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The Search for the Gas-Phase Negative Ion Pinacol Rearrangement

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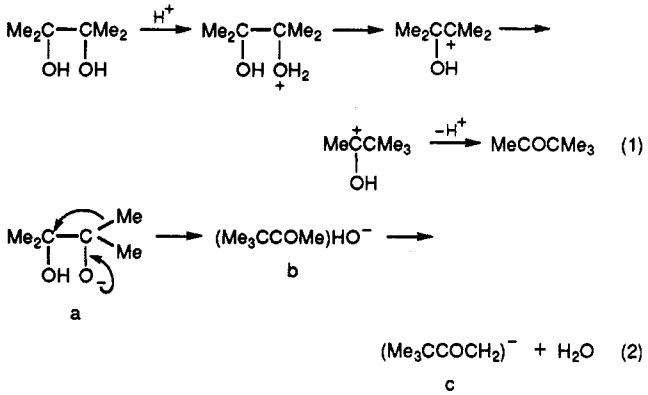
Abstract: Deprotonated 1,2-diols and β-methoxyhydrins often eliminate ROH (R = H, Me) on collisional activation in the gas phase. These losses do not involve a negative ion pinacol rearrangement in acyclic systems in which there are no conformational restraints on the relative positions of the reacting groups. In the case of β-methoxyhydrins, labeling studies show that the product ion is formed by the losses of a methoxide ion and a proton from *adjacent* positions. The absence of a deuterium isotope effect for this process precludes the operation of an elimination process: we propose that the loss of methanol proceeds via an epoxide cyclization viz. $Me_2C(OMe)C(O^-)(Me)_2 \rightarrow (MeO^-)$–$-CH_3(Me)\overset{O}{\overset{\frown}{C}}—C(Me)_2 \rightarrow CH_2{=}C(Me)C(O^-)(Me)_2 + MeOH$. In contrast, epoxide cyclization does not occur when the two oxygenated substituents cannot adopt an *anti* orientation. Thus deprotonated *cis*-2-methoxycyclohexanol loses methanol via a pinacol rearrangement, while loss of methanol from the *trans* isomer produces deprotonated cyclohex-2-en-1-ol, presumably by an epoxide mechanism.

Introduction

We have recently described how the Beckmann rearrangement of oximes, a reaction which occurs under acid-catalyzed conditions in the condensed phase,[1] may occur in the gas phase for negative ions formed by deprotonation of oximes.[2] This has led us to investigate whether there are any other examples of such a scenario, and in this paper, we consider whether there is a gas-phase negative ion counterpart to one of the oldest and most famous of all acid-catalyzed rearrangements, the pinacol/pinacolone rearrangement (eq 1).[3,4] The condensed-phase reaction involves a simple Whitmore 1,2-methyl shift,[5] and the driving force for the reaction is the stabilization of the final carbonium ion intermediate by elimination of a proton to form the neutral product. Many "pinacol-type" reactions are known: the migrating group may be alkyl, aryl, or hydrogen.[4]



It seems possible that in the gas phase, collisional activation of deprotonated pinacol (**a**, eq 2) could effect a 1,2-methyl anion rearrangement to form ion complex **b**, which if formed, should most certainly decompose to yield deprotonated pinacolone **c**. Ion **c** may be readily identified from its characteristic fragmentation behavior.[6] Base-catalyzed reactions of the pinacol type are not common in the condensed phase: a major reason is presumably that HO^- is a poor leaving group under these conditions. Even so, such reactions have been observed, but they involve the release of ring strain,[7,8] e.g. the reaction between HO^- and 1,1′-dihydroxybicyclopropane yields 2-hydroxy-2-ethylcyclobutanone.[7] A few base-catalyzed pinacol-type reactions have been reported for β-chlorohydrins, i.e. where the leaving group is Cl^-.[8,9]

The aim of the work described in this paper is to determine the mechanisms by which H_2O and MeOH are lost in the gas phase from deprotonated 1,2-diols and β-methoxyhydrins, respectively. In particular, do these losses occur by negative ion pinacol rearrangements such as that shown in eq 2?

Experimental Section

Collisional activation and charge-reversal (positive ion)[10] mass spectra (MS/MS) of deprotonated neutrals, and of some source-formed product anions, were determined with a VG ZAB 2HF instrument. Full experimental details for the operation of this instrument have been reported.[11] Specific details are as follows: the chemical ionization slit was used in the ion source, the ionizing energy was 70 eV, the ion source temperature was 150 °C, and the accelerating voltage was 7 kV. Samples were introduced through the septum inlet (which was maintained at 100 °C) to give a measured source pressure of 5×10^{-7} Torr. Deprotonation

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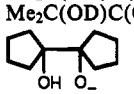
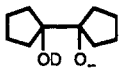
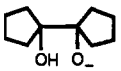
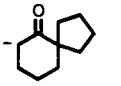
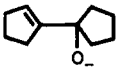
Table I. Collisional Activation Mass Spectral Data for 1,2-Diols

parent (m/z)	m/z (loss or formation) abundance
$Me_2C(OH)C(O^-)(Me_2)$ (117)	116 ($H^•$) 100, 101 (CH_4) 70, 57 (Me_2CHOH) 4
$Me_2C(OD)C(O^-)Me)_2$ (118)	117 ($H^•$) 100, 101 (CH_3D) 72, 57 (Me_2CHOD) 4
 (169)	167 (H_2) 10, 151 (H_2O) 19, 141 (C_2H_4) 42, 85 (C_5H_8O) 12, 83 ($C_5H_{10}O$) 100
 (170)	168/167[a] (H_2, HD) 15, 151 (HOD) 25, 142 (C_2H_4) 38, 86 (C_5H_8O) 18, 83 (C_5H_9DO) 100

[a] Unresolved.

Table II. Mass Spectral Data for Selected Product Ions from Deprotonated 1,2-Diols

parent ion (m/z)	product ion (m/z)	spectrum type	CA: m/z (loss or formation) abundance CR: m/z (abundance)
$Me_2C(OH)C(O^-)Me_2$ (117)	$-CH_4$ (101)	CA MS/MS/MS[a]	57 (Me_2CHOH) 100, 43 ($C_4H_{10}O$) 42
		CR MS/MS/MS[a]	59 (55), 43 (100), 42 (79), 39 (32), 31 (20), 29 (16), 27 (12), 15 (15)
$[MeCOC(OH)Me_2 - H]^-$ (101)		CA MS/MS	100 ($H^•$) 3, 86 ($Me^•$) 2, 85 (CH_4) 3, 83 ($CH_4 + H_2$) 1, 57 (Me_2CHOH) 100, 43 ($C_4H_{10}O$) 36, 41 (HC_2O^-) 1, 15 (Me^-) 0.1
		CR MS/MS	59 (54), 57 (8), 55 (4), 53 (5), 51 (2), 43 (100), 42 (78), 39 (34), 31 (21), 29 (15), 27 (10), 15 (12)
 (169)	$-H_2O$ (151)	CA MS/MS/MS	149 (H_2) 9, 83 (C_5H_8) 100, 67 ($C_5H_7^-$) 7
 (151)		CA MS/MS	149 (H_2) 100, 147 ($2H_2$) 4, 123 (C_2H_4) 8, 109 (42) 6, 107 (44) 2
 (151)		CA MS/MS	149 (H_2) 11, 83 (C_5H_8) 100, 67 ($C_5H_7^-$) 9

[a] Spectra are weak—peaks <5% in abundance are lost in baseline noise.

