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Regiochemical Control of the Ring Opening of 1,2-Epoxides by Means of Chelating Processes. Part 14: Regioselectivity of the Opening Reactions with MeOH of Remote *O*-Substituted 1,2-Epoxycyclohexanes under Gas-Phase Operating Conditions

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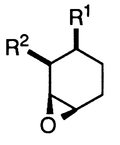
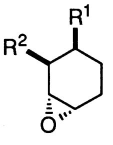
Abstract—The regiochemical behavior of cyclohexene oxides bearing a remote *O*-functionality was determined in the gas-phase in opening reactions with MeOH, using a gaseous acid (D_3^+, $C_nH_5^+$, Me_2F^+) as the promoting agent. The results obtained indicate the incursion in the opening process in the gas phase of H^+(or D^+)-mediated chelated bidentate species completely absent in the corresponding reactions (methanolysis) carried out in the condensed phase. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

The opening reactions of typically aliphatic or cycloaliphatic oxiranes, not bearing particular substituents directly linked to the oxirane ring, proceed with complete inversion of configuration on the attacking site of the nucleophile. This means that one of the most important objectives for an effective synthetic utilization of these systems is the obtainment of the maximum possible control of the regioselectivity trying to find procedures which can selectively lead to one or to the other regioisomer. Considering the large number of nucleophiles that can react with the oxirane functionality, this prospect appears very attractive in the field of synthetic organic chemistry.



1	R^1=OBn, R^2=H	**5**
2	R^1=H, R^2=OBn	**6**
3	R^1=CH_2OBn, R^2=H	**7**
4	R^1=H, R^2=CH_2OBn	**8**



The pairs of diastereoisomeric epoxides **1**–**8** have been extensively studied in our laboratory concerning their regiochemical behavior in many opening reactions in the condensed phase (cd-phase).[1] In particular, it was found that the regioselectivity was in many cases sensitive to the operating opening reactions, that is, if these were carried out under standard or chelating conditions.[1,2] The best results were obtained with the *cis* epoxide **1**[1a,b] in which, while standard conditions[2] afforded mostly *C-2 products*, the use of chelating opening conditions[2] led to the regioisomeric *C-1 products*, furnishing a nice regioalternating process. The results were rationalized by admitting, under chelating conditions, the incursion of an intramolecular chelated bidentate species **9** (Scheme 1) with the metal (M^+=Li^+) coordinating between the two basic *O*-functionalities, and the epoxide necessarily adopting the less stable conformation **1b**. Nucleophilic attack on **9** (M^+=Li^+), in accordance with the Fürst–Plattner rule, selectively affords *C-1 products* as the 'chelation' products (hydroxy ether (HE) **13** in the methanolysis (MeOH/$LiClO_4$)). Under standard opening conditions, the epoxide reacts through its more stable conformer **1a** to give the opposite regiochemical result, that is the *C-2 products* (the 'standard' products) (HE **14** in the acid methanolysis (MeOH/H_2SO_4), Scheme 1).[1a,b] A similar, even if less regioalternating process, was obtained with the homologous *cis* epoxide **3**.[1d] In the case of the *cis* epoxide **2**, compared with a complete C-1 regioselectivity obtained under standard conditions, a consistent amount (up to 50%) of *C-2 products* were obtained under chelating conditions, but only when strong nucleophiles such as $NHEt_2$ and PhSH were used.[1c] It should be noted that, in this case, MeOH was not effective at all in inverting the regioselectivity observed under standard conditions.[1c] Due to its particular structural characteristic, the reactions under chelating conditions of *cis* epoxide **4** led to a reinforcement, and not to an inversion, of the regioselectivity

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Keywords: epoxides; regioselection; gas phase reactions; chelation.

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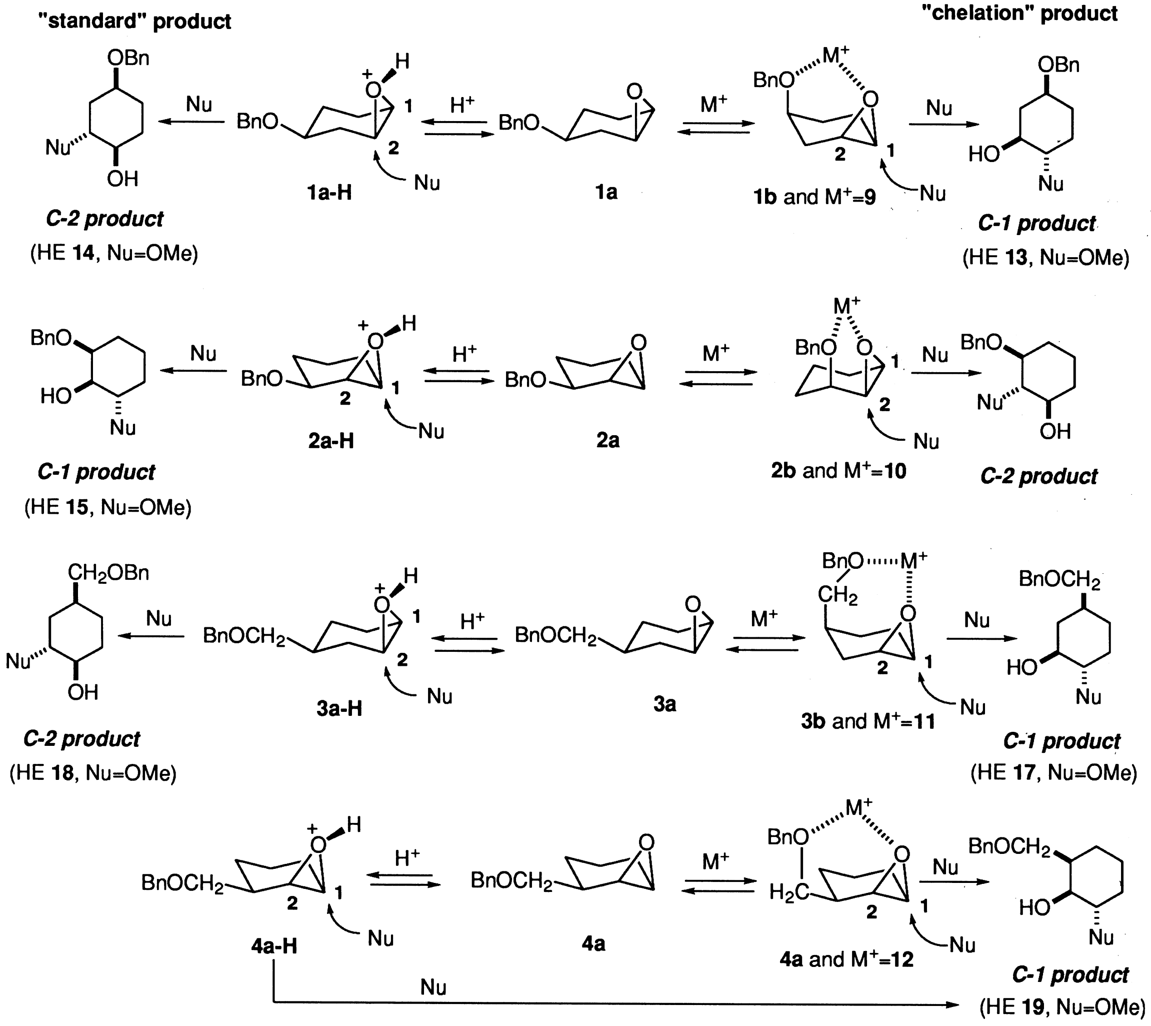
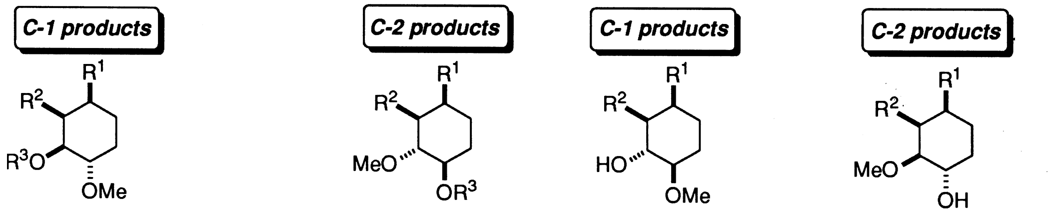


Scheme 1.

observed under standard conditions.[1e] All these results with epoxides **2**–**4** were rationalized, as in the case of **1**, by admitting the incursion, under chelating conditions, of the corresponding metal-mediated intramolecular chelated bidentate species **10**–**12** (M^+=Li^+). At the same time, the constantly different results obtained under protic acid catalysis (standard conditions)[2] clearly indicated that *the proton, in the cd-phase, is not able to give corresponding chelated bidentate structures of type* **9**–**12** (M^+=H).

