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Chiral ions in the gas phase. 5. Acid-induced methanolysis of optically active styrene oxide

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Abstract

The acid induced ring opening of (R)-(+) styrene oxide (**1R**) or (S)-(−) styrene oxide (**1S**) is investigated in the gas phase, at a temperature of 25 °C and in the presence of a labeled nucleophile ($CH_3{}^{18}OH$, CD_3OH, or $H_2{}^{18}O$). Various acid catalysts are generated in situ by γ radiolysis of the bulk gas (720 Torr of CH_4 or CH_3F). The mechanisms of the ring-opening reaction are assessed by modulating the composition of the gaseous mixture. Two reaction pathways are operative in the gas phase, both proceeding with the same regio- (100% at C_α) and stereochemistry (55–67% inversion of the C_α configuration). In the $CH_3F/H_2{}^{18}O$ systems, a slow reaction takes place within a persistent proton-bound complex between the epoxide and the $CH_3{}^{18}OH_2^+$ ion, formed by $(CH_3)_2F^+$-methylation of $H_2{}^{18}O$ (the *intracomplex* pathway). When methanol is present in the gaseous mixtures, the intracomplex process is superseded by a faster *extracomplex* reaction, involving the attack of an external methanol molecule on the O-protonated epoxide. The present results are discussed in the light of related gas-phase and solution data. (Int J Mass Spectrom 185/186/187 (1999) 425–435) © 1999 Elsevier Science B.V.

Keywords: Chirality, Gas-phase ion chemistry; Methanolysis; Ring-opening reaction; Styrene oxide

1. Introduction

Aromatic epoxides are important intermediates in many synthetic and biosynthetic processes and are recognized as potentially toxic metabolites responsible for the carcinogenic and mutagenic activity of polycyclic arenes [1]. The chemical reactivity of arene oxides arises from the strained three-membered ring that may undergo facile ring opening in any reaction media under various experimental conditions [2]. Previous studies have pointed out that the mechanism and the stereochemistry of epoxide ring opening depend to a large extent on many factors, such as the structure, configuration, and conformation of the epoxide; the presence and the nature of substituent groups; the pH, the ionic strength, the polarity, and the nucleophilicity of the reation medium; the nature of the catalyst; the temperature, etc. [2,3]. Thus, for instance, acid-catalyzed alcoholysis of aromatic epoxides was found to proceed by all the possible mechanisms, from A1 to the A2 extremes (Scheme 1) [4], with a stereochemistry ranging from complete retention to complete inversion of configuration [5].

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Dedicated to Michael T. Bowers on the occasion of his 60th birthday and in recognition of his many inspiring contributions to gas-phase ion chemistry.

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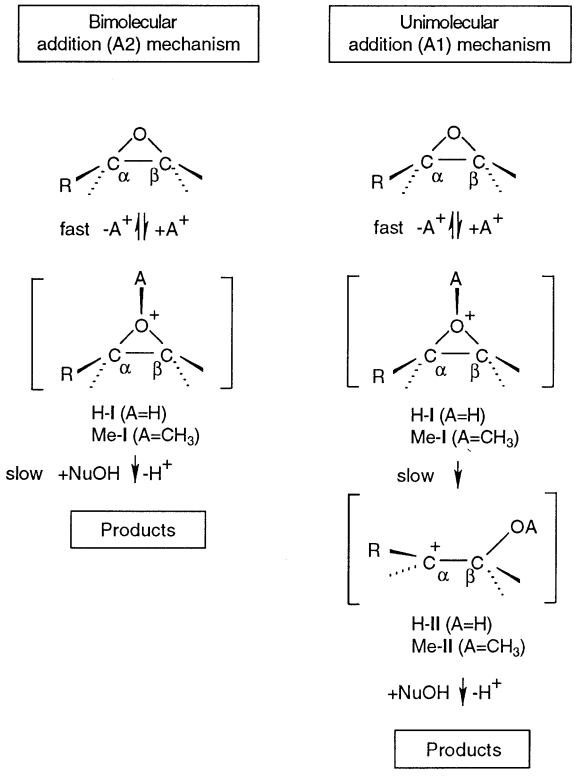
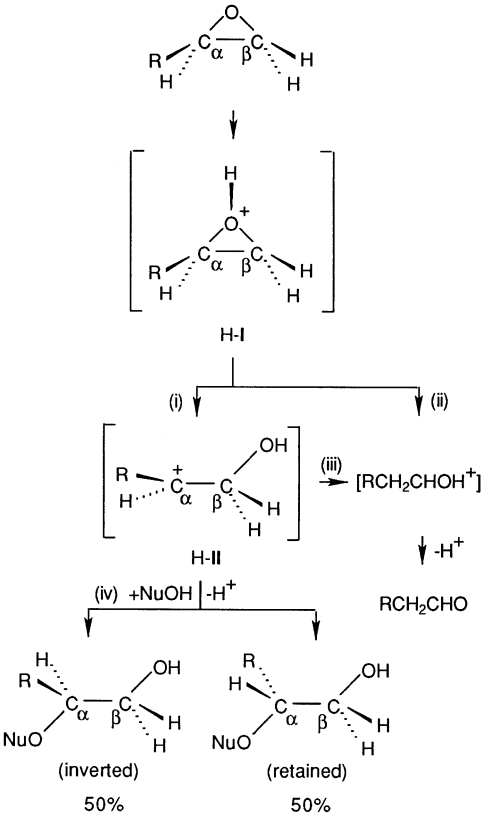


Scheme 1.