Table III. Collisional Activation Mass Spectral Data for Deprotonated β-Methoxyhydrins

parent ion (m/z)	m/z (loss or formation) relative abundance
$Me_2C(OMe)C(O^-)(Me)_2$ (131)	130 ($H^•$) 4, 115 (CH_4) 1, 99 (MeOH) 100, 83 (MeOH + CH_4) 1.5, 57 ($MeCOCH_2^-$) 7, 31 (MeO^-) 1
$Me_2C(OMe)C(O^-)(CD_3)_2$ (137)	136/135[a] ($H^•$, $D^•$) 5, 105 (MeOH) 100, 62 ($CD_3COCD_2^-$) 5, 31 (MeO^-) 0.5
$Me_2C(OMe)C(^{18}O^-)(Me)_2$ (133)	132 ($H^•$) 5, 117 (CH_4) 1, 101 (MeOH) 100, 85 (MeOH + CH_4) 1, 59 ($MeC^{18}OCH_2^-$) 5, 31 (MeO^-) 0.5

[a] Not resolved.

was effected by using NH_2^- (from NH_3; measured source pressure of $NH_3 = 1 \times 10^{-5}$ Torr). The *estimated* total source pressure was 10^{-1} Torr. Helium was used in the second collision cell (measured pressure 2×10^{-7} Torr), giving a reduction of 10% in the main beam. The appropriate collision-induced mass spectrum (MS/MS) was obtained by scanning the electric sector in either negative or positive mode.

Consecutive collision-induced and charge-reversal mass spectra (MS/MS/MS) were recorded with a Kratos MS 50 TA instrument. Operating details for this instrument have been reported previously.[12] Substrates were deprotonated by MeO^- (from MeONO)[13] in a Kratos Mark IV chemical ionization source: source temperature 100 °C, electron energy 280 eV, emission current 500 μA, and accelerating voltage 8 kV. The measured substrate pressure was 2×10^{-5} Torr, the methyl nitrite pressure was 1×10^{-6} Torr, and the *estimated* total source pressure was 10^{-1} Torr. The indicated pressure of helium in each of the two collision cells was 2×10^{-6} Torr, giving an overall 30% reduction in the main beam.

Pinacol, methyl *tert*-butyl ketone, cyclohexanone, and 1-hydroxycyclohex-2-ene were commercial samples. The following compounds were prepared by reported methods: 3-hydroxy-3-methylbutan-2-one,[14] 1,1′-dihydroxybicyclopentane,[15] spiro[4,5]decan-6-one,[16] pinacol monomethyl ether,[17] 2,3-dimethylbut-3-en-2-ol,[18] 1-(1-methylethenyl)cyclopentanol,[19] *cis*-2-methoxycyclohexanol,[20] *trans*-2-methoxycyclohexanol,[21] and 1-formylcyclopentane.[22]

1-Cyclopentenylcyclopentanol. A solution of 1-chloro-1-cyclopentene (2.0 g) in anhydrous tetrahydrofuran (10 cm³) was added dropwise to a suspension of Li (0.5 g) in anhydrous tetrahydrofuran (25 cm³), and the mixture was stirred at 25 °C for 1.5 h. The mixture was filtered (under N_2) into another flask and cooled to −78 °C; cyclopentanone (1.6 g) in anhydrous tetrahydrofuran (5 cm³) was added dropwise, and the mixture stirred at −78 °C for 30 min, warmed to 25 °C, and stirred at that temperature for 15 min. Aqueous ammonium chloride (saturated, 10 cm³) was added, the mixture extracted with diethyl ether (3 × 25 cm³), and the extract dried ($CaCl_2$) and distilled to yield 1-cyclopentenylcyclopentanol (1.7 g, 59%), bp 126–128 °C/40 mmHg. Found $M^{•+}$ = 152.1199; $C_{10}H_{16}O$ requires 152.1201 (all masses given as m/z). ^1H NMR (60 MHz, $CDCl_3$): δ 1.5–2.5 (m, 15H including OH), 5.5–5.65 (m, 1H).

1-(1-Methoxy-1-methylethyl)cyclopentanol. A mixture of 1-(1-methylethenyl)cyclopentanol[19] (0.4 g), anhydrous methanol (5 cm³), and mercuric acetate (1.0 g) was allowed to stir at 25 °C for 1 h and was cooled to 0 °C, followed by addition of aqueous sodium hydroxide (6 N, 4 cm³) and then a solution of sodium borohydride (0.25 g) in aqueous sodium hydroxide (3 N, 5 cm³). The mixture was allowed to stir at 25

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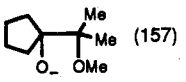
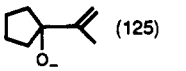
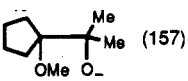
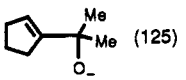
Table IV. Mass Spectral Data for Selected Product Ions from Deprotonated β-Methoxyhydrins