On their own, the diastereoisomeric *trans* epoxides **5**–**8**, due to strictly structural reasons that impede the incursion of any

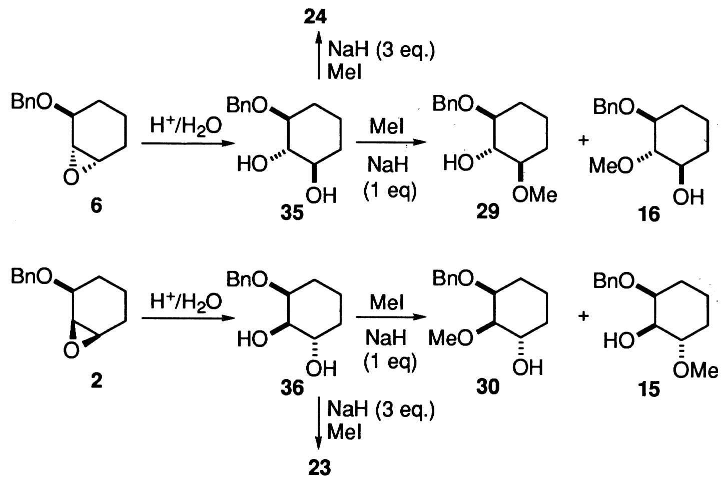


	C-1 products		C-2 products
	13	R^1=OBn, R^2=H, R^3=H	14
	15	R^1=H, R^2=OBn, R^3=H	16
a	17	R^1=CH_2OBn, R^2=H, R^3=H	18
	19	R^1=H, R^2=CH_2OBn, R^3=H	20
	21	R^1=OBn, R^2=H, R^3=Me	22
	23	R^1=H, R^2=OBn, R^3=Me	24
	25	R^1=H, R^2=CH_2OBn, R^3=Me	26

C-1 products		C-2 products
22 $\xleftarrow{a}$ 27	R^1=OBn, R^2=H	28
29	R^1=H, R^2=OBn	30
31	R^1=CH_2OBn, R^2=H	32
26 $\xleftarrow{a}$ 33	R^1=H, R^2=CH_2OBn	34 $\xrightarrow{a}$ 25

a: MeI/NaH/THF

Scheme 2.



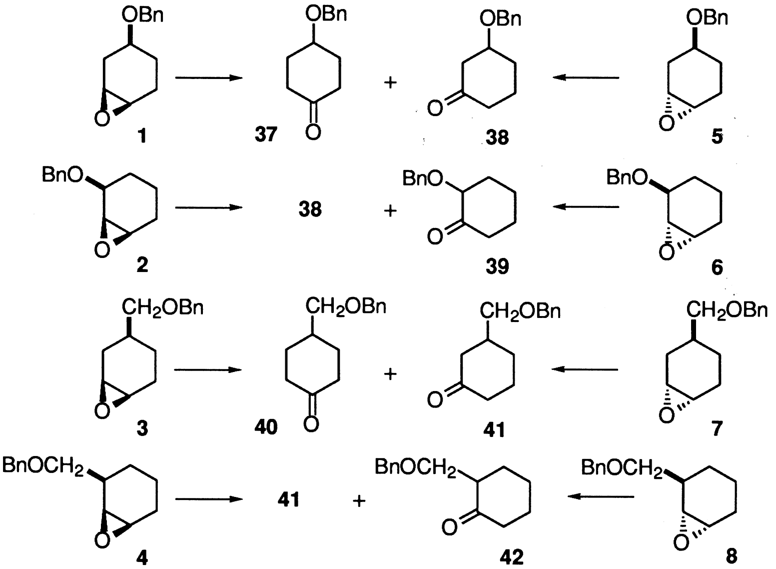
Scheme 3.

intramolecular chelated bidentate species, turned out to be completely insensitive to the different operating conditions and afforded, both under standard and chelating opening conditions, the same regiochemical results.[1]

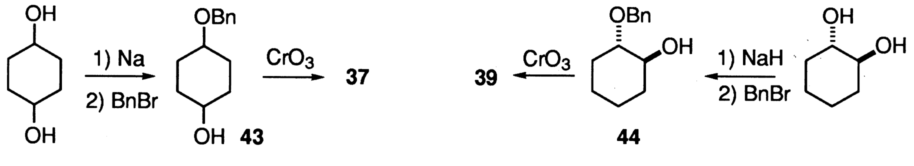
In consideration of the attractive possibilities offered by the gas-phase operating conditions when applied to the opening reactions of oxiranes,[3] we have now extended the application of this technique to the opening reactions of epoxides **1**–**8**, with a neutral nucleophile (MeOH) under acid conditions. In particular, we were interested in checking whether under these conditions, typically devoid of any solvation, the proton, or a corresponding gaseous species, is able to generate in the *cis* systems **1**–**4** chelated bidentate species of types **9**–**12**, where M^+=H, as found for Li^+ in the cd-phase.[1]

Results

Epoxides **1**–**8** and the corresponding reference products, the regioisomeric *C-1* and *C-2 products*, HEs **13**–**20** and **27**–**34** from epoxides *cis* **1**–**4** and *trans* **5**–**8**, respectively, were prepared as described previously (Scheme 2).[1] HEs **16** and **30** which were not obtained before, because not present in the methanolysis products of the corresponding epoxides,



Scheme 4.



Scheme 5.

$$\text{G (bulk gas)} \xrightarrow{\text{irradiation}} \text{GA}^+ \text{ (gaseous acid)}$$

$$\text{GA}^+ (\text{A}^+) = D_3^+ (D^+);\ C_nH_5^+ (H^+);\ Me_2F^+ (Me^+)$$

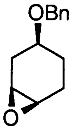
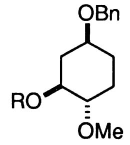
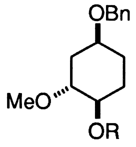
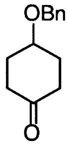
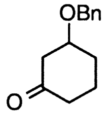
$$\text{G} = D_2,\ CH_4,\ MeF$$

$$\text{Epoxides } \mathbf{1\text{-}8} \xrightarrow[\text{MeOH}]{\text{GA}^+/\text{-G}} \begin{array}{l}\text{addition products (HEs } \mathbf{13\text{-}20}, \mathbf{27\text{-}34} \text{ and DMs } \mathbf{21\text{-}26})\\ \text{and non-addition products (ketones } \mathbf{37\text{-}42})\end{array}$$

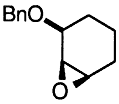
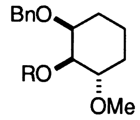
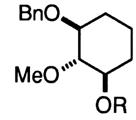
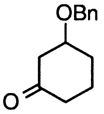
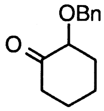
Scheme 6.

