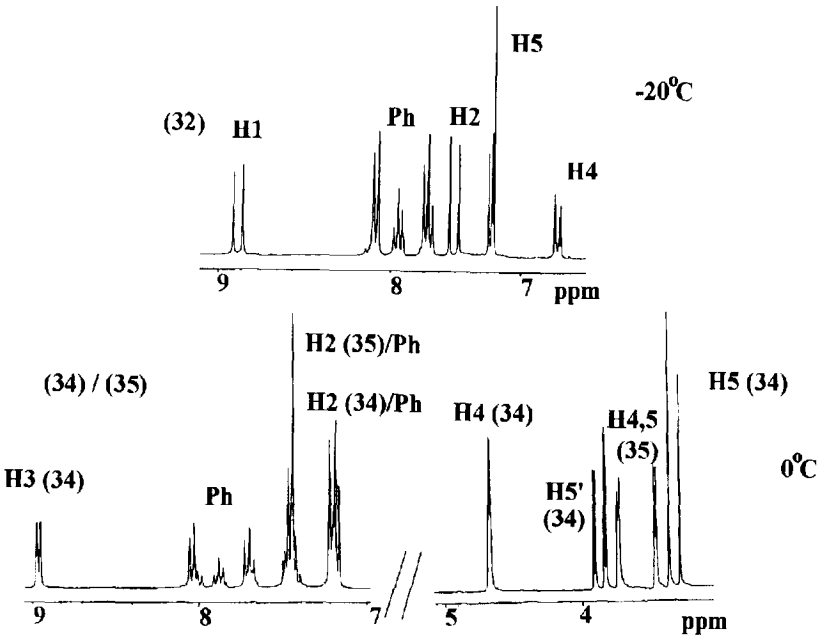
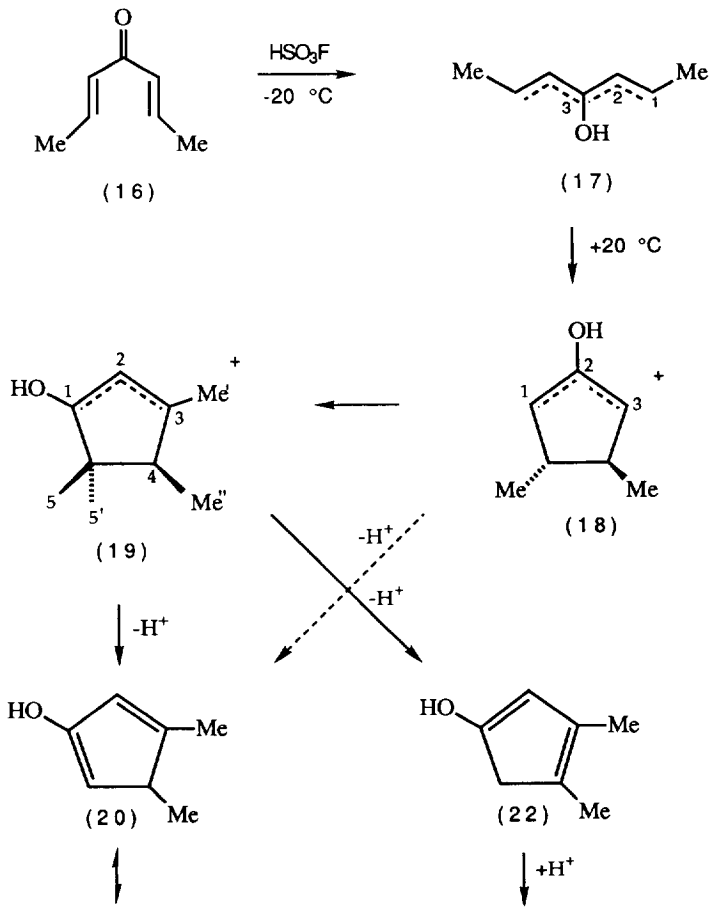
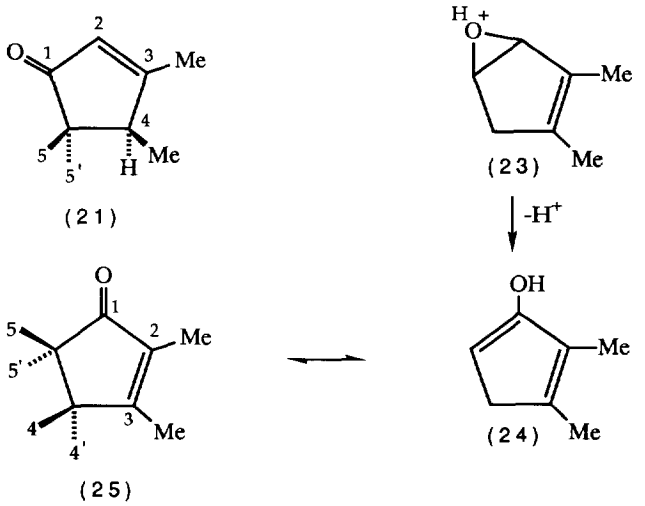