parent ion (m/z)	product ion (m/z)	spectrum type	CA: m/z (loss or formation) abundance CR: m/z (abundance)
$Me_2C(OMe)C(O^-)(Me)_2$ (131)	–MeOH[a] (99)	CA MS/MS	98 ($H^•$) <10,[b] 83 (CH_4) 38, 57 ($MeCOCH_2^-$) 100, 41 (HC_2O^- + $C_3H_5^-$) <10[b]
		CR MS/MS	84 (1), 69 (24), 67 (8), 59 (6), 53 (12), 43 (100), 41 (69), 39 (78), 31 (2), 29 (5), 27 (12), 15 (6), 14 (2)
$Me_2C(OMe)C(^{18}O^-)(Me)_2$ (133)	–MeOH[a] (101)	CA MS/MS	100 ($H^•$) 9, 85 (CH_4) 29, 59 ($MeC^{18}OCH_2^-$) 100, 43 ($HC_2{}^{18}O^-$) 6, 41 ($C_3H_5^-$) 4
$Me_2C(OMe)C(O^-)(CD_3)_2$ (137)	–MeOH[a] (105)	CA MS/MS	104 ($H^•$) 7, 103 ($D^•$) 2, 86 (CD_3H) 5, 85 (CD_4) 18, 62 ($CD_3COCD_2^-$) 100, 42 (DC_2O^-) 2, 41 ($C_3H_5^-$) 4
$^-[CH_2COC(Me)_3]$[6] (99)		CA MS/MS	97 (H_2) 16, 83 (CH_4) 78, 85 (CH_4 + H_2) 12, 57 ($MeCOCH_2^-$) 39, 43 ($^-CH_2CHO$) 11, 41 (HC_2O^-) 100
$CH_2{=}C(Me)C(O^-)(Me)_2$ (99)		CA MS/MS	98 ($H^•$) 14, 83 (CH_4) 34, 57 ($MeCOCH_2^-$) 100, 41 (HC_2O^-) 7
		CR MS/MS	84 (2), 69 (25), 67 (9), 59 (3), 53 (13), 43 (100), 41 (70), 39 (80), 31 (3), 29 (5), 27 (11), 15 (6), 14 (2)
 (157)	–MeOH[a] (125)	CA MS/MS	124 ($H^•$) 100, 83 (Me_2CHOMe) 45[c(i)]
		CR MS/MS	91 (2), 89 (3), 87 (4), 83 (6), 81 (3), 79 (8), 77 (6), 69 (42), 67 (26), 65 (15), 55 (63), 53 (28), 51 (18), 53 (28), 41 (100), 39 (94), 29 (8), 27 (25), 14 (1)
 (125)		CA MS/MS	124 ($H^•$) 100, 83 (Me_2CHOMe) 42[c(ii)]
		CR MS/MS	91 (2), 89 (3), 87 (4), 83 (7), 81 (3), 79 (7), 77 (6), 69 (40), 67 (25), 65 (14), 55 (60), 53 (30), 51 (17), 43 (24), 41 (100), 39 (98), 29 (7), 27 (23), 14 (1)
 (157)	–MeOH[a] (125)	CA MS/MS	124 ($H^•$) 100, 109 (CH_4) 40,[c(iii)] 67 ($C_5H_7^-$) 16, 57 ($MeCOCH_2^-$) 59[c(iv)]
		CR MS/MS	95 (47), 93 (12), 91 (15), 81 (8), 79 (22), 77 (18), 67 (65), 65 (60), 55 (18), 53 (26), 51 (25), 43 (100), 41 (76), 39 (87), 27 (28), 15 (6)
 (125)		CA MS/MS	124 ($H^•$) 100, 109 (CH_4) 45,[c(v)] 67 ($C_5H_7^-$) 14, 57 ($MeCOCH_2^-$) 64[c(vi)]
		CR MS/MS	95 (45), 93 (10), 91 (18), 81 (7), 79 (20), 77 (20), 67 (65), 65 (58), 55 (16), 53 (26), 51 (27), 43 (100), 41 (73), 39 (85), 27 (26), 15 (5)

[a] Product ions formed in ion source. [b] This spectrum is weak: an accurate abundance for this peak cannot be given because of baseline noise. [c] Width of peaks at half-height [average of 10 measurements (volts ± 0.5): (i) 30.1; (ii) 30.2; (iii) 48.3; (iv) 29.1; (v) 47.9; (vi) 28.8.

Table V. MS/MS and Kinetic Isotope Data for Deprotonated 3-Alkoxy-3-methyl-2-phenylbutan-2-ols and Their Deuterated Analogues

$Me_2C(OMe)C(O^-)(Me)(Ph)$	CA MS/MS: see Figure 2
	(–MeOH):(–PhH) = (21.25 ± 0.3):1[a]
$(CD_3)_2C(OMe)C(O^-)(Me)(Ph)$	(–MeOD):(–PhH) = (21.55 ± 0.3):1[a]
	CA MS/MS: 198 ($H^•$) 26, 166 (MeOD) 100, 121 (PhH) 4.7, 119 [$(CD_3)_2CH(OMe)$] 3, 88 (MeOD + PhH) 2, 77 (Ph^-) 2, 31 (MeO^-) 1
$Me_2C(OEt)C(O^-)(Me)(Ph)$	CA MS/MS: 206 ($H^•$) 23, 161 (EtOH) 100, 129 (PhH) 5.2, 119 [$Me_2CH(OEt)$] 4, 83 (EtOH + PhH) 3, 77 (Ph^-) 2, 45 (EtO^-) 1
	(–EtOH):(–PhH) = (19.61 ± 0.3):1[a]
$(CD_3)_2C(OEt)C(O^-)(Me)(Ph)$	(–EtOD):(–PhH) (19.44 ± 0.3):1[a]
	CA MS/MS: 212 ($H^•$) 22, 166 (EtOD) 100, 135 (PhH) 5.2, 119 [$(CD_3)_2CH(OEt)$] 4, 88 (EtOD + PhH) 3, 77 (Ph^-) 2, 45 (EtO^-) 1

[a] This ratio is an average of 10 measurements.

Table VI. Collision Activation Mass Spectral Data for Deprotonated 2-Methoxycyclohexanols

parent ion (m/z)	m/z (loss of formation) relative abundance
[*trans*-2-methoxycyclohexanol – H]$^-$ (129)	128 ($H^•$) 25, 127 (H_2) 12, 97 (MeOH) 100, 95 (MeOH + H_2) 8, 79 (MeOH + H_2O) 15, 69 (MeOH + C_2H_4) 2, 31 (MeO^-) 8
[*cis*-2-methoxycyclohexanol – H]$^-$ (129)	127 (H_2) 100, 125 ($2H_2$) 5, 114 ($Me^•$) 1, 112 ($Me^•$ + H_2) 7, 97 (MeOH) 12, 95 (MeOH + H_2) 3, 69 (MeOH + C_2H_4) 1, 31 (MeO^-) 1

°C for 2.5 h, filtered through Celite, and extracted with diethyl ether (3 × 25 cm^3). The organic extract was dried (Na_2SO_4) and distilled *in vacuo* to yield 1-(1-methoxy-1-methylethyl)cyclopentanol (0.44 g, 87%), bp 64–67 °C/3 mmHg. Found ($M^{•+}$ – $Me^•$) = 143.1071; $C_8H_{15}O_2$ requires 143.1072. ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.2 (s, 6H), 1.5–1.85 (m, 8H), 2.5 (s, 1H, OH), 3.25 (s, 3H).