Table 1. Distribution of products in the gas-phase acid-induced ring-opening with MeOH and in the methanolysis (condensed phase) of *cis* epoxides **1** and **2**

Gas Phase
system composition (Torr)[a] product distribution[b]

 **1**			*C-1 Product*  R=H, Me		*C-2 Product*  R=H,Me						
epoxide	bulk gas	MeOH	G	%	G	%	G	%	G	%	total abs. yield %[c]
(0.58)	D_2 (100)	(1.72)	(0.13)[e]	6	(1.49)[e]	65	(0.29)	13	(0.37)	16	76
(0.60)	D_2 (760)	(1.79)	(0.19)[e]	12	(1.14)[e]	70	(0.13)	8	(0.16)	10	54
(0.62)	D_2 (760)	(1.84)[d]	(0.23)[e]	**37**	(0.31)[e]	**49**	(0.04)	**6**	(0.05)	**8**	21
(0.64)	CH_4 (100)	(1.91)	(0.11)[e]	5	(1.32)[e]	63	(0.28)	13	(0.39)	19	75
(0.71)	CH_4 (760)	(2.07)	(0.17)[e]	11	(1.13)[e]	69	(0.15)	9	(0.18)	11	58
(0.61)	CH_4 (760)	(1.83)[d]	(0.19)[e]	**36**	(0.24)[e]	**45**	(0.04)	**8**	(0.06)	**11**	19
(0.63)	MeF (100)	(1.86)	(0.35)[f]	15	(1.41)[f]	59	(0.27)	11	(0.35)	15	70
(0.59)	MeF (760)	(1.79)	(0.24)[f]	14	(1.26)[f]	71	(0.12)	7	(0.14)	8	52
(0.64)	MeF (760)	(1.90)[d]	(0.07)[f]	**13**	(0.41)[f]	**75**	(0.03)	**5**	(0.04)	**7**	16
Condensed Phase[g]											
	MeOH/H^+			**15**		**85**					
	MeOH/$LiClO_4$			**98**		**2**					

Gas Phase
system composition (Torr)[a] product distribution[b]

 **2**			*C-1 Product*  R=H, Me		*C-2 Product*  R=H, Me						
epoxide	bulk gas	MeOH	G	%	G	%	G	%	G	%	total abs. yield %[c]
(0.57)	D_2 (100)	(1.75)	(0.58)[e]	24	(1.17)[e]	48	(0.42)	17	(0.26)	11	81
(0.63)	D_2 (760)	(1.91)	(0.44)[e]	24	(1.02)[e]	56	(0.24)	13	(0.13)	7	61
(0.60)	D_2 (760)	(1.82)[d]	(0.22)[e]	**38**	(0.26)[e]	**46**	(0.05)	**9**	(0.04)	**7**	19
(0.55)	MeF (100)	(1.75)	(1.57)[f]	55	(0.34)[f]	12	(0.57)	20	(0.37)	13	84
(0.56)	MeF (760)	(1.79)	(1.36)[f]	72	(0.17)[f]	9	(0.25)	13	(0.10)	6	55
(0.61)	MeF (760)	(1.89)[d]	(0.56)[f]	**78**	(0.04)[f]	**6**	(0.08)	**11**	(0.04)	**5**	21
Condensed Phase[h]											
	MeOH/H^+			**>99**		**<1**					
	MeOH/$LiClO_4$			**>99**		**<1**					

[a] O_2: 4 Torr, radiation dose 1.5×10^4 Gy (dose rate 1×10^4 Gy h^{-1}).

[b] G values expressed as the number of molecules produced per 100 eV absorbed energy.

[c] Total absolute yields (%) estimated from the percentage ratio of the combined G(M) values of products and the literature G(GA^+) values.[5]

[d] 3 Torr of NMe_3 added to the gaseous mixture.

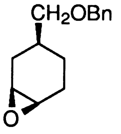
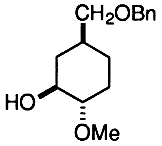
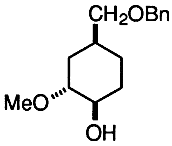
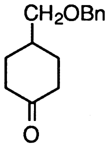
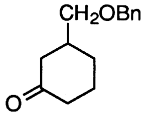
[e] R=H.

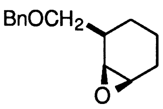
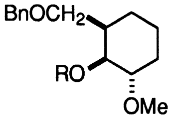
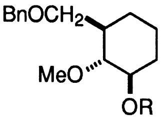
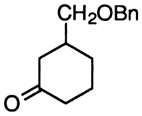
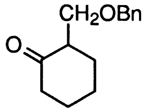
[f] R=Me.

[g] Ref. 1a.

[h] Ref. 1c.

Table 2. Distribution of products in the gas-phase acid-induced ring-opening with MeOH and in the methanolysis (condensed phase) of *cis* epoxides **3** and **4**

Gas Phase system composition (Torr)[a]					product distribution[b]						
			C-1 Product		*C-2 Product*						
 **3**											
epoxide	bulk gas	MeOH	G	%	G	%	G	%	G	%	total abs. yield %[c]
(0.61)	D$_2$ (100)	(1.83)	(0.85)	36	(1.04)d	45	(0.24)	10	(0.21)	9	78
(0.64)	D$_2$ (760)	(1.91)	(0.64)	34	(0.95)d	50	(0.17)	9	(0.14)	7	63
(0.58)	D$_2$ (760)	(1.81)[d]	(0.21)	**33**	(0.33)d	**53**	(0.05)	**8**	(0.04)	**6**	21
Condensed Phase[g]											
	MeOH/H$^+$			**4**		**96**					
	MeOH/LiClO$_4$			**27**		**73**					

Gas Phase system composition (Torr)[a]					product distribution[b]						
			C-1 Product		*C-2 Product*						
 **4**			 R=H, Me		 R=H, Me						
epoxide	bulk gas	MeOH	G	%	G	%	G	%	G	%	total abs. yield %[c]
(0.62)	D$_2$ (100)	(1.88)	(1.54)[e]	61	(0.17)[e]	7	(0.39)	15	(0.42)	17	84
(0.59)	D$_2$ (760)	(1.84)	(1.36)[e]	69	(0.06)[e]	3	(0.26)	13	(0.30)	15	66
(0.64)	D$_2$ (760)	(1.94)[d]	(0.64)[e]	**76**	(0.02)[e]	**2**	(0.08)	**10**	(0.10)	**12**	28
(0.57)	MeF (100)	(1.79)	(1.62)[f]	58	(0.29)[f]	10	(0.39)	14	(0.49)	18	82
(0.64)	MeF (760)	(1.91)	(1.55)[f]	73	(0.17)[f]	8	(0.18)	8	(0.23)	11	63
(0.56)	MeF (760)	(1.84)[d]	(0.46)[f]	**72**	(0.06)[f]	**9**	(0.05)	**8**	(0.07)	**11**	19
Condensed Phase[h]											
	MeOH/H$^+$			**92**		**8**					
	MeOH/LiClO$_4$			**98**		**2**					

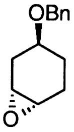
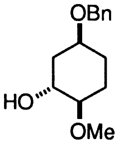
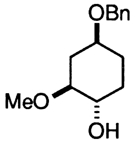
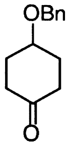
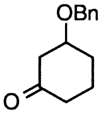
[a] O$_2$: 4 Torr, radiation dose 1.5×10^4 Gy (dose rate 1×10^4 Gy h^{-1}).
[b] G values expressed as the number of molecules produced per 100 eV absorbed energy.
[c] Total absolute yields (%) estimated from the percentage ratio of the combined G(M) values of products and the literature G(GA$^+$) values.[5]
[d] 3 Torr of NMe$_3$ added to the gaseous mixture.
[e] R=H.
[f] R=Me.
[g] Ref. 1d.
[h] Ref. 1e.