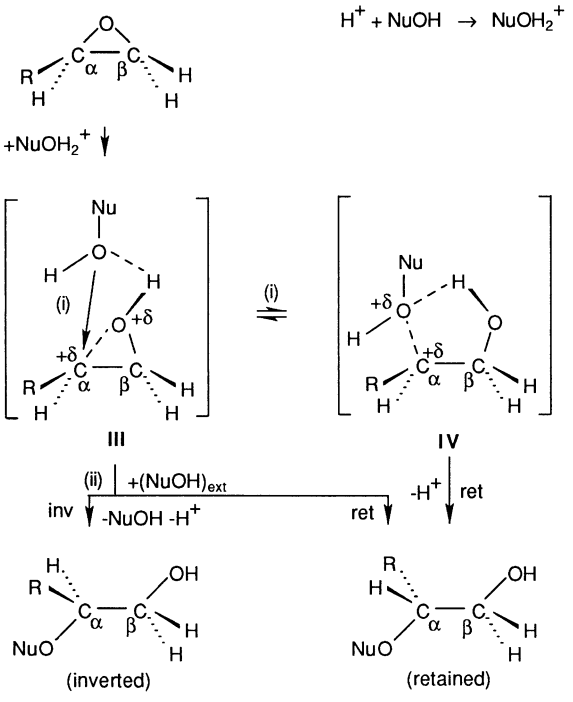


Scheme 2.

Under acidic conditions, the simplest unsymmetric aromatic epoxide, i.e. the styrene oxide, undergoes nucleophilic attack only at the benzylic C_α atom, a behaviour clearly correlated to the effect of the aromatic substituent in favoring the C_α–O bond breaking. The stereochemistry of the process has been related to the specific reaction mechanisms (Scheme 1). Thus, the higher percentage of inversion of the C_α configuration in the methanolysis of styrene oxide (89%), relative to hydrolysis (67%), has been interpreted in terms of the higher nucleophilicity and lower polarity of methanol that provides less stabilization of the open carbocation H-**II** and, therefore, favors occurrence of the A2 mechanism [4]. The significant change in the antistereoselectivity of HCl-induced ring opening of styrene oxide [6] from 24% in dioxane to 83% in chloroform provides an outstanding example of the pronounced solvent effect in the reaction mechanism.

The results of these studies, implemented by those from specifically designed investigations carried out in the gas phase [7], i.e. in the absence of complicating solvent and ion-pairing phenomena, have been embodied in a general mechanistic model, depicted in Schemes 2 and 3 [8].

Accordingly, any structural and electronic factors favoring localization of the positive charge at the C_α atom promote occurrence of the unimolecular mechanism of Scheme 2, thus leading to extensive acid-induced isomerization of the starting epoxide to the RCH_2CHO aldehyde and to the formation of the racemate of the substitution derivatives. In the framework of the bimolecular mechanism, the same factors favor occurrence of the intramolecular rearrangement **III** → **IV** (path (i) in Scheme 3) prior to attack by an external nucleophile $(NuOH)_{ext}$ and, therefore, formation of the retained substitution product. The high C_α



Scheme 3.

retention (97%) attained in the gas-phase acid-induced methanolysis of 1-phenyl-cyclohexene oxide [7c] and the complete C_α inversion of the same reaction with 1-para-nitrophenyl-cyclohexene oxide [7b], are fully consistent with the model in Scheme 3. Increasing the $(NuOH)_{ext}$ concentration leads to an increase of the inverted versus retained product yield (path (ii) in Scheme 3). The same is true in solution, where, however, polar aprotic solvents favour the polar **III** → **IV** transition structure (path (i) in Scheme 3), whereas the competing unimolecular ring opening to structure H-**II** is favored in polar protic solvents (Scheme 2).

The same model applies to the gas-phase methanolysis (NuOH = CH_3OH) of optically active propene oxides [9]. In **III** (R = Me; Scheme 3), the positive charge is not adequately localized at the C_α atom and, therefore, both the unimolecular mechanism of Scheme 2 and the intramolecular rearrangement **III** → **IV** (R = Me) of Scheme 3 are prevented. In the absence of an external CH_3OH, a slow intracomplex substitution takes place in complex **III** (R = Me) proceeding through the rate-limiting rupture of the O–H· · ·O hydrogen bond followed by a backside attack of the NuOH moiety at the epoxy ring carbons (41.5% at C_α; 58.5% at C_β). In the presence of an external CH_3OH, such an intracomplex process is superseded by attack of the external CH_3OH with the same regio- and stereochemistry of the companion intracomplex pathway.

Owing to the general interest in the behaviour of ion-molecule complexes in the gase phase and in the discrimination between intrinsic and environmental factors governing ring opening in aryl epoxides, we undertook a comprehensive investigation of acid-induced ring opening in (R)-(+)- (**1R**) and (S)-(−)-styrene oxide (**1S**), under typical gas-phase nucleophilic conditions. To stand comparison with the corresponding processes in solution, the investigation is carried at room temperature in an inert bulk gas (CH_4 or CH_3F), at a pressure high enough (720 Torr) to ensure efficient collisional thermalization of all the reaction intermediates. For these purposes, stationary concentrations of gaseous Brønsted, i.e. $C_nH_5^+$ (n = 1, 2), and Lewis acids, i.e. $(CH_3)_2F^+$, have been generated from γ radiolysis of the corresponding bulk gas, i.e. CH_4 and CH_3F, respectively, in the presence of traces of the chiral epoxide **1R** or **1S** (1.0 Torr) and of a nucleophile NuOH (Nu = H or CH_3) (0.2–4.1 Torr). The regio- and stereochemistry of the acid-induced epoxide ring opening may be inferred from the yield and the distribution of the neutral final products. Evaluation of the intrinsic structural and environmental factors governing these ring opening processes may arise from a comparison of the present gas-phase results with relevant solution and gas-phase data.