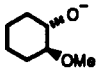
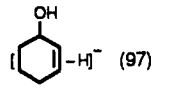
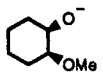
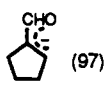
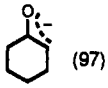
2-(1-Methoxycyclopentyl)propan-2-ol. 1-(1-Ethoxyethenyl)cyclopentanol[23] (1.0 g) in anhydrous tetrahydrofuran (10 cm^3) was added dropwise, at 0 °C, to a suspension of sodium hydride (0.3 g) in anhydrous tetrahydrofuran (10 cm^3). After the mixture was stirred at 25 °C for 15 min, iodomethane (1.4 g) in anhydrous tetrahydrofuran (5 cm^3) was added dropwise; the mixture was heated under reflux for 2 h, quenched with water (10 cm^3), and extracted with diethyl ether (3 × 25 cm^3), and the organic extract was dried (Na_2SO_4). Removal of the solvent, followed by hydrolysis,[23] gave 1-acetyl-1-methoxycyclopentane (0.74 g, 82%), bp 62–63 °C/13 mmHg, which was treated under standard Grignard conditions[24] with methylmagnesium iodide to yield 2-(1-methoxycyclopentyl)propan-2-ol (0.6 g, overall yield 61%), bp 66–68 °C/3 mmHg. Found (M – H)$^-$ = 157.1223; $C_9H_{17}O_2$ requires 157.1228. ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.2 (s, 6H), 1.4–1.9 (m, 8H), 2.35 (s, 1H, OH), 3.2 (s, 3H).

3-Methoxy-3-methyl-2-phenylbutan-2-ol. Phenylmagnesium bromide [from bromobenzene (1.6 g) and magnesium (0.25 g)] in anhydrous diethyl ether (25 cm^3) was added dropwise to a solution of 3-methoxy-3-methyl-2-butanone[25] (1 g) in diethyl ether (25 cm^3) at 0 °C. The mixture was allowed to stir at 0 °C for 0.5 h and at 25 °C for 3 h, and then aqueous ammonium chloride (saturated, 25 cm^3) was added. The ethereal layer was washed with water (2 × 10 cm^3) and dried (Na_2SO_4). Removal of the diethyl ether, followed by recrystallization of the product from diethyl ether/hexane (1:1), gave 3-methoxy-3-methyl-2-phenylbutan-2-ol as colorless crystals, mp 32–33 °C (0.95 g, yield 57%). Found (M – H)$^-$ = 193.1230; $C_{12}H_{17}O_2$ requires 193.1223. ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.0 (s, 3H), 1.2 (s, 3H), 1.6 (s, 3H), 3.2 (s, 3H), 7.1–7.6 (m, 5H).

3-Ethoxy-3-methyl-2-phenylbutan-2-ol was prepared as for 3-methoxy-3-methyl-2-phenylbutan-2-ol, except that 3-ethoxy-3-methyl-2-butanone[25] was used. Yield: 64%. Bp: 130–135 °C/0.2 mmHg. Found (M – H)$^-$ = 207.1374; $C_{13}H_{19}O_2$ requires 207.1380. ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.0 (s, 3H), 1.15 (s, 3H), 1.2 (t, J = 7 Hz, 3H), 1.6 (s, 3H), 3.3 (q, J = 7 Hz, 2H), 7.0–7.5 (m, 5H).

(23) Baldwin, J. E.; Hofle, G. A.; Lever, O. W. *J. Am. Chem. Soc.* **1974**, *96*, 7125.
(24) Guillerm-Dron, D.; Capman, M. L.; Chodkiewicz, W. *Bull. Soc. Chim. Fr.* **1973**, *4*, 1417.
(25) Hennion, G. F.; Boisselle, A. P. *J. Org. Chem.* **1961**, *26*, 2677.

Table VII. Mass Spectral Data for Product Ions from Deprotonated 2-Methoxycyclohexanols

parent ion (m/z)	product ion (m/z)	MS/MS spectrum type	CA: m/z (loss or formation) abundance CR: m/z (abundance)
 (129)	–MeOH[a] (97)	CA	see Figure 3A[b(i)]
 (97)		CA	96 (H•) 8, 95 (H_2) 44, 93 ($2H_2$) 1, 79 (H_2O) 100, 69 (C_2H_4) 15, 43 ($^-CH_2CHO$) 1
 (97)		CA	96 (H•) 6, 95 (H_2) 48, 93 ($2H_2$) 2, 79 (H_2O) 100,[b(ii)] 69 (C_2H_4) 17,[b(iii)] 43 ($^-CH_2CHO$) 1
 (129)	–MeOH[a] (97)	CA CR	see Figure 3B[b(iv)] 97 (2), 96 (8), 95 (13), 94 (2), 81 (4), 79 (14), 77 (6), 67 (54), 65 (19), 63 (5), 55 (34), 53 (28), 51 (22), 50 (22), 43 (8), 41 (86), 39 (100), 29 (18), 27 (41), 26 (23), 14 (1)
 (97)		CA CR	96 (H•) 16, 95 (H_2) 100, 93 ($2H_2$) 3, 69 (C_2H_4) 14,[b(v)] 41 (HC_2O^-) 1 97 (2), 96 (8), 95 (14), 94 (2), 81 (4), 79 (12), 77 (6), 67 (51), 65 (20), 63 (5), 55 (28), 53 (29), 51 (21), 50 (20), 43 (10), 41 (81), 39 (100), 29 (20), 27 (39), 26 (24), 14 (1)
 (97)		CA CR	96 (H•) 8, 95 (H_2) 100, 93 ($2H_2$) 2, 69 (C_2H_4) 8,[b(vi)] 41 (HC_2O^-) 0.5 81 (2), 79 (10), 77 (1), 67 (16), 65 (6), 55 (49), 53 (29), 50 (28), 41 (65), 39 (100), 29 (8), 27 (64), 15 (1), 14 (1)

[a] Product ions formed in the ion source. [b] Width of peaks at half-height [average of 10 measurements (volts ● 0.5)]: (i) 28.8 (m/z 79), 111.0 (m/z 69); (ii) 29.2; (iii) 110.3; (iv) 82.2 (m/z 69); (v) 81.6; (vi) 92.0.

The Labeled Compounds. The ions $Me_2C(OD)C(O^-)(Me)_2$ and $c\text{-}C_5H_8C(OD)C(O^-)\text{-}c\text{-}C_5H_8$ were produced by allowing the unlabeled compounds to react with D_2O in the septum inlet system prior to dedeuteration (D_1 > 80%).[26]

2-(Methyl-d_3)-4-methyl-3-methoxybutan-2-ol-*1,1,1-d*$_3$. The standard reaction[18] between 2-lithiopropene and acetone-d_6 gave 3-hydroxy-3-(methyl-d_3)but-1-ene-*4,4,4-d*$_3$ (58% yield), which when reacted with methanol [as described for 1-(1-methoxy-1-methylethyl)cyclopentanol, above] gave the required product in 65% yield (D_6 = 99%).