Figure 3. ^{1}H NMR Spectra of (32) & (34)/(35) (CD_2Cl_2/HSO_3F)

On warming to +20 °C, however, a clean cyclisation is observed ($t_{\frac{1}{2}}$ = 53 minutes at +20 °C) to give a spectrum [Figure 2] which indicates the product cation to have structure (19) rather than cation (18) which is presumed to be the initial product of conrotatory cyclisation. Particularly characteristic are the singlet allyl proton at 6.8 ppm and the methyl region which indicates that one methyl is bound to an allyl carbon.

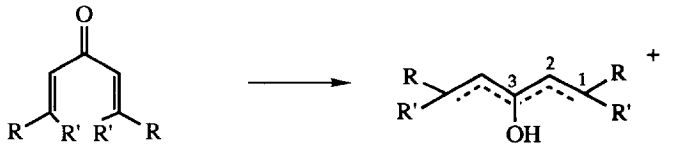




Conversion of (18) to (19) may be accomplished by a formal 1,3-hydrogen shift, which has shown to be a facile process in alkyl substituted cyclopentenyl cations.[12a-c] Provided the kinetic barrier is small, isomerisation of (18) to (19) is also consistent with computational results in the unsubstituted series (Table 2) which show the relative stabilities of the hydroxycyclopentenyl cations to be in the order 1-hydroxy >> 2-hydroxy ≈ 4-hydroxy. Cyclisation of (16) on a synthetic scale (HSO_3F, CH_2Cl_2, 25 °C) yields 3,4-dimethylcyclopent-2-en-1-one (21), the product derived from either (19) or (18) by deprotonation and tautomerisation of the enol intermediate (20). In contrast, cyclisation using the conventional Nazarov conditions (phosphoric acid/formic acid, 90 °C) yields instead 2,3-dimethylcyclopent-2-en-1-one (25).[13] Other reagents commonly used for Nazarov cyclisations are less selective. H_3PO_4 alone[15] or concentrated HBr/CH_3COOH[14b] yielded (25) and (21) in ratios of 10:1 and 3.4:1 respectively. Treatment with $AlCl_3$[16] yielded only (21), but the products from this reaction, and that from the HBr/CH_3COOH reaction, were contaminated by impurities containing ^1H resonances in the 3.4-4.5 ppm region indicative of reductive halogenation. $FeCl_3$[17] did not catalyse the cyclisation of (16).

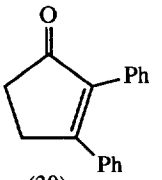
The mechanistic origin of the "carbonyl shift" product (25) is not clear. It has previously been suggested[14b] that attack at C1/C3 of cation (18) by hydroxylic solvents (water, carboxylic acid) yields an acyloin equivalent which undergoes a series of elimination, rearrangement and deprotonation reactions to give (25). This seems unlikely, since we have not been able to observe detectable concentrations of (18) during cyclisation of (17) to (19). An alternative mechanism may involve proton loss to the enol (22) followed by an acid catalysed "oxygen walk"[18] to give (24), the enol precursor of (25). Indeed, treatment of (21) with $H_3PO_4/HCOOH$ results in a small (ca. 4%) conversion of (21) to (25).