2. Experimental

2.1. Materials

Methane, methyl fluoride, oxygen, and trimethylamine were high purity gases from Matheson Co., used without further purification. $CH_3{}^{18}OH$ (^{18}O = 95%) was purchased from ICON Service Inc. Co.,

whereas $H_2{}^{18}O$ ($^{18}O > 97\%$) and CD_3OH (D = 99.8%) were obtained from Aldrich Chemical Co. The (R)-(+)-styrene oxide (**1R**) and (S)-(−)-styrene oxide (**1S**), with a chemical purity of >98%, were purchased from Fluka Co. Their enantiomeric purity exceeds 99%, according to gas chromatography-mass spectrometry (GC-MS) analysis. Aldrich Chemical Co. provided (R)-(−)-2-methoxy-2-phenyl-ethanol (**2R**) and its (S)-enantiomer (**2S**) as well as (R)-(−)- and (S)-(+)-styrene glycols, which were used as starting compounds to synthesize the corresponding methoxy derivates, namely the 1,2-dimethoxy-2-phenyl-ethane enantiomers (**3R** and **3S**) and the 1-phenyl-2-methoxy-ethanol enantiomers (**4R** and **4S**) [10]. The configuration of these derivatives was assigned according to that of their glycol precursor.

2.2. Procedure

The gaseous mixtures were prepared by conventional techniques using a greaseless vacuum line. The reagents and the additives were introduced into carefully degassed 130 mL Pyrex vials, each equipped with a break-seal tip. The vials were filled with the required mixture of gases, cooled to liquid nitrogen temperature, and sealed off. Then, they were γ irradiated (^{60}Co γ source) at 25 °C to a dose of 2×10^4 Gy (dose rate 1×10^4 Gy h^{-1}), as determined by a neopentane dosimeter. The resulting irradiated mixture was analyzed by gas liquid chromatography (GLC) on a 25 m × 0.25 mm DACTBS-Beta-CDX (30% diacetil-tert-butylsilyl-β-cyclodextrin on OV 1701 from MEGA Co.), operated at 40–160 °C, 3 °C min^{-1}, and on a 25 m × 0.25 mm Chrompack WCOT-CP CHIRASIL-DEX CB, operated at 40–170 °C, 3 °C min^{-1}. The products were identified by comparison of their retention volumes with those of authentic standard compounds, and their identity checked by GC-MS using a Hewlett-Packard 5890 A gas chromatograph in line with a HP 5970 B mass selective detector. A Chrompack CP 9002 gas chromatograph, equipped with a flame ionization detector, was employed for the quantitative analysis of the reaction products, whose yield was determined from the area of the GC signals, using the internal standard (benzyl alcohol) method and individual calibration factors to correct for the detector response. Blank runs were carried out to confirm the lack of undesired thermal ring opening of the starting styrene oxide under the irradiation conditions.

3. Results

The yield and distribution of the products from γ radiolysis of the gaseous systems containing the optically active substrate **1S** or **1R** in CH_4 or CH_3F, as bulk gas, together with trace amounts of O_2, as a thermal radical scavenger, and of a labeled nucleophile NuOH (Nu = H or CH_3) are given in Table 1. The table reports mean values obtained from several determinations, whose reproducibility is expressed by the uncertainty level quoted. The products of Table 1 can be classified into two different categories, namely the substitution derivatives, i.e. 2-phenyl-2-methoxy-ethanol (**2R** and **2S**) and 1,2-dimethoxy-1-phenyl-ethane (**3R** and **3S**) and an isomerization product, i.e. phenylacetaldehyde (**5**). Their absolute yields, expressed as the number of molecules *M* produced per 100 eV of energy absorbed by the gaseous mixtures [$G(M)$ values], were measured at a total dose of 2×10^4 Gy (dose rate 1×10^4 Gy h^{-1}) and found to depend critically upon the composition of the reaction mixture. Indeed, the substitution versus isomerization yield ratio [$G(M)_{subst}/G(M)_{isom}$] is found to decrease by decreasing the concentration of the labeled CH_3OH nucleophile and reaches the minimum value of 0.014 when replacing labeled CH_3OH with $H_2{}^{18}O$, as the added nucleophile. With NuOH = $CH_3{}^{18}OH$ or CD_3OH, the combined $G(M)_{isom} + G(M)_{subst}$ values approximately double if the CH_3F bulk gas is replaced by CH_4. When a powerful ion trap, i.e. trimethylamine (3–5 Torr), is introduced in the gaseous mixture, more than 75% reduction of the total absolute yield was observed.