2,3-Dimethyl-3-methoxybutan-2-ol-^{18}*O*. A mixture of 2-methoxy-2-methylpropanoyl chloride[27] (1.0 g), $H_2{}^{18}O$ (0.3 g) (^{18}O = 24%), and anhydrous tetrahydrofuran was allowed to stand at 25 °C for 4 h. The solvent was removed, and the residue was dried *in vacuo* (0.02 mmHg) for 2 h, dissolved in anhydrous diethyl ether (10 cm^3), and then subjected to a standard[24] Grignard reaction with methylmagnesium iodide (2.2 equiv). Distillation gave the required product in 60% yield (^{18}O = 12%).

3-Methoxy-3-(methyl-d_3)-2-phenylbutan-2-ol-*4,4,4-d*$_3$. 1-Lithio-1-methoxyethene was treated with acetone-d_6 by a reported procedure[23] to form 3-methoxy-1-(methyl-d_3)-3-buten-2-ol-*1,1,1-d*$_3$, which was methylated with sodium hydride and methyl iodide in tetrahydrofuran (see above) and hydrolyzed[23] to 3-methoxy-3-(methyl-d_3)butan-2-one-*4,4,4-d*$_3$, which upon treatment with phenylmagnesium bromide (see above) gave the required labeled derivative in 27% overall yield, mp 32–33 °C (D_6 = 99%).

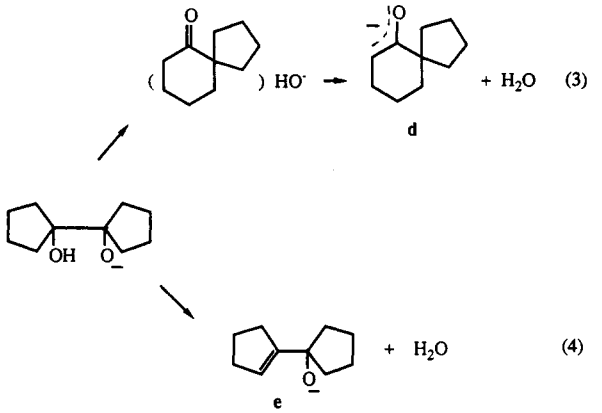
3-Ethoxy-3-(methyl-d_3)-2-phenylbutan-2-ol-*4,4,4-d*$_3$ was prepared as for 3-methoxy-3-(methyl-d_3)-2-phenylbutan-2-ol-*4,4,4-d*$_3$ (above), except that ethyl iodide replaced methyl iodide: overall yield 15%; bp 130–135 °C/0.2 mmHg (D_6 = 99%).

Results and Discussion

1. Deprotonated 1,2-Diols. The collisional activation (CA)[28] mass spectra (MS/MS) of deprotonated diols are recorded in Table I. Mass spectral data for selected product ions [MS/MS/MS, CA, and charge-reversal (CR)[9] (as appropriate)] are listed in Table II. The CA data of the prototypical species, deprotonated pinacol, are recorded in Table I. Loss of water, which might indicate a pinacol rearrangement (eq 2), is not observed in this spectrum. Instead, the spectrum shows losses of H•,[29] together with the standard processes[30] (i) loss of methane[31,32] and (ii) formation of $(MeCOCH_2)^-$.

We next chose to investigate a bicyclic alkyl diol which cannot undergo the loss of methane that is so prominent in the spectrum of deprotonated pinacol. Deprotonated 1,1′-dihydroxybicyclopentane is such a system; its spectrum (Table I), although

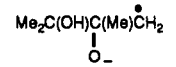
Scheme I



dominated by the simple cleavage/deprotonation reaction that forms deprotonated cyclopentanone, also shows loss of water. If this loss of water occurs by the pinacol rearrangement, the product ion will be the enolate **d** (eq 3, Scheme I). Comparison of the CA mass spectrum of m/z 151 (from deprotonated 1,1′-dihydroxydicyclopentane) with that of authentic **d** (formed by deprotonation of the corresponding neutral) shows the two species to have quite different structures (see Table II). Thus the pinacol rearrangement does not occur in this system. The product ion formed by loss of water is identified as **e** (eq 4, Scheme I) by the

(26) Shannon, J. S. *Aust. J. Chem.* **1962**, *15*, 265.
(27) Richardson, W. H.; Koskinin, W. C. *J. Org. Chem.* **1976**, *41*, 3182.
(28) For a discussion of the experimental method see: Stringer, M. B.; Bowie, J. H.; Holmes, J. L. *J. Am. Chem. Soc.* **1986**, *108*, 3888.

(29) Loss of H• in this system occurs exclusively from methyl (see Table I) to form



(30) For a review see: Bowie, J. H. *Mass Spectrom Rev.* **1990**, *9*, 351 and references cited therein.
(31) The loss of methane could occur by the standard[30] process $Me_2C(OH)C(O^-)Me \rightarrow [Me_2C(OH)COMe]Me^- \rightarrow [Me_2C(OH)COMe - H]^- + CH_4$. The identity of the product ion is confirmed by the data listed in Table II. However, it is possible that the loss of methane might occur by an epoxide reaction analogous to that shown in Scheme III, since this process would also yield the product ion $[Me_2C(OH)COMe - H]^-$.
(32) Even though the reactions are probably kinetically controlled, it is of interest that ΔH for the pinacol process, $Me_2C(OH)C(O^-)(Me)_2 \rightarrow (Me_3CCOCH_2)^- + H_2O$, is 15 kcal mol^{-1} more endothermic than that for $Me_2C(OH)C(O^-)(Me)_2 \rightarrow [MeCOC(OH)Me - H]^- + CH_4$ [using Benson's rules (Benson, S. W. *Thermochemical Kinetics*; J. Wiley and Sons: New York, 1968) and assuming that the electron affinities of the radicals corresponding to the two ionic products are the same.] Should the electron affinity of [MeCOC(OH)Me – H]• be the more positive, the second reaction will be even more favored thermodynamically.