Protonation of the diphenyl and tetramethyl derivatives (26) and (27) *in situ* clearly provides cations (28) and (29), but no evidence of cyclisation is apparent on warming to 20 °C for several hours. While (27) undergoes only decomposition on treatment with $H_3PO_4/HCOOH$, (26) is converted over a longer period in moderate yield to the "carbonyl shift" product 2,3-diphenylcyclopent-2-en-1-one (30).



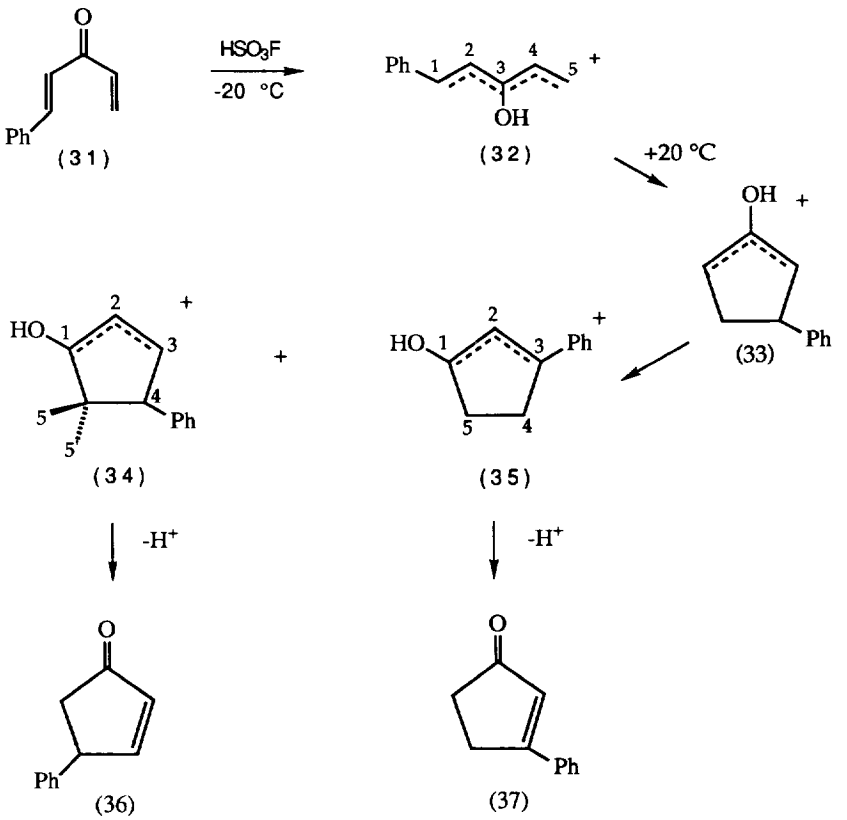
(26) R=Ph,R'=H
(27) R=R'=Me

(28)
(29)



(30)

Finally, we have examined the regioselectivity of the cyclisation process in HSO_3F in the case of the asymmetric monosubstituted ketone (31). Protonation at -20 °C clearly yields the expected pentadienyl cation (32) (Figure 3) which undergoes smooth cyclisation on warming ($t_{\frac{1}{2}}$ = 27 minutes, + 20 °C).



(31) (32) (33) (34) (35) (36) (37)

Spectra again provide no evidence for the presumed initial 2-hydroxycyclopentenyl intermediate (33), but show the presence of the two 1-hydroxy cations (34) and (35) available via alternative 1,3-hydrogen shift processes. The ratio of (34) : (35) (2.6:1) does not change during the cyclisation reaction. Particularly diagnostic in the spectra of (34) and (35) (Figure 3) are the lack of H4, H5 geminal coupling and singlet allyl resonance for (35) and coupled allyl resonances and strong geminal coupling of the H5 pair in (34). Consistent with this interpretation, neutralization of the NMR solution (H_2O, washing with saturated $NaHCO_3$) provides a 70% recovery of a mixture of (36) and (37) in a ratio (2.9:1)[19] which differs little from the ratio of cations (34) and (35) in solution. The regiospecificity is thus not high, but may be dependent on the acid used; cyclisation of (31) using $AlCl_3$ is reported to yield only (36).[16]

EXPERIMENTAL

NMR spectra were obtained on a JEOL GSX 270 spectrometer; temperatures were measured using the in-built copper/constantan thermocouple. Line shape analyses were performed using the EXCHANGE program (R.E.D. McClung, University of Alberta). ^1H and ^{13}C chemical shifts were measured internally relative to dichloromethane solvent resonances at 5.32 and 53.8 ppm respectively.