The 2-phenyl-2-methoxy-ethanols **2R** and **2S** are the substitution products exlusively recovered in the CH_4/methanol systems and are accompanied by minor amounts of 1,2-dimethoxy-1-phenyl-ethanes **3R** and **3S** (<20%) in the CH_3F/methanol samples. The

Table 1
Product yields in the gas-phase attack of $C_nH_5^+$ (n = 1, 2) and $(CH_3)_2F^+$ ions on **1S** and **1R** in the presence of several labeled nucleophiles NuOH

System composition (Torr)[a]			Relative yield of substitution products, %[b]				Absolute yield (G(M))[c]	
			Ph − CH(MeO) − CH_2(OH)		Ph − CH(MeO) − CH_2(OMe)			
Bulk gas	Substrate	NuOH	**2S**	**2R**	**3S**	**3R**	$G(M)_{subst}$ (**2** + **3**)	$G(M)_{isom}$ (**5**)
CH_3F	**1S**	$H_2{}^{18}O$, 1.8	39 (46)	61 (39)	—	—	0.01	0.72
CH_3F	**1R**	$H_2{}^{18}O$, 1.9	67 (26)	33 (28)	—	—	0.01	0.65
CH_4	**1S**	$CH_3{}^{18}OH$, 0.2	34 (88)	66 (87)	—	—	0.07	1.10
CH_4	**1S**	$CH_3{}^{18}OH$, 1.2	42 (91)	58 (92)	—	—	0.67	0.60
CH_4	**1S**	$CH_3{}^{18}OH$, 4.1	41 (92)	59 (93)	—	—	0.58	0.52
CH_4	**1R**	$CH_3{}^{18}OH$, 0.9	58 (92)	42 (93)	—	—	0.47	0.46
CH_3F	**1S**	$CH_3{}^{18}OH$, 0.9	37 (91)	51 (93)	5 (91)	7 (91)	0.32	0.31
CH_3F	**1R**	$CH_3{}^{18}OH$, 0.8	47 (93)	33 (92)	11 (92)	9 (92)	0.21	0.28
CH_3F	**1S**	CD_3OH, 1.2	32 (95)	51 (96)	7 (95)	10 (96)	0.25	0.29
CH_3F	**1R**	CD_3OH, 1.0	51 (95)	35 (95)	8 (95)	6 (95)	0.30	0.29

[a] Bulk gas = 720 Torr, substrate = 1.0 Torr, O_2 = 4 Torr. Radiation dose 2×10^4 Gy (dose rate 1×10^4 Gy h^{-1}).
[b] Derived from GC-MS and GC-FID analyses and expressed as the percent ratio between the yield of any given product and the total yield of the substitution products. The figures in parentheses refer to the percent of labeling for each product.
[c] Absolute yields, expressed as the $G(M)$ values of products, i.e. the number of molecules M produced per 100 eV of energy absorbed by the gaseous mixture. Each value is the average of several determinations, with an uncertainty level of ~5%. **5** = phenylacetaldehyde.

product with a configuration *inverted* with respect to that of the starting epoxide invariably prevails (55–67%) over the retained one. Under no circumstances were styrene glycols and 1-phenyl-2-methoxy-ethanols **4R** and **4S** detected. Finally, no appreciable racemization of the starting epoxide **1S** (or **1R**) was observed under any conditions.

The GC-MS analysis of the phenylacetaldehyde **5** from all systems investigated excludes incorporation in its structure of the isotopic markers (^{18}O or D) initially present in the labeled NuOH. Extensive uptake of the isotopic labels is instead observed in the substitution products **2** and **3**, whose GC-MS spectra are characterized by the predominant $C_\alpha - C_\beta$ bond cleavage in the corresponding molecular ions. In fact, unlabeled **2** exhibits a major peak at m/z = 121, attributed to the $[C_6H_5CHOCH_3]^+$ fragment, accompanied by a minor signal at m/z = 31 ($[CH_2OH]^+$). The same major fragment $[C_6H_5CHOCH_3]^+$ (m/z = 121), accompanied by a minor peak at m/z = 45 ($[CH_2OCH_3]^+$), characterizes the spectrum of unlabeled **3**. The same fragmentation patterns are observed from labeled **2** and **3**. The lack of significant isotope effect in their fragmentation spectra allows one to determine the presence, position, and extent of incorporation of the marker in their structure (Table 1). Thus, the extent of ^{18}O incorporation at the C_α center of the **2** and **3** products, recovered in the mixtures with ^{18}O-labeled NuOH, is determined from the intensity of their m/z = 123 signal ($[C_6H_5CH^{18}OCH_3]^+$) relative to the combined m/z = 123 and m/z = 121 ($[C_6H_5CH^{16}OCH_3]^+$) peak intensities. Obviously, the presence of the CD_3O group bonded at the C_α center of **2** and **3** from the samples with NuOH = CD_3OH is witnessed by the observation of a signal at m/z = 124, corresponding to the $[C_6H_5CHOCD_3]^+$ fragment. The percents of isotope incorporation are reported in parentheses in Table 1. Products **2** from the samples with ^{18}O-labeled NuOH display no label incorporation at their C_β center, as shown by the absence of an m/z = 33 signal ($[CH_2{}^{18}OH]^+$) in the corresponding spectra. Similarly, products **3** from the CH_3F mixtures with $CH_3{}^{18}OH$ or CD_3OH do not exhibit any label incorporation at their C_β center, as demonstrated by the absence in their spectra of the

m/z = 47 ($[CH_2{}^{18}OCH_3]^+$) and m/z = 48 fragments ($[CH_2OCD_3]^+$), respectively.

The recovery of low amounts (<13%) of *unlabeled* **2** and **3** from systems containing labeled methanol (Table 1) suggests that, apart from the operation of the trace amounts of unlabeled $CH_3{}^{16}OH$ (~5%) present in the used $CH_3{}^{18}OH$, other unlabeled nucleophiles may take part in the epoxy ring opening. Water is probably the most important one, since it is invariably present as a ubiquitous impurity either introduced into the mixture together with its bulk components or formed from its radiolysis. The action of ubiquitous $H_2{}^{16}O$ is reflected by the comparatively low extent of ^{18}O incorporation in products **2** from the $CH_3F/H_2{}^{18}O$ systems (26–46%).