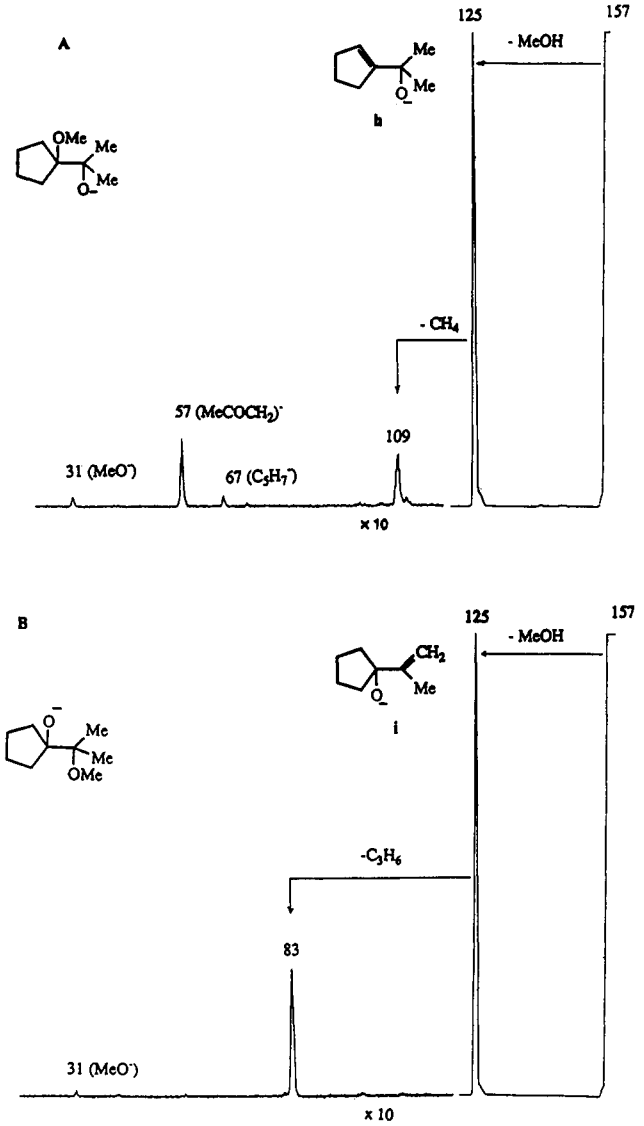


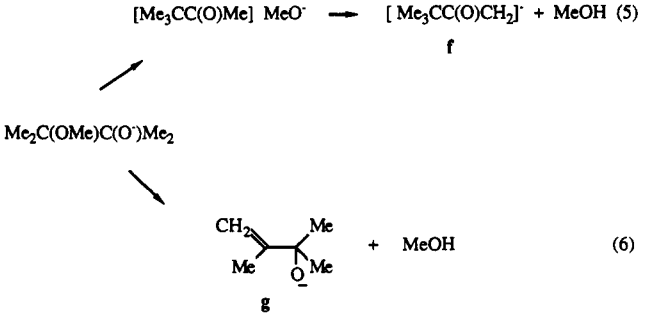
Figure 1. Collisional activation mass spectra of deprotonated (A) 2-(1-methoxycyclopentyl)propan-2-ol and (B) 1-(1-methoxy-1-methylethyl)-cyclopentanol (VG ZAB 2HF instrument).

data contained in Table II. The mechanism of this process will be considered below.

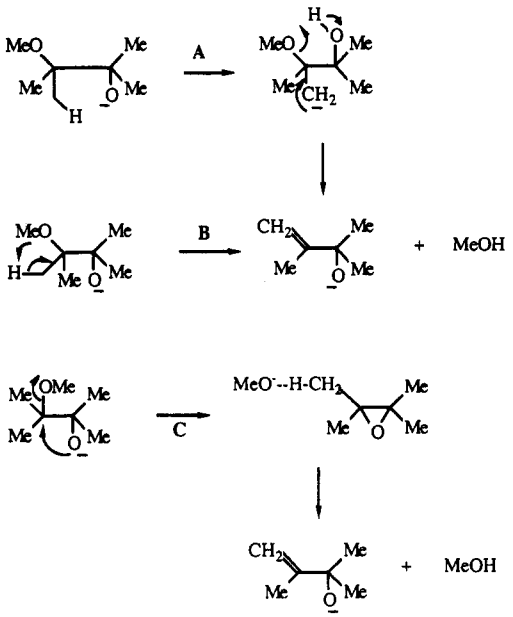
2. Deprotonated β-Methoxyhydrins. We next studied deprotonated β-methoxyhydrins for three principal reasons: (i) we wished to restrict those neutral losses from the $(M - H)^-$ ion which had previously involved deprotonation at OH, (ii) we expected that the losses of methanol from β-methoxyhydrins would be more pronounced than the quite modest losses of water from deprotonated 1,2-diols, and (iii) the inherent nonsymmetry of the β-methoxyhydrins should enable us to determine the deprotonation center(s) associated with the expected losses of methanol. All of these expectations were realized.

The spectral data for deprotonated pinacol methyl ether and of the labeled ions $Me_2C(OMe)C(O^-)(CD_3)_2$ and $Me_2C(OMe)C(^{18}O^-)(Me)_2$ are listed in Table III. The unlabeled ion loses MeOH to yield the base peak of the spectrum, and both labeled derivatives specifically lose MeOH. The data from the labeled compounds are of particular interest. First, the specific loss of MeOH from the ^{18}O-labeled derivative establishes that there is no methyl migration occurring between the two oxygens; i.e., the two oxygens are not equivalent. Second, the specific loss of MeOH from the deuterium-labeled derivative establishes that the loss involves MeO and H from *adjacent* carbons. Thus, this reaction cannot involve the pinacol rearrangement shown in eq 5 since this process requires deprotonation at a methyl group adjacent to the original O^- group. The data recorded in Table IV support this, since the product ion formed by loss of MeOH from deprotonated pinacol methyl ether is not **f** (eq 5, Scheme II), but **g** (eq 6).[33] The regiospecificity of the deprotonation reaction which accompanies the loss of methanol is further illustrated by a consideration of the fragmentation behavior of the isomeric ions shown in Figure 1. Both spectra are dominated by losses of methanol: the data recorded in Table IV identify the product ions as **h** and **i**, respectively (see Figure 1).

Scheme II



Scheme III



There are three mechanisms which could account for the regiospecificity of the loss of MeOH from deprotonated β-methoxyhydrins (and presumably also the loss of water from deprotonated 1,2-diols, even though labeling data are not available in these systems), viz. (i) an elimination reaction which is preceded by proton transfer to the O^- site as shown in sequence **A** (Scheme III), (ii) an elimination reaction in which the charged center plays no part (sequence **B**; a charge "remote" reaction[34]), and (iii) a process which involves initial epoxide formation, followed by deprotonation of an adjacent alkyl group by the methoxide anion either in synchronous fashion or in a stepwise process via a transient intermediate in which $MeOH^-$ may only react with an adjacent methyl group [sequence **C** (Scheme III)].