(E)-2,4-pentadienal was prepared and used as a dilute solution in CH_2Cl_2 due to its instability.[20] (E,E)-3,5-heptadien-2-one,[21] (E)-1-phenyl-1,4-pentadien-3-one[16], (E,E)-2,5-heptadien-4-one, [22] and the n-butylimine of 2,4-hexadienal[8] were prepared by literature methods; (E,E)-2,4-hexadienal, (E,E)-1,5-diphenyl-1,4-pentadien-3-one and 1,7-dimethyl-2,5-heptadien-4-one were purchased commercially. The imine (6) darkens rapidly on exposure to air and was used immediately after microdistillation.

(a) *Preparation of 5-benzoyloxy-2,4-pentadien-1-ol (11a).* 5-Benzoyloxy-2,4-pentadienal[23] (1g, 4.95 mmol) was dissolved in anhydrous methanol (20 ml) and cooled to 0 °C. $NaBH_4$ (0.38 g, 10 mmol) was added with stirring. After tlc showed complete reaction (ca. 10 minutes), H_2O (40 ml) and diethyl ether (30 ml) were added sequentially. After separation, the aqueous layer was further extracted with diethyl ether (2 x 50 ml) and the combined extracts were dried over $MgSO_4$. Removal of solvent and recrystallization from diethyl ether/petroleum ether (60-80) gave an off-white semi-solid [0.77 g, 76%; M^+ 204.0786 (calculated and found)].

Compound (11b) was prepared in a similar way as an off-white oil by slow addition of a methanol solution of 5-acetyloxy-2,4-pentadienal[23] to a suspension of $NaBH_4$ in methanol at O °C; (11b) polymerised over a period of hours and was used immediately.

(b) *NMR Data for Substrates (CD_2Cl_2).*

(3) ^1H: 9.53 (d,H1, $J_{1\text{-}2}$ =7.9), 6.13 (dd,H2,$J_{2\text{-}3}$=15.0), 7.08 (dd,H3, $J_{3\text{-}4}$=10.2), 6.58 (m,H4), 5.70 (d,H5E, $J_{4\text{-}5}$=17.6), 5.59 (d,H5Z, $J_{4\text{-}5}$=9.3).

(4) ^1H: 9.50 (d,H1, $J_{1\text{-}2}$ = 8.0), 6.03 (q, H2, $J_{2\text{-}3}$ = 15.1), 7.11 (m, H3), 6.32 (m, H4,5), 1.89 (d,3H6, $J_{5\text{-}6}$ = 5.8); ^{13}C: 193.8(C1), 152.6, 141.8, 130.0, 129.7(C2-5), 18.8(C6).

(5) ^{1}H: 2.21(s, 3H1), 6.02 (d, H3, J_{3-4} = 15.1), 7.09 (m, H4), 6.22 (m, H5, 6), 1.85 (d, 3H7, J_{6-7} = 5.1); ^{13}C: 25.9 (C1), 198.6 (C2), 143.9, 140.5, 130.5, 128.9 (C3-6), 18.9 (C7).

(6) ^{1}H: 7.83 (d, H1, J_{1-2} = 8.8), 6.20 (m, H2, H4), 6.55 (q, H3), 5.95 (m, H5, J_{4-5} = 15.0), 1.81 (d, 3H6, J_{5-6} = 6.8), 3.40(t), 1.53(m), 1.31(m), 0.89(t)(Bu^n, $J_{\alpha-\beta}$ = 6.9, $J\gamma-\delta$ = 7.3); ^{13}C: 162.4(C1), 141.6, 134.9, 131.0, 129.7 (C2-5), 18.6(C6), 61.4, 33.3, 20.6, 14.9 (Bu^n).