4. Discussion

4.1 Nature of the gaseous acid catalyst and its attack on the epoxide

The conditions typical of the present experiments, in particular the low molar fraction of the starting substrates **1S** and **1R** (~0.56 mol %), diluted in a large excess of the bulk gas (CH_4 or CH_3F), exclude their direct radiolysis as a significant route to epoxy ring opening products of Table 1. The presence of an effective radical scavenger, such as O_2, largely limits any free-radical pathways to products in favor of the competing ionic routes, whose large predominance is witnessed by over 75% reduction of the total absolute yield observed in the presence of a powerful ion trap, such as trimethylamine (3–5 Torr).

Gamma radiolysis of the bulk gas, either CH_4 or CH_3F, gives rise to stationary concentration of the Brønsted acids $C_nH_5^+$ (n = 1, 2) or the Lewis acid $(CH_3)_2F^+$, respectively. These ions are effectively thermalized by multiple unreactive collision (~10^{10} s^{-1}) with the parent molecules before their first encounter with the nucleophiles present in the gaseous mixture, including H_2O. Therefore, in the CH_4/$CH_3{}^{18}OH$ systems, the initially formed $C_nH_5^+$ (n = 1, 2) ions efficiently attack both the epoxy substrate, yielding the corresponding O-protonated derivative H-**I** (R = Ph, A = H; Scheme 1), and the added $CH_3{}^{18}OH$ (or the ubiquitous H_2O impurity) yielding eventually the $CH_3{}^{18}OH_2^+$ Brønsted acid. By the same token, in the CH_3F/NuOH (NuOH = $H_2{}^{18}O$, $CH_3{}^{18}OH$, or CD_3OH) systems, the initially formed $(CH_3)_2F^+$ Lewis acid can attack either the epoxide, yielding the corresponding O-methylated derivative Me-**I** (R = Ph, A = CH_3; Scheme 1), or the added NuOH, yielding the corresponding $NuO(H)CH_3^+$ (Nu = H, CH_3, or CD_3) Brønsted acids.

The evaluation of the thermochemistry of the attack of the above gaseous acids on styrene oxide meets with some difficulty owing to the lack of experimental thermochemical data for the involved ionic, e.g. H-**I** and Me-**I**, and neutral species, i.e. **1R** and **1S**. However, the formation enthalpy of styrene oxide can be estimated by using the group additivity method [$H°_f$(**1R** or **1S**) = ~13 kcal mol^{-1})] [11]. Its proton affinity (PA) can be taken as ~202 kcal mol^{-1}, in view of the fact that PA of a monosubstituted epoxide is typically ~2 kcal mol^{-1} lower than that of its isomeric methylketone [12]. On these grounds, $H°_f$(H-**I**) = ~177 kcal mol^{-1}. Moreover, the strict relationship between PA's and methyl cation affinities (MCA's) of *n*-type bases allows one to estimate approximately the MCA (**1R** or **1S**) = ~102 kcal mol^{-1} [13]. From this value, the $H°_f$(Me-**I**) can be taken as large as ~170 kcal mol^{-1}. From the above enthalpy values, O-protonation of **1R** or **1S** by $C_nH_5^+$ (n = 1, 2) is exothermic by ~70 (n = 1) and ~39 kcal mol^{-1} (n = 2), respectively. The same reaction is exothermic by only ~20 and ~10 kcal mol^{-1}, when the Brønsted acid is $CH_3OH_2^+$ and $(CH_3)_2OH^+$, respectively [12]. O-methylation of **1R** or **1S** by $(CH_3)_2F^+$ is exothermic by ~47 kcal mol^{-1} [12]. Therefore, if we make the reasonable assumption that all these exothermic processes are highly efficient, it follows that the H-**I** and Me-**I** intermediates are formed in the CH_3F systems in proportions approximately reflecting those of their ionic precursors $(CH_3)_2F^+$ and $NuO(H)CH_3^+$ (Nu = H or CH_3), respectively.

Another fact, particularly relevant in gaseous systems at high pressures, concerns the possibility that O-protonation of **1R** or **1S** by $NuO(H)CH_3^+$ (Nu = H or CH_3) may give rise to hydrogen-bonded adducts,

such as **III** of Scheme 5 [14], stabilized by multiple unreactive collisions with the bulk gas.

4.2. Isomerization and substitution patterns

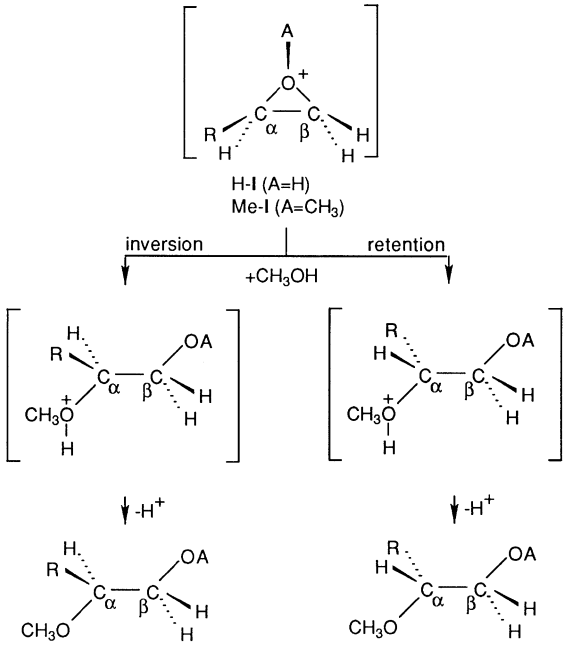
The recovery of substantial amounts of *unlabeled* phenylacetaldehyde **5** from all the investigated systems points to an extensive unimolecular rearrangement in its ionic precursors **I** or **III** before their encounters with NuOH. As shown in Scheme 2, aldehyde **5** may in principle arise directly from H-**I** via a concerted process (ii) or, alternatively, through a stepwise sequence (i) → (iii) involving the intermediacy of the free carbocations H-**II**, whose occurrence and lifetime in the investigated gaseous systems is relevant for evaluating the origin of the substitution products **2** (and **3**) of Table 1.