It may be possible to differentiate between the elimination and epoxide mechanisms by the use of deuterium isotope effects. Both

(33) The major fragmentations of **g** are (i) $CH_2{=}C(Me)C(O^-)Me_2 \rightarrow [CH_2{=}C(Me)COCH_2]^- + CH_4$ and (ii) $CH_2{=}C(Me)C(O^-)Me_2 \rightarrow (MeCOCH_2)^- + CH_2{=}CHMe$, as evidenced by the labeling data listed in Table IV.

(34) For a review of "charge remote" fragmentations see: Adams, J. *Mass Spectrom. Rev.* **1990**, *9*, 141.

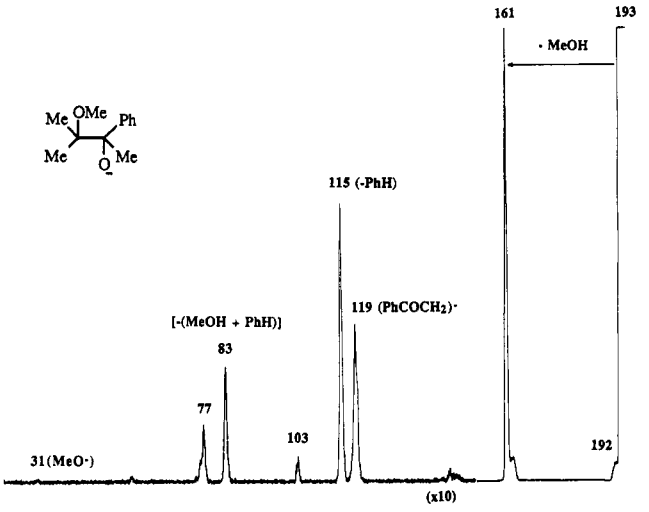


Figure 2. Collisional activation mass spectrum of 3-methoxy-3-methyl-2-phenylbutan-2-ol (VG ZAB 2HF instrument).

of the elimination reactions (sequences **A** and **B**) involve deprotonation and/or proton transfer in the rate-determining step and should show primary kinetic deuterium isotope effects.[35] In contrast, if the cyclization step of sequence **C** is rate determining, no deuterium isotope effect should be observed. The experiment is not so straightforward however. The dangers of using intermolecular isotope effects for ionic decompositions in the gas phase have been documented.[36] If we are therefore to compare the losses of MeOH and MeOD from, e.g., deprotonated pinacol and from $(CD_3)_3C(OMe)C(O^-)Me_2$, then these must be compared with an internal standard which must be the same in both cases and show no isotope effect. An obvious example might be to compare the ratios of the abundances of $[CH_3C(O)CH_2]^-$ peaks to those formed by losses of MeOH and MeOD in the spectra of unlabeled and labeled pinacol methyl ether spectra. However, this may not be an appropriate system since there could be a significant secondary deuterium isotope effect operating for the simple cleavage/deprotonation reation.[37]

An appropriate system to overcome this problem is shown in Figure 2. The abundance ratios to be compared are the losses of MeOH:PhH for the unlabeled compound and those of MeOD:PhH for $(CD_3)_2C(OMe)C(O^-)(Me)(Ph)$.[38] The appropriate data are recorded in Table V: the relative abundances are the same within experimental error. We have carried out a similar experiment with the unlabeled and labeled ethyl ethers (Table V); again the appropriate ratios are identical. Since deprotonation (or proton transfer) is not involved in the rate-determining step of the reaction, the elimination mechanisms **A** and **B** are not operative. We propose that the various losses of MeOH proceed by the cyclization mechanism **C**, as summarized in Scheme III.

3. *Syn* and *Anti* Reactions. The aliphatic systems so far studied undergo loss of ROH through "epoxide" reactions to the exclusion of the pinacol rearrangement. There is a close analogy to these

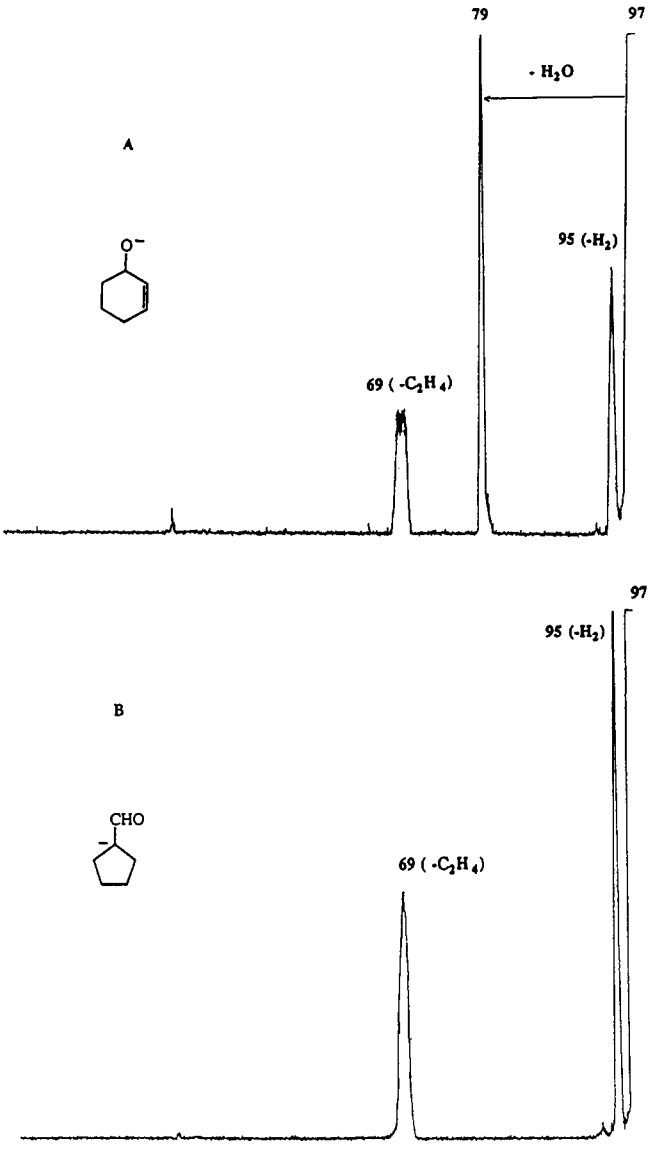


Figure 3. Collisional activation mass spectra of ions formed in the ion source following the losses of methanol from deprotonated (A) *trans*-2-methoxycyclohexanol and (B) *cis*-2-methoxycyclohexanol (VG ZAB 2HF instrument). The widths at half-height of the m/z 69 and 79 peaks in part A are 110.0 and 28.8 (±0.5) V, and that of the m/z 69 peak in part B is 82.2 ± 0.5 V.