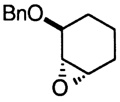
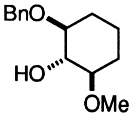
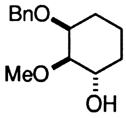
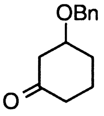
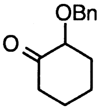
cis **2** and *trans* **6**, respectively,[1c] were prepared as shown in Scheme 3. Trans diols **35** and **36**, obtained in the acid hydrolysis of the corresponding epoxides **6** and **2**, were monomethylated (MeI/NaH) to give a 7:3 and an 8:2 mixture of HEs **16** and **29** (from **35**) and HEs **30** and **15** (from **36**), respectively, from which HEs **16** and **30** were obtained pure by preparative TLC.

As we intended to carry out the opening reactions of *cis* epoxides **1**, **2** and **4** with MeOH also in the presence of Me$_2$F$^+$ as the gaseous acid, in order to verify whether Me$^+$ (Scheme 6) was able to give evidence of the incursion of corresponding intramolecular chelated bidentate species of the type described above (**9**, **10** and **12**, M$^+$=Me, Scheme 1), the pairs of dimethoxy derivatives (DMs) **21**–**22**, **23**–**24**, and **25**–**26**, as corresponding opening products of *cis* epoxides **1**, **2** and **4**, respectively, were also prepared. DMs **21**, **22**, **25** and **26** were prepared by methylation (MeI/NaH) of HEs **13**, **27**, **34** and **33**,[1a,e] respectively (Scheme 2). DMs **23** and **24** were prepared by methylation of the corresponding *trans* diols **36** and **35** (Scheme 3).

The tendency to undergo isomerization processes in the gas-phase, due to the significantly higher ion lifetime (10^{-8} to 10^{-7} s) available in these conditions with respect to the cd-phase (about 10^{-14} s), made reasonable that some non-addition products, such as cyclohexanones **37**–**42** (**37** and **38** from **1** and **5**, **38** and **39** from **2** and **6**, **40** and **41** from **3** and **7**, and **41** and **42** from **4** and **8**, Scheme 4), not present in the corresponding reaction in the cd-phase, could be formed in the gas-phase operating opening reactions. As a consequence, reference ketones **38** and **40**–**42** were prepared by oxidation of the corresponding alcohols obtained in the LAH reduction of epoxides **2** for **38**, **3** for **40**, **7** for **41** and

Table 3. Distribution of products in the gas-phase acid-induced ring-opening with MeOH and in the methanolysis (condensed phase) of *trans* epoxides **5** and **6**

Gas Phase system composition (Torr)[a]			product distribution[b]								
			C-1 Product		*C-2 Product*						
 **5**											
epoxide	bulk gas	MeOH	G	%	G	%	G	%	G	%	total abs. yield %[c]
(0.64)	D_2 (100)	(1.93)	(1.73)	72	(0.05)	2	(0.24)	12	(0.33)	14	78
(0.67)	D_2 (760)	(2.00)	(1.14)	68	(0.25)	15	(0.13)	8	(0.16)	9	56
(0.59)	D_2 (760)	(1.79)[d]	(1.42)	**70**	(0.10)	**17**	(0.04)	**6**	(0.04)	**7**	20
(0.71)	CH_4 (100)	(2.11)	(1.54)	66	(0.06)	3	(0.33)	14	(0.39)	17	83
(0.64)	CH_4 (760)	(1.90)	(0.99)	66	(0.25)	7	(0.13)	8	(0.14)	9	54
(0.68)	CH_4 (760)	(2.05)[d]	(0.35)	**68**	(0.09)	**18**	(0.03)	**6**	(0.04)	**8**	18
Condensed Phase[e]											
	MeOH/H^+			**79**		**21**					
	MeOH/$LiClO_4$			**71**		**29**					

Gas Phase system composition (Torr)[a]			product distribution[b]								
			C-1 Product		*C-2 Product*						
 **6**											
epoxide	bulk gas	MeOH	G	%	G	%	G	%	G	%	total abs. yield %[c]
(0.63)	D_2 (100)	(1.91)	(1.77)	72	(0.20)	7	(0.35)	14	(0.14)	7	83
(0.61)	D_2 (760)	(1.88)	(1.56)	81	(0.05)	3	(0.20)	10	(0.11)	6	64
(0.58)	D_2 (760)[d]	(1.79)	(0.53)	**84**	(0.01)	**2**	(0.06)	**9**	(0.03)	**5**	21
Condensed Phase[f]											
	MeOH/H^+			**>99**		**<1**					
	MeOH/$LiClO_4$			**>99**		**<1**					

[a] O_2: 4 Torr, radiation dose 1.5×10^4 Gy (dose rate 1×10^4 Gy h^{-1}).

[b] G values expressed as the number of molecules produced per 100 eV absorbed energy.

[c] Total absolute yields (%) estimated from the percentage ratio of the combined G(M) values of products and the literature G(GA^+) values.[5]

[d] 3 Torr of NMe_3 added to the gaseous mixture.

[e] Ref. 1a.

[f] Ref. 1c.

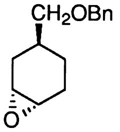
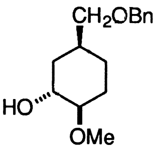
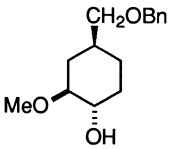
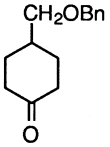
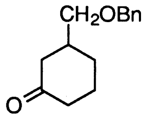
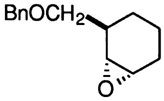
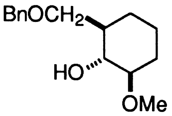
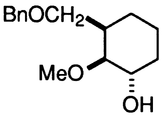
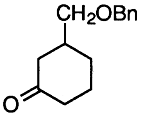
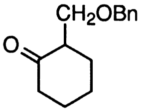
4 for **42**.[1c–e] Ketones **37** and **39** were prepared by oxidation of the corresponding alcohols **43**[4] and **44** obtained in the monobenzylation of 1,4-cyclohexanediol (a commercial mixture of *cis* and *trans* isomers) and *trans* 1,2-cyclohexanediol, respectively (Scheme 5).

Epoxides **1**–**8** were subjected to opening reactions in the gas-phase in the presence of MeOH under the catalysis of a gaseous Brönsted ($GA^+=D_3^+$, $C_nH_5^+$(n=1, 2)) or Lewis acid ($GA^+=Me_2F^+$) obtained by γ-radiolysis of the corresponding neutral bulk gas precursor (G=D_2, CH_4 and MeF, respectively) (Scheme 6). The bulk gas pressure was varied and different operating conditions were used: low (100 Torr) and high pressure bulk gas (760 Torr) (Tables 1–4). In this last case the opening reactions were repeated also in the presence of NMe_3 (3 Torr). Low pressure bulk gas conditions correspond to long-lived excited-ion conditions, because of the reduced collapse of the ionic species with the molecules of the bulk gas, while the use of a high pressure and the contemporary presence of NMe_3 correspond to a low ion lifetime.[3]

The crude reaction mixture from the gas-phase opening reactions of epoxides **1**–**8** turned out to be particularly clean and simple: GC-MS examination shows only the presence of the addition products (the corresponding regioisomeric HEs or DMs, Tables 1–4) and the non-addition products (the corresponding substituted cyclohexanones). The sharp yield decrease when NMe_3 is introduced demonstrates the ionic origin of the reaction products, independently ensured by the presence of O_2, an effective radical scavenger.