(11a) ^{1}H: 4.18 (d, 2H1, J_{1-2} = 5.1), 5.90 (m, H2), 6.30 (m, H3,4), 7.76 (d, H5, J_{4-5} = 11.2), 7.4-8.1 (m, Ph); ^{13}C: 163.3 (CO_2), 138.5, 133.8, 131.9, 129.8, 128.5, 128.2, 126.0, 115.0 (C2-5, Ph), 63.3 (C1).

(11b) ^{1}H: 4.17 (d, 2H1, J_{1-2} = 5.8), 5.87 (m, H2), 6.0-6.3 (m, H3, 4), 7.38 (d, H5, J_{4-5} = 12.2), 2.14 (s, MeCO).

(16) ^{1}H: 1.90 (dd, 6H1,7, J_{1-2} = 6.8, J_{1-3} = 1.5), 6.30 (dq, 2H2,6 J_{2-3} = 15.7), 6.88 (m, 2H3,5); ^{13}C: 188.9 (C4), 129.9, 142.6 (C2, 3, 5, 6), 18.1 (C1, 7).

(26) ^{1}H: 7.12, 7.73 (d, H1,2,J_{1-2} = 16.1), 7.4-7.7 (m, Ph); ^{13}C: 188.8 (C3), 143.2, 135.2, 130.8, 129.3, 128.6, 125.8 (C1, C2, Ph).

(27) ^{1}H: 6.03 (m, H3, J_{3-Me} = 1.4), 1.87, 2.12 (d, Me); ^{13}C: 191.5(C4), 126.4(C3), 154.4(C2), 20.5, 27.7 (Me).

(31) ^{1}H: 7.03, 7.68 (d, H1, 2, J_{1-2} = 16.1), 6.71 (dd, H4, J_{4-5E} = 17.4, J_{4-5Z} = 10.5), 6.35 (dd, H5E, J_{5E-5Z} = 1.5), 5.87 (dd, H5Z); ^{13}C: 189.4(C3), 143.8, 135.8, 135.1, 130.9, 129.3, 128.6, 128.5, 124.6 (C1, C2, C4, C5, Ph).

(c) *Preparation of NMR Samples.* The substrate (10-15 mg for ^{1}H, 50-60 mg for ^{13}C) was dissolved in CD_2Cl_2 (1.5 ml) in a 5 mm NMR tube, degassed with nitrogen and cooled to -80 °C. After addition of HSO_3F (0.1 ml, triply distilled) by syringe, the solution was mixed by shaking, placed in the NMR spectrometer and warmed to -20 °C. The mixture remains two phase (yellow/orange CD_2Cl_2 layer over smaller orange HSO_3F layer), but nevertheless provides good quality spectra.

(d) *NMR Data for Cations (CD_2Cl_2/HSO_3F)*

(7) ^{1}H:9.09 (d, H1, J_{1-2} = 10.8), 7.01 (dd, H2, J_{2-3} = 15.2), 8.43 (dd, H3, J_{3-4} = 10.4), 7.13 (m, H4), 6.80 (m, 2H5).

(8) ^{1}H: 8.80 (d, H1, J_{1-2} = 10.8), 6.82 (dd, H2, J_{2-3} = 13.5), 8.35 (dd, H3, J_{3-4} = 11.2), 6.97 (t, H4, J_{4-5} = 14.7), 7.64 (m, H5), 2.32 (d, Me, J_{5-Me} = 6.3); ^{13}C: 196.4, 183.6, 175.3, 133.8, 122.1, 22.2 ppm.

(9) ^{1}H: 6.63 (d, H2, J_{2-3} = 14.7), 8.30 (dd, H3, J_{3-4} = 11.1), 6.83 (t, H4, J_{4-5} = 15.0), 7.46 (m, H5), 2.25 (d, Me, J_{5-Me} = 7.3), 2.83 (s, Me).

(10) ^{1}H: 8.00 (dd, H1, J_{1-2} = 14.7), 6.37 (dd, H2, J_{2-3} = 11.6), 7.48 (dd, H3, J_{3-4} = 11.6), 6.52 (t, H4, J_{4-5} = 14.7), 6.82 (m, H5), 2.05 (d, Me, J_{5-Me} = 7.3), 3.72 (m, α-CH_2, $J_{\alpha-\beta}$ = 7.5, $J_{\alpha-NH}$ = 6.8), 1.73 (m, β-CH_2), 1.39 (m, γ-CH_2), 0.95 (t, CH_3, $J_{\gamma-CH_3}$ = 7.3), 8.70 (br, NH).