reactions in the condensed phase. For example, base-catalyzed cyclization of β-halohydrins may form epoxides: this process is particularly facile when the halo and hydroxyl groups are *anti*-coplanar.[39] Epoxide formation in the gas phase should also involve *anti* cyclization (e.g. via **j**); this reaction is unlikely to occur by a *syn* process through the eclipsed conformer **k**. The pinacol

process is arguably more likely to occur through **k**. If we could construct a geometrically rigid system which might preclude cyclization to an epoxide, for example a suitably substituted *cis*

(35) Since the reaction is only endothermic by some 5 kcal mol^{-1} [using Benson's rules (Benson, S. W. *Thermochemical Kinetics*; J. Wiley and Sons: New York, 1968) and assuming that the electron affinities of the radicals corresponding to the reactant and product anions are the same], the transition states should be "symmetrical" and the deuterium kinetic isotope effect should be high.

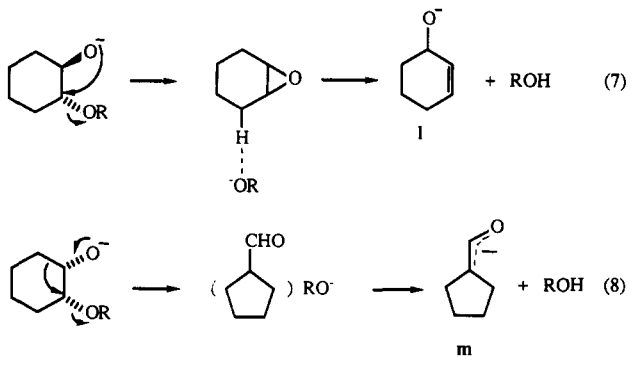
(36) Derrick, P. J.; Donchi, K. F. In *Comprehensive Chemical Kinetics*; Bamford, C. H., Tipper, C. F. H. Eds.; Elsevier: Amsterdam, 1983; Suppl. Vol. 1. Stringer, M. B.; Underwood, D. J.; Bowie, J. H.; Allison, C. E.; Donchi, K. F.; Derrick, P. J. *Org. Mass Spectrom.* **1992**, *27*, 270.

(37) The cleavage/deprotonation reaction is as follows: $Me_2C(OMe)C(O^-)Me_2 \rightarrow Me_2(MeO)C^- (Me_2CO) \rightarrow [MeC(O)CH_2]^- + Me_2(MeO)CH$. The basicities of $Me_2(MeO)C^-$ and $(CD_3)_2(MeO)C^-$ will be marginally different: this could produce a secondary kinetic deuterium isotope effect if the deprotonation step is rate determining.

(38) The loss of benzene involves the process $Me_2C(OMe)C(O^-)(Me)(Ph) \rightarrow [Me_2C(OMe)C(O)Me]Ph^- \rightarrow [Me_2C(OMe)C(O)CH_2]^- + PhH$, which does not involve deuterium in the labeled compound.

(39) Barton, D. H. R.; Lewis, D. A.; McGhie, J. F. *J. Chem. Soc.* **1957**, 2907. vanTamelen, E. E. *Acc. Chem. Res.* **1968**, *1*, 111. Vogel, E.; Altenbach, H.-J.; Sommerfeld, C.-D. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 939. Barton, D. H. R.; Ollis, W. D. *Comprehensive Organic Chemistry*; Pergamon Press Ltd.: London, 1979; p 862.

Scheme IV



cyclohexane,[40] it may then be possible for the gas-phase negative ion pinacol rearrangement to occur.

The *cis*- and *trans*-2-methoxycyclohexanols are the simplest models to test these proposals. The *trans* isomer should follow the epoxide route (eq 7, Scheme IV) while the *cis* isomer is unlikely to cyclize in this way but might undergo the pinacol rearrangement (eq 8, Scheme IV). The spectral data for these ions are listed in Table VI, while product ion spectra are shown in Figure 3 and the data are given in Table VII. The results are in complete accord with the above hypothesis. Consider the spectral data for the geometric isomers listed in Table VI. Loss of methanol is pronounced in both spectra, but the product ions so formed have different structures. The spectra of the two $[(M-H)^- - MeOH]$ product ions are shown in Figure 3. The product from the *trans* isomer is deprotonated cyclohex-2-en-1-ol (**l**, eq 7), while that from the *cis* isomer is deprotonated formylcyclopentane (**m**, eq 8) (see Table VII).[41] The latter product can only be produced by a pinacol rearrangement.

Conclusion

The loss of ROH (R = H or Me) from deprotonated pinacols or β-methoxyhydrins occurs by an initial epoxidation reaction. The epoxide reaction also occurs for deprotonated 2-methoxycyclohexanol when the substituents are *trans* to each other. However, the kinetically favored epoxide reaction is suppresed when the two substituents cannot adopt an *anti* orientation. This is the scenario for deprotonated *cis*-2-methoxycyclohexanol: *the negative ion pinacol reaction is operative for this system.*

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(40) A number of analogues have been reported in the condensed phase: (i) Treatment of 2-chloro-1-methylcyclohexanol (presumably the OH and Cl are *cis*) with sodium hydroxide gives cyclopentyl methyl ketone in 50% yield (Bartlett, P. D.; Rosewald, R. H. *J. Am. Chem. Soc.* **1934**, *56*, 1990). (ii) Treatment of 2-chlorocyclohexanol (presumably the *cis* isomer) with lithium aluminum hydride gives 1-formylcyclopentane in low yield (Mousseron, M.; Jacquier, R. J.; Mousseron-Canet, M.; Zagdoun, R. *Bull. Soc. Chim. Fr.* **1952**, 1042). (iii) When the Grignard derivatives of *cis*- and *trans*-2-chloro-1-methyl-1-indanol are heated, the *cis* isomer smoothly converts to 2-methylindanone by a negative pinacol rearrangement, while the *trans* compound is unable to undergo this reaction and forms polymeric material via the intermediacy of an epoxide (Geissman, T. A.; Akawie, R. I. *J. Am. Chem. Soc.* **1951**, *73*, 1993).

(41) The data in Table VII clearly differentiate among the isomers deprotonated: cyclohex-2-en-1-ol (**l**), formylcyclopentane (**m**), and cyclohexanone. Deprotonated formylcyclopentane and cyclohexanone can be distinguished by (i) the widths of the m/z 69 peaks in the two CA spectra and (ii) the CR spectra (see Table VII).