As a different product distribution is obtained in both deuterium and methane as a function of the experimental conditions (low or high bulk gas pressure) and the presence or absence of NMe_3, first of all it is necessary to single out which experimental protocol is to be taken into consideration for an effective comparison between the regiochemical results presently obtained with epoxides **1**–**8** in the opening reaction with MeOH in the gas-phase and those previously obtained in the corresponding methanolysis reaction conducted in the cd-phase. Considering that in the cd-phase

Table 4. Distribution of products in the gas-phase acid-induced ring-opening with MeOH and in the methanolysis (condensed phase) of *trans* epoxides **7** and **8**

Gas Phase system composition (Torr)[a]			product distribution[b]								
			C-1 Product		*C-2 Product*						
 **7**											
epoxide	bulk gas	MeOH	G	%	G	%	G	%	G	%	total abs. yield %[c]
(0.57)	D_2 (100)	(1.78)	(1.85)	76	(0.08)d	3	(0.30)	12	(0.22)	9	82
(0.62)	D_2 (760)	(1.85)	(1.48)	76	(0.11)d	6	(0.19)	10	(0.16)	8	65
(0.60)	D_2 (760)[d]	(1.83)	(0.53)	**85**	(0.01)d	**2**	(0.05)	**8**	(0.03)	**5**	21
Condensed Phase[e]											
	MeOH/H$^+$			**98**		**2**					
	MeOH/LiClO$_4$			**94**		**6**					
Gas Phase system composition (Torr)[a]			product distribution[b]								
			C-1 Product		*C-2 Product*						
 **8**											
epoxide	bulk gas	MeOH	G	%	G	%	G	%	G	%	total abs. yield %[c]
(0.57)	D_2 (100)	(1.85)	(1.30)	54	(0.50)d	21	(0.29)	12	(0.31)	13	80
(0.61)	D_2 (760)	(1.87)	(1.17)	60	(0.31)d	16	(0.22)	11	(0.25)	13	65
(0.59)	D_2 (760)[d]	(1.88)	(0.47)	**65**	(0.12)d	**17**	(0.06)	**8**	(0.07)	**10**	24
Condensed Phase[f]											
	MeOH/H$^+$			**65**		**35**					
	MeOH/LiClO$_4$			**75**		**25**					

[a] O_2: 4 Torr, radiation dose 1.5×10^4 Gy (dose rate 1×10^4 Gy h^{-1}).

[b] G values expressed as the number of molecules produced per 100 eV absorbed energy.

[c] Total absolute yields (%) estimated from the percentage ratio of the combined G(M) values of products and the literature G(GA$^+$) values.[5]

[d] 3 Torr of NMe$_3$ added to the gaseous mixture.

[e] Ref. 1d.

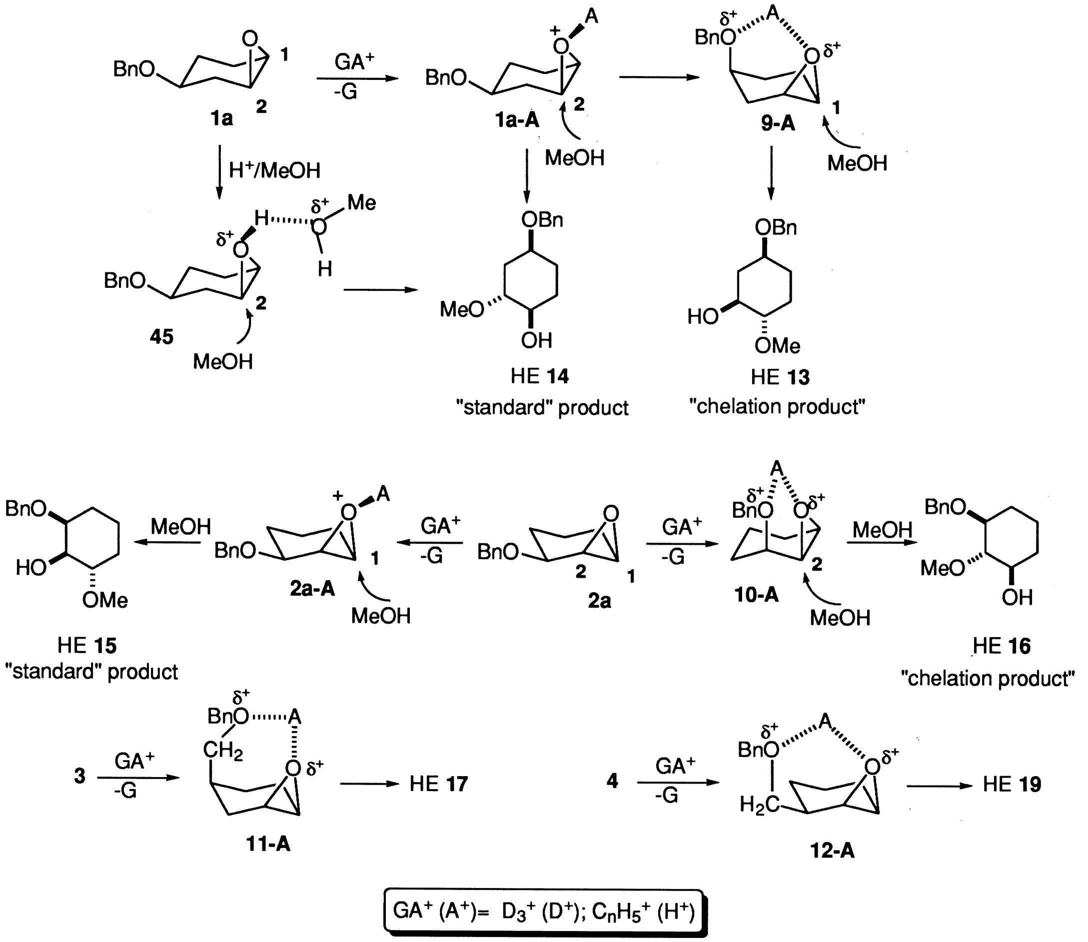
[f] Ref. 1e.

(protic acid- and LiClO$_4$-promoted methanolysis), the ionic species formed after 'protonation' of the oxirane oxygen (as structures **1**–**4a-H** and **9**–**12**, M$^+$=Li$^+$, Scheme 1), rapidly go towards their definitive destiny (nucleophilic addition) because of the close proximity of the nucleophile (MeOH) which is also the solvent, the gas-phase reactions carried out in conditions of low ion lifetime, that is under high pressure and in the presence of NMe$_3$ (see above), appear to be more similar to the cd-phase operating conditions and, as a consequence, more appropriate for an effective comparison between the results obtained in the cd-phase and gas-phase (Tables 1–4, bolded results).

Discussion

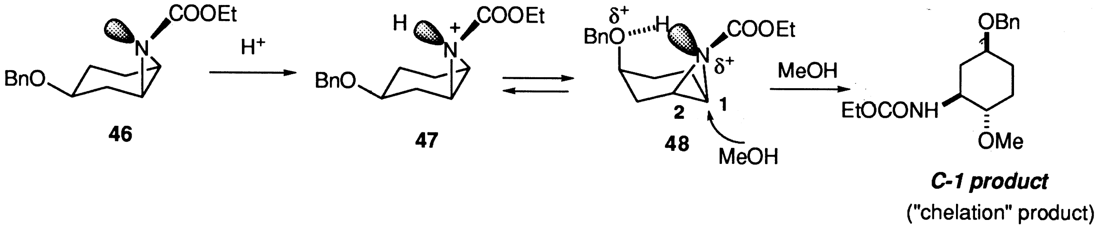
The rationalization of the results first starts by examining the results obtained with the *trans* epoxides **5**–**8**, that is with those epoxides which, for strictly structural reasons, are not able to lead to any type of chelated bidentate intramolecular species.[1] The regioselectivities observed with these epoxides in the gas-phase are practically identical to those previously obtained in the cd-phase, both under standard and chelating conditions, with the only exception of the presence of a certain amount of non-addition products (5–10%, Tables 3 and 4). This observation makes it reasonable to admit that the chemical behavior of *trans* epoxides **5**–**8** and, by a reasonable extension, also of *cis* epoxides **1**–**4**, is governed in the gas-phase by the same factors as in the cd-phase, and can be rationalized by means of the same considerations previously utilized to rationalize the results obtained with epoxides **1**–**8** in the cd-phase.[1] As a consequence, all the differences in regioselectivity observed in the gas-phase with respect to the corresponding results obtained in the cd-phase under standard conditions will reasonably be ascribed to the incursion of chelated bidentate species, as done in the cd-phase when comparing the different regiochemical results from standard and chelating conditions.[1]