(17) ^{1}H: 8.23 (m, H1, $J_{1\text{-Me}}$ = 7.3), 6.84 (dd, H2, $J_{1\text{-}2}$ = 15.2, $J_{2\text{-Me}}$ = 1.5), 2.38 (dd, Me); ^{13}C: 195.4, 173.4, 123.9, 22.6 ppm.

(28) ^{1}H: 8.65 (d, H1, $J_{1\text{-}2}$ = 15.4), 7.45 (d, H2), 7.6-8.0 (m, Ph); ^{13}C: 190.3, 162.5, 137.6, 132.9, 132.7, 130.3, 117.2 ppm.

(29) ^{1}H: 6.53 (s, H2), 2.39, 2.49 (s, Me); 13C: 192.2, 189.3, 121.9, 25.8, 32.2 ppm.

(32) ^{1}H: 8.91 (d, H1, $J_{1\text{-}2}$ = 16.2), 7.50 (d, H2), 6.86 (dd, H4, $J_{4\text{-}5}$ = 8.1, 3.5), 7.28 (m, H5), 7.6-8.0 (m, Ph); ^{13}C; 195.3, 168.6, 146.0, 139.0, 133.8, 132.8, 130.6, 127.9, 117.3 ppm.

(19) ^{1}H: 6.79 (s, H2), 3.40 (m, H4), 3.51 (m, H5', $J_{5\text{-}5'}$ = 22.3, $J_{4\text{-}5'}$ = 3.5, $J_{4\text{-}5}$ = 0, $J_{4\text{-Me}''}$ = 7.6, $J_{5'\text{-Me}'}$ ≈ $J_{5\text{-Me}'}$ = 1.5), 2.90 (m, H5), 2.65 (t, Me'), 1.43 (d, Me''); 13C: 224.8, 221.9, 127.8, 44.9, 43.8, 22.2, 16.8 ppm.

(34) ^{1}H: 7.15 (m, H2, $J_{2\text{-}3}$ = 5.9, $J_{2\text{-}4}$ = 2.5), 8.97 (dd, H3, $J_{3\text{-}4}$ = 2.5), 4.74 (dd, H4), 3.86 (dd, H5', $J_{5\text{-}5'}$ = 23, $J_{4\text{-}5'}$ = 3.5), 3.26 (d, H5), 7.1-8.1 (m, Ph); ^{13}C: 229.4 (C1), 196.8 (C3), 45.2 (C5), 52.1 (C4), 120-140 ppm (C2, Ph).

(35) ^{1}H: 7.42 (s, H2), 3.42, 3.71 (m, H4,5), 7.1-8.1 (m, Ph); ^{13}C: 219.5 (C1), 205.1(C3), 33.3, 35.6 (C4,5), 120-140 ppm (C2, Ph).

(e) *Synthetic Cyclisation of (16)*

(i) *HSO_3F method.* Compound (16) (1 g, 9 mmol) was dissolved in dry CH_2Cl_2 (50 ml) and cooled to 0 °C under nitrogen. HSO_3F (3 ml) was added slowly and the mixture allowed to warm to room temperature with stirring. After stirring at room temperature for 20 hours, water (30 ml) was added. The aqueous phase was separated and extracted with CH_2Cl_2 (2 x 30 ml) and the combined CH_2Cl_2 fraction was washed with saturated sodium bicarbonate solution and brine before drying over $MgSO_4$. Removal of solvent and short-path distillation (35 °C/0.55 mm Hg) gave (21) as a clear liquid (0.44 g, 44%). Infrared (thin film): ν_{co} 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$): 5.83 (m, H2, $J_{2\text{-}4}$ = 1.5, $J_{2\text{-Me(3)}}$ = 1.0), 2.05 (d, Me(3)), 1.15 (d, Me(4), $J_{4\text{-Me(4)}}$ = 7.1), 2.78 (m, H4, $J_{4\text{-}5'}$ = 6.2, $J_{4\text{-}5}$ = 2.1), 1.96 (dd, H5, $J_{5\text{-}5'}$ = 17.6), 2.60 (dd, H5'); ^{13}C: 208.9 (C1), 182.6 (C2), 130.2 (C3), 44.2, 38.8 (C3, C4), 18.7, 17.0 (Me(3), Me(4)).