In the framework of the latter hypothesis, addition of NuOH to the open carbocations H-**II** is expected to give rise, in diluted gaseous media, to the racemate of the substitution products [path (iv) of Scheme 2] [15]. In this case, the observed imbalance between the inverted and the retained substitution products **2** of Table 1 may reflect the occurrence of a substitution route [(i) → (iv) of Scheme 2], competing with the bimolecular attack of the external nucleophile on H-**I** or **III** [path (ii) of Scheme 3]. However, this mechanistic model is inconsistent with: (1) the absolute insensitivity of the enantiomeric distribution of the substitution products **2** of Table 1 by a twentyfold variation of [$CH_3{}^{18}OH$], and (2) the fact that gas-phase $C_nH_5^+$ (n = 1, 2) protonation of 1-phenylcyclohexene oxide [7b], a more strained and substituted analog of styrene oxide, does not induce any significant formation of the corresponding free, open-chain benzylic carbocation, despite its greater stability relative to H-**II** (R = Ph; Scheme 2). Therefore, the unbalanced enantiomeric distribution of products **2** of Table 1 and its total independence of [$CH_3{}^{18}OH$] can find a viable explanation only by excluding the intermediacy of a long lived carbocation H-**II**, as a precursor of the substitution products, namely path (iv) of Scheme 2. This condition can be satisfied either by a concerted unimolecular isomerization of H-**I** or **III** to O-protonated phenylacetaldehyde (path (ii) of Scheme 2) or via the stepwise sequence (i) → (iii) of Scheme 2, but with the second step much faster than the first collison of H-**II** with the external nucleophile [path (iv) of Scheme 2]. Both hypotheses are consistent with the observed increase of the phenylacetaldehyde yield by decreasing [$CH_3{}^{18}OH$] (Table 1). Accordingly, once formed, intermediates H-**I** or **III** may undergo nucleophilic attack by NuOH in competition with unimolecular isomerization to O-protonated phenylacetaldehyde either through a concerted process or by a stepwise sequence involving an open carbocation H-**II**, as a transient intermediate. In both cases, the substitution products **2** must necessarily arise from the nucleophilic attack on the cyclic ions H-**I** or **III**. The complete analogy between the **2** and **3** product patterns suggests that the same mechanism applies to Me-**I** as well (Scheme 1).

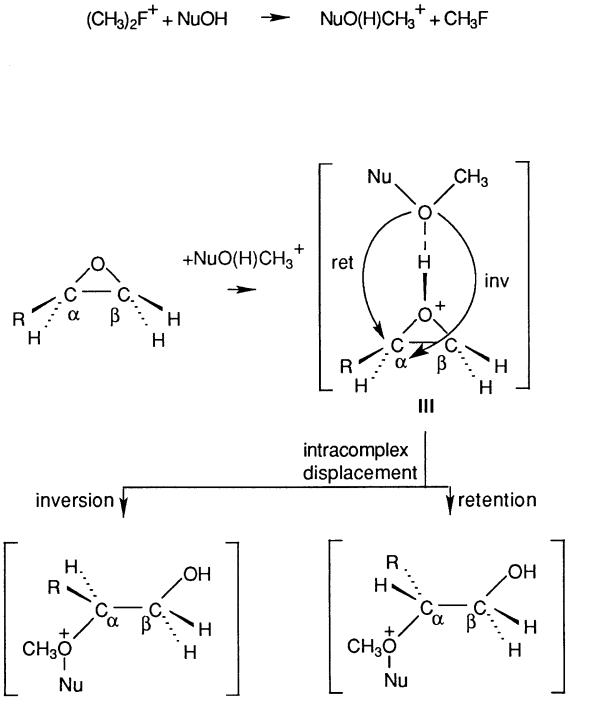
An accurate estimate of the thermochemistry of these bimolecular processes is prevented by the lack of sufficient thermochemical data for the ionic species involved. However, in view of the enthalpy changes involved in the NuOH (Nu = H or CH_3)-induced ring opening of 1-Me-oxiranium ($\Delta H°$ (kcal mol^{-1}) = ~ -32 (Nu = CH_3) and $+4$ (Nu = H), respectively) [12,13] and of O-protonated oxirane ($\Delta H°$ (kcal mol^{-1}) = -21 (Nu = CH_3) and -7 (Nu = H), respectively) [12], the same reactions on Me-**I** and H-**I** can be considered as thermodynamically feasible, except perhaps the slightly endothermic ring opening of Me-**I** by water. It follows that CH_3OH displacement on H-**I** (Scheme 4) (and on **III** of Scheme 3; vide infra) is the pathway operative in the CH_4/$CH_3{}^{18}OH$ mixtures. This process is accompanied by CH_3OH displacement on Me-**I** in the CH_3F/$CH_3{}^{18}OH$ or CD_3OH systems (Scheme 4).

Accordingly, the exclusive formation in these systems of the substitution products **2** and **3**, with the isotopic signature at the methoxy group bound to the C2 center, indicates that the labeled methanol attacks exclusively the benzylic C_α carbon of H-**I** and Me-**I** and preferentially from the rearside, as demonstrated by the predominance of the inverted product (55–66%) over the retained one (34–45%).