The *cis* epoxide **1**, both in the presence of D$_3^+$ and C$_n$H$_5^+$ as the gaseous acid (GA$^+$), yields in the reaction with MeOH a substantial amount of the *C-1 product*, HE **13** (36–37%) ('chelation' product, Scheme 7), that is of that product which, though obtained practically pure when

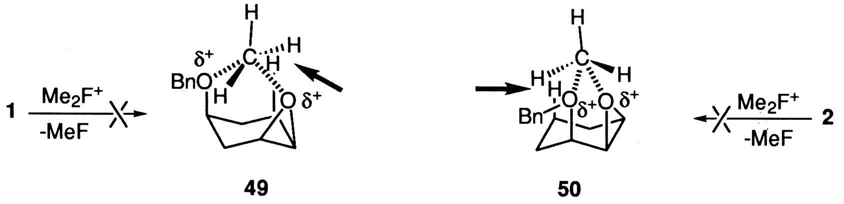


Scheme 7.

the corresponding opening reaction in the cd-phase is carried out in the presence of $LiClO_4$ as the promoting agent, is present at a level of only 15% under standard conditions (protic acid methanolysis).[1a,2] These results may be rationalized only by admitting that H^+ and D^+ (derived from the corresponding GA^+) in the gas-phase reaction conditions are able to chelate by means of a bridgehead structure of type **9-A** (A=D or H, Scheme 7, corresponding to structure **9** of Scheme 1, with the epoxide reacting in its less stable conformation **1b**) in which the gaseous acid species (A^+) is contemporarily coordinated to the two oxygen atoms of the oxirane and ether functionalities. The successive nucleophilic attack of MeOH on C(1) of **9-A** affords HE **13**. At this point the question is: why does not the proton show the same chelating behavior in the cd-phase? Very probably in the cd-phase, the gathering of the basic solvent (MeOH) all around the substrate (the protonated epoxide) determines the incursion of an *intermolecular* chelated bidentate species between the protonated species and an external MeOH molecule, as shown in **45** (Scheme 7), impeding de facto the possibility of any intramolecular chelation pathway. Clearly, all this has no effect on the regioselectivity (HE **14**, the 'standard' product, is mostly obtained, Scheme 7), because the epoxide can maintain, in the nucleophilic opening process, the more stable conformation **1a**. Confirmation of the validity of this rationalization descends from the previous observation on the activated aziridine **46** which was shown to give an intramolecular H^+-mediated chelation process in the opening reaction in the cd-phase with MeOH under protic acidic conditions.[6] In that case, the presence of the ethoxycarbonyl substituent on the nitrogen, more favorably disposed, for steric reasons, outside the molecule, leaves the remaining nitrogen lone pair necessarily directed inside the molecule.



Scheme 8.



Scheme 9.

As a consequence, protonation of the aziridine necessarily occurs inside the molecule giving structure **47** in which the proton is appropriately disposed to give the supposed corresponding chelated bidentate species **48** able to rationalize the C-1 regioselectivity observed in these conditions (Scheme 8).[6]

Epoxide **2** has a behavior similar to that of epoxide **1**, but the result obtained is much more interesting: under gas-phase conditions with D_3^+ and $C_nH_5^+$ as the gaseous acid, the *cis* epoxide **2** yields both the 'chelation product', HE **16** (46%), and the 'standard product', HE **15** (38%), whereas in the corresponding methanolysis reaction in the cd-phase the 'standard' product, HE **15**, was the only opening product observed (>99%) in all the conditions tried (Table 1 and Scheme 1). This means that in this system, under gas-phase conditions, it is possible to obtain the 'chelation' product, HE **16**, never observed in the cd-phase.[1c] Accordingly, the regiochemical result is easily explained by admitting the incursion of H^+- or D^+-mediated chelated bidentate species, such as **10-A** (A=H or D, Scheme 7) which necessarily determines nucleophilic attack on the C(2) oxirane carbon.

Corresponding results have been observed also with the remaining two *cis* epoxides **3** and **4**, where the chelation products, HEs **17** and **19**, respectively, are obtained in the gas-phase in an amounts similar to those previously obtained in the cd-phase under chelating conditions (Table 2).[1d,e] Also in these cases, the incursion of corresponding chelated bidentate species **11-A** from **3** and **12-A** from **4** (A=D or H, Scheme 7) is reasonably admitted.

The regiochemical behavior of epoxides **1**, **2** and **4** in the gas-phase when Me_2F^+ is the gaseous acid is very similar to that obtained with the same epoxides in the cd-phase under standard conditions (Tables 1 and 2).[1a,c,e] This result indicates the almost complete absence of any chelation process in these gas-phase conditions, probably as a consequence of the steric hindrance between Me^+ and the *syn* axial hydrogen in the corresponding chelated bidentate structure as tentatively shown in **49** from **1** and **50** from **2** (Scheme 9).

As for the presence of non-addition products in the opening reactions of epoxides **1**–**8** in the gas-phase, the relative amount of the pairs of regioisomeric cyclohexanones **37**–**42** (Scheme 4) appears to reflect the corresponding calculated relative stability shown in Table 5.

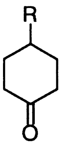
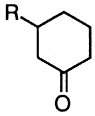
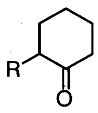
Conclusion

In conclusion, it was verified whether in the well-established radiolytic conditions excluding the complicating interference of the solvent and counterion effects, it was possible to observe the incursion of intramolecular chelating processes mediated by the proton (H^+ or D^+) in opening reactions with MeOH under acid conditions of a series of cyclohexane-derived epoxides bearing a remote heterofunctionality in a variable relationship to the oxirane ring. In all the *cis* oxirane systems examined (epoxides **1**–**4**), a regiochemical result was obtained similar to the one previously obtained in the cd-phase when the opening reaction was carried out in the presence of a metal such as $LiClO_4$.[1] This means that the proton, which turned out to be completely uneffective in the cd-phase as a chelating agent, possesses chelating properties[7]in the gas-phase which correspond precisely to those of Li^+ in the cd-phase. To our knowledge, this is the first time that a chelating behavior of the proton has been observed in opening reactions of epoxides in the gas-phase. The result obtained in the gas-phase with epoxide *cis* **2** is significant, as it was possible to directly obtain HE **16** (a 'chelation' product), which was completely absent in the corresponding methanolysis reactions carried out in the cd-phase.[1c]

Experimental

^1H and ^{13}C NMR spectra were determined with a Bruker AC 200 spectrometer on $CDCl_3$ solution using tetramethylsilane as the internal standard. IR spectra for the determination of OH stretching bands (compounds **35**, **36**, **16** and **30**) were taken in dried CCl_4 with a Mattson 3000

Table 5. Heats of formation (kcal mol^{-1}) for ketones **37**–**42** (data obtained by semiempirical calculation AM1 (HyperChem))

						
R=OBn	**37**	-71.987	**38**	-72.951	**39**	-69.987
R=CH$_2$OBn	**40**	-78.021	**41**	-76.863	**42**	-77.608

FTIR spectrophotometer: the concentration of the solution was 5×10^{-3} M, or lower. All reactions were followed by TLC on Alugram SIL G/UV_{254} silica gel sheets (Machery–Nagel) with detection by UV. Silica gel 60 (Machery–Nagel 230–400 mesh) was used for flash chromatography. THF was distilled from sodium/benzophenone ketyl under a nitrogen atmosphere immediately prior to use. Epoxides **1**–**8**, HEs **13**–**15**, **17**–**20**, **27**–**29** and **31**–**34**[1a,c–e] and alcohol **43**[4] were prepared as previously described.