(ii) *Phosphoric/formic acid method.* To compound (16) (1 g, 9 mmol) under nitrogen were added 85% phosphoric acid (22.5 ml) and 90% formic acid (22.5 ml). The mixture was heated to 90 °C for 4 hours; after cooling, water (30 ml) was added and the mixture extracted with diethylether (3 x 50 ml). The combined ether extracts were washed with saturated sodium bicarbonate solution, brine and dried over $MgSO_4$. Removal of solvent followed by short-path distillation (35 °C, 0.5 mm Hg) gave (25) as a clear liquid (0.11 g, 11%). Infrared (thin film): ν_{co} 1692 cm^{-1}; ^{1}H NMR ($CDCl_3$): 2.04 (d, Me(2), $J_{Me(2)\text{-}Me(3)}$ =

1.0), 1.68 (m, Me(3), $J_{Me(3)-4} \approx J_{Me(3)-4'} = 1.9$), 2.38 - 2.43 (m, H4, 4', 5, 5'); ^{13}C: 209.9(C1), 170.0, 136.2 (C2, 3), 34.1, 31.4 (C4, C5), 17.1, 7.8 (Me(2), Me(3)).

NMR spectra of (21) and (25) agree with those in the literature.[24a,b]

Treatment of (26) (0.75 g, 3.2 mmol) under the same conditions for 28 hours, followed by workup as above gave a crude product which was purified by chromatotron (4:1 petroleum ether/ ethyl acetate). After elution of an unidentified orange band, the product (30) was eluted to give a viscous oil (0.30 g, 40%) which was further purified by sublimation (85 °C, 0.1 mm Hg) to give a white solid (mp: 72-74 °C (lit: 73-74 °C);[25] ν_{CO} (nujol): 1682 cm^{-1}; ^1H NMR ($CDCl_3$): 2.68, 3.04 (m, H4, 5), 7.1-7.4 (m, Ph); ^{13}C: 208.0 (C1), 167.9, 139.7 (C2,C3), 29.5, 34.8 (C4,C5), 127-135 (Ph).

Treatment of (16) with H_3PO_4 only under the above conditions yielded a 10: 1 mixture of (25) and (21).

(iii) *HBr/CH_3COOH method.* Compound (16) (0.5 g, 4.46 mmol), glacial acetic acid (27 ml) and 45% HBr (9 ml) were stirred under N_2 at 85 °C for 3 hours. After cooling, the reaction was quenched with water (30 ml) and extracted with diethylether (3 x 30 ml). After washing with water, saturated $NaHCO_3$ and brine and drying over $MgSO_4$, removal of solvent gave a brown oil (0.35 g) which was microdistilled (35-40 °C, 0.1 mm Hg) to give a 3.4:1 mixture of (25) and (21).

(iv) *$AlCl_3$ method.* Freshly sublimed $AlCl_3$ (1.05 g, 7.89 mmol) was suspended in CCl_4 (20 ml) and heated to 50 °C under N_2. A solution of (16) (1.0 g, 9.09 mmol) in CCl_4 (3 ml) was added and the solution refluxed gently for 30 minutes. After cooling, the solution was poured onto ice (30 g) containing NH_4Cl (3.75 g). Separation followed by extraction of the aqueous layer with CH_2Cl_2 (4 x 40 ml), washing of the organic phase with water, saturated $NaHCO_3$ and drying over $MgSO_4$ gave (after removal of solvent) a brown oil (0.4 g, 40%) which was microdistilled (35-40 °C, 0.1 mm Hg). NMR analysis indicated only (21) to be present.

(f) *Computational Results.* Semiempirical molecular orbital calculations were performed with the AM1 Hamiltonian in the MOPAC 6.0 program[26,27] running on a Sun SparcCenter 2000 at Keele University. Transition state structures and energies were determined by using the SADDLE and XYZ keywords.

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