A similar isotopic signature and stereodistribution is observed for 2-methoxy-2-phenyl-ethanols **2**, re-



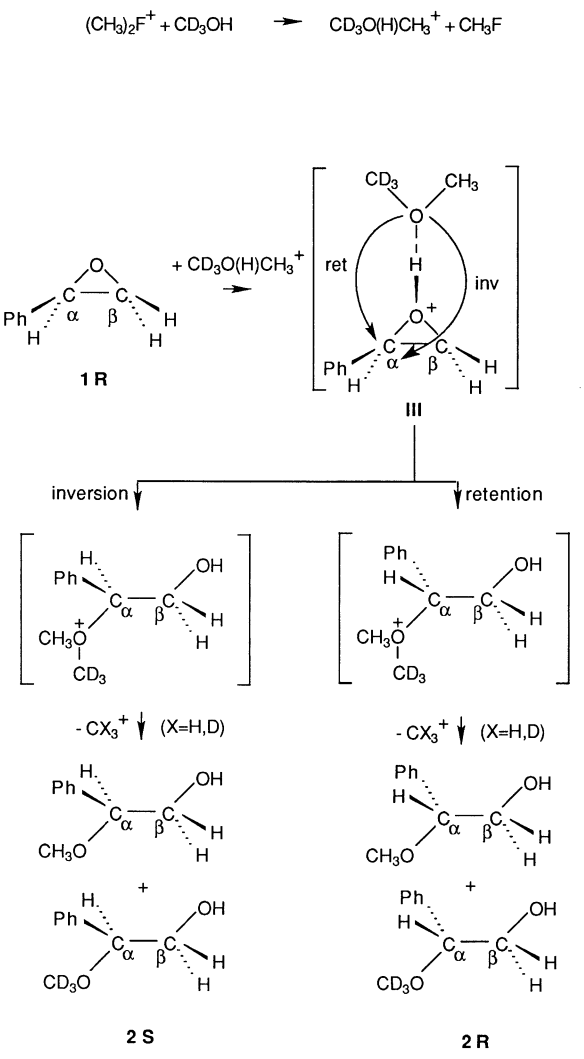
Scheme 4.



Scheme 5.

covered in much smaller yields in the $CH_3F/H_2{}^{18}O$ mixtures [$G(M)_{subst}$ = 0.01]. In these systems, the high inefficiency of the presumably endothermic H_2O attack at the benzylic C_α carbon of Me-**I** is witnessed by the complete absence of 1-methoxy-2-phenylethanols **4** [16]. Exclusive formation of labeled **2**, as the substitution products, testifies to the role of the Brønsted acid $CH_3{}^{18}OH_2^+$, generated by efficient $(CH_3)_2F^+$ methylation of $H_2{}^{18}O$, in the **1S** and **1R** ring opening (Scheme 5; Nu = H). In this regard, given the enormous excess of the epoxy substrate and of water, relative to neutral $CH_3{}^{18}OH$ released by proton transfer from $CH_3{}^{18}OH_2^+$ to **1S** or **1R**, the small, but appreciable yields of products **2** provide compelling evidence for the operation of the *intracomplex* displacement illustrated in Scheme 5. The same sequence, but involving the ubiquitous $H_2{}^{16}O$ impurity, accounts for the sizeable amounts of unlabeled **2**, recovered in these systems.

Having in mind the complete backside stereoselectivity of the *intracomplex* process in **III** (R = CH_3), observed in a previous study [9], the pronounced *intracomplex* frontside displacement taking place in **III** (R = C_6H_5) (33–39%) may well reflect some unimolecular **III** → **IV** rearrangement [path (i) of Scheme 3], favored by the proximity of the $CH_3{}^{18}OH$ moiety to the C_α reaction center [7b]. However, this hypothesis is readily discarded by considering the comparatively high yield of the products **2** [$G(M)_{subst}$ = 0.07–0.67; Table 1), recovered in the $CH_4/CH_3{}^{18}OH$ systems, and their enantiomeric distribution, which closely approaches that measured in the $CH_3F/H_2{}^{18}O$ samples. In fact, taking into account the relatively high diffusion rate of $CH_3{}^{18}OH$ (and of the ubiquitous H_2O impurity), the predominant catalysts eventually formed in the $CH_4/CH_3{}^{18}OH$ mixtures is by far the $CH_3{}^{18}OH_2^+$ Brønsted acid, especially at the highest $CH_3{}^{18}OH$ concentrations. As in the $CH_3F/H_2{}^{18}O$ systems, $CH_3{}^{18}OH_2^+$ interacts with epoxy substrate giving rise to the proton-bound complex **III** of Schemes 3 and 5. However, the fact that the absolute yield of products **2** from the $CH_4/CH_3{}^{18}OH$ mixtures is one order of magnitude or more higher than that measured in the $CH_3F/H_2{}^{18}O$ samples indicates that the presence and the concentration of the $CH_3{}^{18}OH$



Scheme 6.

additive in the first system is sufficient to make path (ii) of Scheme 3 (henceforth denoted as the *extracomplex* pathway) supersede any conceivable *intracomplex* evolution of **III** to the substitution products, whether proceeding through path (i) of Scheme 3 or via Scheme 5.