Acid hydrolysis (0.2N H_2SO_4–H_2O/dioxane) of epoxides 2 and 6

The following procedure is typical. Epoxide **6** (0.090 g, 0.44 mmol) was added to a 1:1 0.2N H_2SO_4/dioxane (15 ml) and the reaction mixture was stirred at rt for 40 min. Dilution with saturated aqueous $NaHCO_3$, extraction with ether and evaporation of the ether extracts afforded *c-3-benzyloxy-r-1,t-2-cyclohexanediol* (**35**) (0.080 g), as a liquid (Found: C, 70.42; H, 7.95. $C_{13}H_{18}O_3$ requires C, 70.24; H, 8.16%): IR (CCl_4) 3600 (1,2 OH···O) and 3525 cm^{-1}(1,3 OH···O). ^1H NMR δ 7.19–7.39 (m, 5H), 4.58 (d, 1H, J=11.2 Hz), 4.42 (d, 1H, J=11.2 Hz), 3.08–3.43 (m, 4H), 3.26 (t, 1H, J=8.8 Hz). ^{13}C NMR δ 139.7, 129.1, 128.9, 128.4, 81.5, 80.0, 73.5, 72.0, 32.1, 29.7, 20.6.

The same reaction carried out on epoxide **2** (0.10 g, 0.49 mmol) afforded pure *t-3-benzyloxy-r-1,t-2-cyclohexanediol* (**36**), as a liquid (0.070 g) (Found: C, 69.98; H, 8.04. $C_{13}H_{18}O_3$ requires C, 70.24; H, 8.16%): IR (CCl_4) 3593 and 3596 cm^{-1}(1,2 OH···O). ^1H NMR δ 7.26–7.41 (m, 5H), 4.66 (d, 1H, J=11.7 Hz), 4.40 (d, 1H, J=11.7 Hz), 3.86–3.89 (m, 1H), 3.67–3.81 (m, 1H), 3.32 (dd, 1H, J=8.8, 3.4 Hz). ^{13}C NMR δ 138.9, 129.2, 128.5, 128.3, 78.2, 77.1, 72.2, 71.6, 32.0, 27.9, 19.0.

Monomethylation of *trans* 1,2-cyclohexanediol and diols 35 and 36

The following procedure is typical. A solution of diol **35** (0.080 g, 0.36 mmol) in anhydrous THF (2.0 ml) was added at 40°C to a suspension of NaH (0.020 g of a 60% dispersion in mineral oil, 0.50 mmol) in anhydrous THF (2 ml). After 4 h stirring at the same temperature, MeI (0.2 ml) was added and the resulting reaction mixture was stirred at 50°C for 18 h. Dilution with ether and water, and evaporation of the washed (water) organic solution afforded a crude liquid product (0.080 g) consisting of a 7:3 mixture of HEs **16** and **29** which was subjected to preparative TLC (an 8:2 hexane/AcOEt mixture was used as the eluant). Extraction of the two most intense bands afforded pure HE **29** (0.010 g) and *c-3-benzyloxy-t-2-methoxy-r-1-cyclohexanol* (**16**), as a liquid (0.010 g) (Found: C, 71.39; H, 8.25. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53%): IR (CCl_4) 3588 (1,2 OH···O) and 3509 cm^{-1}(1,3 OH···O). ^1H NMR δ 7.26–7.35 (m, 5H), 4.67 (d, 1H, J=11.2 Hz), 4.58 (d, 1H, J=11.2 Hz), 3.66 (s, 3H), 3.33–3.55 (m, 2H), 3.02 (t, 1H, J=8.8 Hz). ^{13}C NMR δ 129.3, 129.1, 128.4, 128.3, 88.9, 81.6, 72.9, 72.3, 67.6, 31.8, 30.4, 20.1.

Application of the same procedure to diol **36** afforded a crude liquid product (0.080 g) consisting of an 8:2 mixture of HEs **30** and **15** which was subjected to preparative TLC (an 8:2 hexane/AcOEt mixture was used as the eluant). Extraction of the two most intense bands afforded pure HE **15** (0.010 g) and *t-3-benzyloxy-t-2-methoxy-r-1-cyclohexanol* (**30**), pure as a liquid (0.030 g) (Found: C, 70.91; H, 8.30. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53%): IR (CCl_4) 3597 cm^{-1}(1,2 OH···O). ^1H NMR δ 7.24–7.40 (m, 5H), 4.66 (d, 1H, J=12.2 Hz), 4.54 (d, 1H, J=12.2 Hz), 3.90–4.02 (m, 2H), 3.36 (s, 3H), 2.94 (dd, 1H, J=9.3, 2.9 Hz), 1.98–2.06 (m, 2H). ^{13}C NMR δ 139.4, 128.9, 128.3, 128.1, 87.4, 72.4, 71.4, 69.7, 57.4, 32.2, 28.3, 18.9.

The same procedure carried out on *trans*-1,2-cyclohexanediol afforded pure *trans-2-benzyloxy-cyclohexanol* (**44**),[1c] as a liquid: ^{13}C NMR δ 129.2, 128.4, 128.3, 84.2, 74.5, 72.8, 29.9, 24.9, 24.6.

Dimethoxy derivatives 21–26

Typical procedure. Following the usual procedure, the treatment of HE **27** (0.10 g, 0.42 mmol) in anhydrous THF (12 ml) with MeI (0.05 ml) in the presence of 60% NaH (0.050 g, 1.3 mmol) afforded a crude product mostly consisting of DM **22** which was subjected to preparative TLC (an 8:2 hexane/AcOEt mixture was used as the eluant). Extraction of the most intense band afforded pure *r-1-benzyloxy-t-3,c-4-dimethoxycyclohexane* (**22**), as a liquid (0.080 g) (Found: C, 71.72; H, 8.59. $C_{15}H_{22}O_3$ requires C, 71.97; H, 8.86%): ^1H NMR δ 7.22–7.37 (m, 5H), 4.55 (d, 1H, J=11.9 Hz), 4.47 (d, 1H, J=11.9 Hz), 3.63–3.75 (m, 1H), 3.41–3.54 (m, 1H), 3.40 (s, 3H), 3.38 (s, 3H), 3.14–3.23 (m, 1H), 2.00–2.12 (m, 1H). ^{13}C NMR δ 139.7, 128.9, 128.0, 80.6, 79.5, 73.7, 70.6, 57.8, 57.3, 33.6, 32.7, 27.5, 24.3.

Application of the same procedure to HE **13** (0.070 g, 0.30 mmol) afforded pure *r-1-benzyloxy-c-3,t-4-dimethoxycyclohexane* (**21**), as a liquid (0.070 g) (Found: C, 72.15; H, 8.54. $C_{15}H_{22}O_3$ requires C, 71.97; H, 8.86%): ^1H NMR δ 7.23–7.35 (m, 5H), 4.55 (s, 2H), 3.44 (s, 6H), 3.30–3.44 (m, 1H), 3.02–3.16 (m, 2H), 2.42–2.53 (m, 1H), 2.05–2.17 (m, 2H). ^{13}C NMR δ 139.2, 129.0, 128.2, 83.4, 81.7, 75.7, 71.0, 58.1, 57.9, 36.4, 30.3, 26.6.

Application of the same procedure to HE **33** (0.10 g, 0.40 mmol) afforded pure *r-1-benzyloxymethyl-t-2,c-3-dimethoxycyclohexane* (**26**), as a liquid (0.010 g) (Found: C, 72.94; H, 8.95. $C_{16}H_{24}O_3$ requires C, 72.69; H, 9.15%): ^1H NMR δ 7.26–7.35 (m, 5H), 4.51 (s, 2H), 3.55–3.59 (m, 2H), 3.50 (s, 3H), 3.44 (s, 3H), 2.92–3.15 (m, 2H), 2.03–2.13 (m, 2H J=19.0 Hz). ^{13}C NMR δ 139.5, 129.0, 128.2, 85.7, 84.8, 73.8, 71.9, 61.0, 58.0, 44.1, 30.9, 29.0, 23.6.

The same reaction carried out on HE **34** (0.10 g, 0.40 mmol) afforded pure *r-1-benzyloxymethyl-c-2,t-3-dimethoxycyclohexane* (**25**), as a liquid (0.010 g) (Found: C, 72.41; H, 8.90. $C_{16}H_{24}O_3$ requires C, 72.69; H, 9.15%): ^1H NMR δ 7.25–7.35 (m, 5H), 4.51 (s, 2H), 3.30–3.71 (m, 4H), 3.36 (s, 6H), 2.10–2.21 (m, 1H, $W_{1/2}$=21.0 Hz). ^{13}C NMR δ 139.6, 129.0, 128.2, 128.0, 78.7, 78.3, 76.3, 73.6, 58.8, 57.1, 37.5, 25.7, 24.3, 19.9.

The same reaction carried out on diol **35** (0.090 g, 0.40 mmol)) afforded pure *r-1-benzyloxy-t-2,c-3-dimethoxycyclohexane* (**24**), as a liquid (0.060 g) (Found: C, 72.23; H, 8.63. $C_{15}H_{22}O_3$ requires C, 71.97; H, 8.86%): ^{1}H NMR δ 7.26–7.40 (m, 5H), 4.68 (s, 2H), 3.66 (s, 3H), 3.45 (s, 3H), 3.22–3.32 (m, 1H), 3.02–3.10 (m, 2H), 1.72–2.06 (m, 2H). ^{13}C NMR δ 139.7, 129.0, 128.2, 128.1, 89.5, 83.7, 82.0, 73.0, 61.7, 58.4, 31.1, 30.3, 20.5.

Application of the same procedure to diol **36** (0.090 g, 0.40 mmol) afforded pure *r-1-benzyloxy-c-2,t-3-dimethoxycyclohexane* (**23**) (0.030 g), as a liquid (Found: C, 71.89; H, 8.72. $C_{15}H_{22}O_3$ requires C, 71.97; H, 8.86%): ^{1}H NMR δ 7.23–7.40 (m, 5H), 4.61 (s, 2H), 3.74–3.84 (m, 1H), 3.53–3.67 (m, 1H), 3.44 (s, 3H), 3.39 (s, 3H) 3.26 (dd, 1H J=7.3, 2.9 Hz). ^{13}C NMR δ 139.7, 128.9, 128.2, 128.0, 83.1, 79.0, 71.4, 58.7, 57.6, 27.9, 27.6, 19.0.

Ketones 37–42

The following procedure is typical. A solution of alcohol **43**[4] (0.050 g, 0.24 mmol) in acetone (5 ml) was treated with 8 N CrO_3 in H_2SO_4 (0.06 ml) and the reaction mixture was left 5 min at rt. Dilution with ether and evaporation of the washed (saturated aqueous $NaHCO_3$ and water) afforded pure *4-benzyloxycyclohexanone* (**37**) (0.045 g), as a liquid:[4,8a,b] IR 1721 cm^{-1}; ^{1}H NMR δ 7.18–7.31 (m, 5H), 4.54 (s, 2H), 3.75–3.80 (m, 1H), 2.50–2.64 (m, 2H), 2.27–2.81 (m, 6H).

Following the usual procedure, oxidation of *cis*-3-benzyloxy-1-cyclohexanol (0.050 g, 0.24 mmol), obtained in the LAH reduction of *cis* epoxide **1**,[1a] and of alcohol **44** (0.10 g, 0.48 mmol) afforded pure *3-benzyloxycyclohexanone* (**38**)[1a] (0.040 g) and *2-benzyloxycyclohexanone* (**39**)[8c] (0.020 g), respectively, as liquids.

The same procedure applied to a mixture of alcohols (0.10 g) obtained in the LAH reduction of the mixture of *cis* and *trans* epoxides **3** and **7**[1d] afforded a mixture of ketones **40** and **41** which was subjected to preparative TLC (a 4:1 hexane/Et_2O mixture was used as the eluant). Extraction of the two most intense bands afforded pure *3-benzyloxymethylcyclohexanone* (**41**)[1d,8d] (0.045 g), and *4-benzyloxymethylcyclohexanone* (**40**) (0.040 g), a liquid:[1d] IR 1712 cm^{-1}; ^{1}H NMR δ 7.26–7.36 (m, 5H), 4.53 (s, 2H), 3.39 (d, 2H, J=6.1 Hz).

Following the same procedure, oxidation of *cis*-2-benzyloxymethyl-1-cyclohexanol (0.050 g, 0.22 mmol), obtained in the LAH reduction of *cis* epoxide **4**,[1e] afforded pure *2-benzyloxymethylcyclohexanone* (**42**), as a liquid (0.030 g).[1d,8e]

Reactions in the gas-phase

Materials. Deuterium, methane, oxygen and trimethylamine were high-purity gases from Matheson Gas Products Inc. and were used without further purification. The purity of the starting substrates, with special regard to the absence of their substituted and isomerized derivatives, was checked by analytical gas chromatography on the same columns employed for the analysis of the irradiated mixtures.

Procedure. The samples were prepared by introducing fragile ampoules, containing weighed amounts of selected epoxide and methanol, into 250 ml Pyrex bulbs, equipped with a break-seal arm, and connected to a greaseless vacuum line. Following the introduction of the gaseous components (deuterium or methane, oxygen and trimethylamine) at the desired partial pressures into the carefully evacuated and outgassed vessels, the latter were then allowed to come to room temperature, the fragile ampoules were broken, and the gaseous components were allowed to mix before being subjected to irradiation. Irradiation of the mixtures were carried out at 37.5°C in a ^{60}Co 220 gammacell from Nuclear Canada Ltd. The total dose received by the samples was 1.5×10^4 Gy, at a dose rate of 1×10^4 Gy h^{-1}, as measured with a Fricke dosimeter. Control irradiations carried out at much higher doses (up to 1×10^5 Gy) showed no significant changes in the relative yields of products.

Product analysis. The analysis of the products was performed by injecting measured portions of the homogeneous reaction mixture into a Hewlett–Packard 5890 series II gas chromatograph, equipped with a flame ionization detection unit. In order to prevent selective loss of the reaction products by adsorption on the glass of the reaction bulb (and to obtain reproducible and meaningful reaction yields), the analysis was repeated after careful washing of the bulb walls with freshly purified pentane. Satisfactory agreement between the results of the gaseous mixture and the pentane solution analysis was found in all runs. The products were identified by comparison of their retention volumes with those of authentic standard compounds on the following columns: (i) a 30 m×0.32 mm (i.d.) Supelcowax 10™ fused silica capillary column, operating at temperatures ranging from 50 to 200°C, 4°C min^{-1}; (ii) a 25 m×0.2 mm (i.d.) Carbowax 20™ Ultra performance capillary column, operating at 180°C. The identity of the products was further confirmed by GLC-MS, using a Model 5971A Hewlett–Packard quadrupole spectrometer. The yields of the products were measured, using the internal standard method and individual calibration factors to correct for the detector response. The results given in Tables 1–4 are the average of at least three measurements taken on at least two different runs for each point.

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2. *Standard reaction conditions:* epoxide opening reactions carried out with the nucleophile (MeOH in the methanolysis, as an example) under protic acid catalysis (MeOH/H_2SO_4), or without any catalysis in an appropriate solvent (MeONa/MeOH). *Chelating reaction conditions:* epoxide opening reactions carried with the nucleophile (MeOH) in the presence of a metal salt (MeOH/$LiClO_4$).

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