This conclusion is further supported by the predominant formation (>95%) of *labeled* 2-methoxy-2-phenyl-ethanols **2** from the CH_3F/CD_3OH mixtures. Indeed, a predominant *intracomplex* process in the proton-bound complex **III** between **1S** (or **1R**) and the $CD_3O(H)CH_3^+$ Brønsted acid (Scheme 6), generated by $(CH_3)_2F^+$-methylation of CD_3OH, would eventually produce approximately equal amounts of both labeled and *unlabeled* 2-methoxy-2-phenyl-ethanols **2**, in contrast with the experimental evidence. In this perspective, the *intracomplex* process, shown in Schemes 5 and 6, must necessarily involve a sizable activation barrier, much larger than that involved in the ring opening of **III** induced by an external $CH_3{}^{18}OH$ molecule [path (ii) of Scheme 3]. It can be attributed to the cleavage of the hydrogen bond in **III** necessary to make the $CH_3{}^{18}ONu$ moiety react with the C_α center of the protonated epoxide structure. A rough estimate of the lower limit of this activation barrier can be made by assuming a unit efficiency for the *extracomplex* pathway (ii) of Scheme 3 in the CH_3F mixtures with 0.2 Torr of $CH_3{}^{18}OH$. In this frame, the *intracomplex* process (Scheme 5; Nu = CH_3) in **III** must take place in a time largely exceeding 10^{-7} s, namely after ~3000 collisons of **III** with the CH_3F molecules at 720 Torr [17]. Hence, it is reasonable to consider complexes **III** as thermally equilibrated with the gaseous reaction medium before undergoing the *intracomplex* process of Scheme 5, which therefore obeys thermal kinetics. In this context, if the preexponential factor of the **III** *intracomplex* reaction approaches the typical bond vibration upper limit of 10^{13} s^{-1}, the activation barrier of the process must necessarily exceed ~8 kcal mol^{-1}, which represents a significant fraction of the proton-bond energy in **III** [14].

4.3. Comparison with related gas-phase and solution data

The stereoselectivity of the acid-induced methanolysis of H-**I**, **III**, and Me-**I** (R = C_6H_5) in the dilute gas state can be inferred from the enantiomeric distribution of the substitution products **2** and **3** listed in Table 1. The slight predominance of the inverted products (55–67%), observed under all conditions, denotes the relative insensitivity of the acid-induced ring opening in styrene oxide whether (1) involving the clustered (i.e. **III**) or the unclustered O-protonated epoxide (i.e. H-**I**); or (2) proceeding through the *intracomplex* reaction or via the *extracomplex* path-

way in **III**, or (3) promoted by different acid catalysts. In all cases, gas-phase methanolysis takes place exclusively at the C_α center of H-**I**, **III**, and Me-**I** (R = Ph), with essentially the same stereochemistry. This clearly reflects a loose ring-opening transition structure in H-**I**, **III**, and Me-**I** (R = Ph), characterized by an advanced rupture of the C_α–O bond favored by conjugative stabilization of the positive charge at the C_α center by the phenyl π system (a borderline A1–A2 process). Indeed, when conjugative stabilization is not operative, as in H-**I**, **III**, and Me-**I** (R = CH_3) [9], the positive charge is much more delocalized over the epoxy structure and methanolysis takes place at both the C_α and the C_β reaction centers of the epoxy moiety. Besides, methanolysis of H-**I**, **III**, and Me-**I** (R = CH_3) takes place with complete inversion of the configuration of the C_α site, pointing to a relatively tight ring-opening transition structure, characterized by a very limited rupture of the C_α–O bond (an A2 process). However, the reluctance of **III** (R = Ph) to undergo efficient *intracomplex* methanolysis (Schemes 5 and 6) strikingly contrasts with the highly efficient *intracomplex* frontside substitution taking place in the proton-bound complex between 1-phenylcyclohexene oxide and $CH_3OH_2^+$ [path (i) of Scheme 3] [7b]. This different behavior is attributed to the high propensity of the more strained 1-phenyl-cyclohexene oxide to undergo C_α–O bond fission when interacting with $CH_3OH_2^+$, favored by the phenyl group stabilization of the positive charge at the tertiary C_α atom (an A1 process). Development of a large fraction of the positive charge at this site favors collapse of the vicinal proton-bound CH_3OH moiety to the syn substituted intermediate. Indeed, when the presence of an electron-withdrawing substituent (i.e. para-NO_2) on the phenyl ring hinders localization of the positive charge at the tertiary C_α atom, the regio- and stereochemistry of the process better conform to an A2 mechanism [7b], much like that involved in the gas-phase reaction with H-**I**, **III**, and Me-**I** (R = CH_3) [9].

The present gas-phase results display some analogies with those obtained in acidic solutions [4b]. Indeed, styrene oxide reacts in acidic methanol mainly (89%) by inversion of configuration at the benzylic carbon, and the reaction is characterized by a sizable negative entropy of activation (~ -12 to -13 eu) and a Hammett ρ value of -4.1 [18]. These values have been interpreted in terms of a borderline A2 mechanism, similar to that operating in the gas phase. The main difference between gas-phase and solution data concerns the larger extent of inversion of configuration (89%), measured in solution, relative to that observed in the gas phase (55–67%). The greater stereoselectivity in solution may reflect a larger dispersal of the positive charge away from the benzylic carbon of the O-protonated epoxide due to solvation and, thus, a greater A2 character of the ring opening mechanism. Apart from this, the present data provide further support to previous conclusions in related systems [9] that the mechanism, the regiochemistry, and the stereochemistry of the acid-induced ring opening of epoxides are only moderately influenced by the nature of the reaction medium, but are essentially determined by the intrinsic structural and electronic properties of the substrate and of the nucleophile.

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