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Methanolysis of 1-aryl-1,2-epoxycyclohexanes in the condensed and in the gas phase: importance of the substituent for the reaction mechanism

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ABSTRACT: The stereoselectivity of a series of 1-aryl-1,2-epoxycyclohexanes substituted on the phenyl group was determined in acid methanolysis in the condensed phase (0.2 N H_2SO_4–MeOH) and in the reaction with MeOH in the gas phase under catalysis by a gaseous Brønsted acid (D_3^+). The results obtained show the presence of a clear Hammett-type dependence of the *syn*/*anti* adduct ratio on the Brown σ^+ of the substituent on the phenyl group, thus confirming the validity of the ion–dipole pair mechanism in order to rationalize the stereochemical behavior of 2-aryloxiranes in opening reactions under acidic conditions. Only in the cases of the *p*-OMe- and *p*-NO_2-substituted epoxides, does an S_N1 and an S_N2 process, respectively, appear to be involved. Copyright © 2004 John Wiley & Sons, Ltd.

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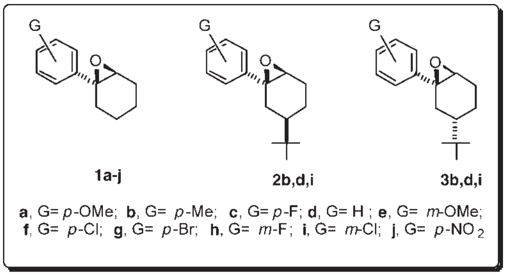
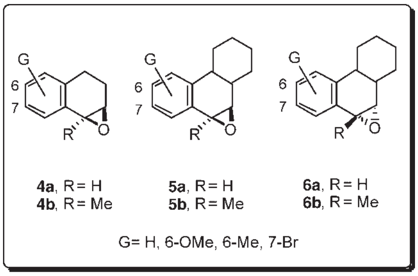
KEYWORDS: 2-aryloxiranes; opening reactions; reaction mechanism; gas phase; radiolytic method

INTRODUCTION

The mechanism of the ring opening of 2-aryloxiranes, and the related regio- and stereoselectivity, have been exstensively investigated in recent years by our group in Pisa and by Jerina and Whalen's groups in Bethesda and Baltimore. In particular, two different 2-aryloxirane systems have been examined: the semi-rigid epoxides **1a**–**j** and their conformationally constrained analogues **2** and **3b**,**d**,**h** derived from 1-arylcyclohexene (***S*₁** oxirane system) (Pisa group)[1,2] and the semi-rigid **4a** and the rigid benzo-condensed epoxides **5a** and **6a** derived from 3,4-dihydronaphthalene (epoxide **4a**) and *trans*-1,2,3,4,4a,10a-hexahydrophenanthrene (epoxides **5a** and **6a**) (***S*₂** oxirane system) (Bethesda and Baltimore groups).[3]



***S*₁ oxirane system**



***S*₂ oxirane system**

On the basis of the Hammett-type linear correlation between the Brown σ^+ of the substituent on the phenyl group and the *syn*/*anti* adduct ratio obtained in the acid hydrolysis (0.2 N H_2SO_4) of epoxides **1a**–**j**,[1] a general mechanism was proposed by our group in order to rationalize the stereochemical behavior of these epoxides in opening reactions under acidic conditions (mechanism A, Scheme 1).[1,2] The proposed rationalization is based on the incursion, after protonation of the oxirane oxygen of the epoxide reacting in its conformation **1′** (structure **7**, Scheme 1) (conformation **1′** allows a favorable axial

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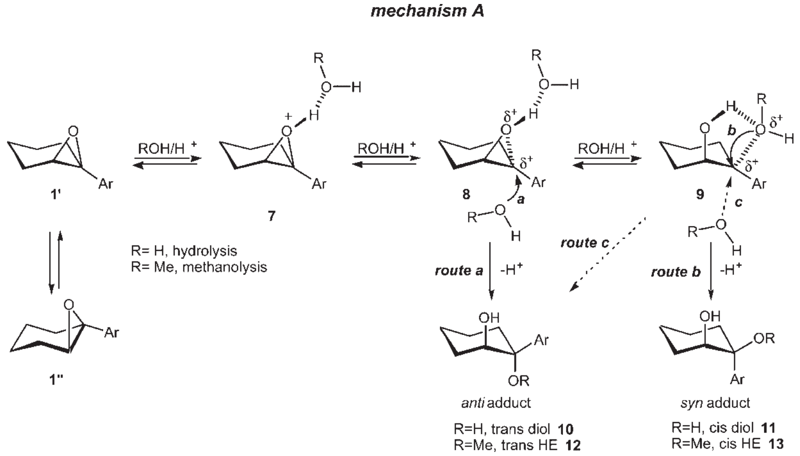


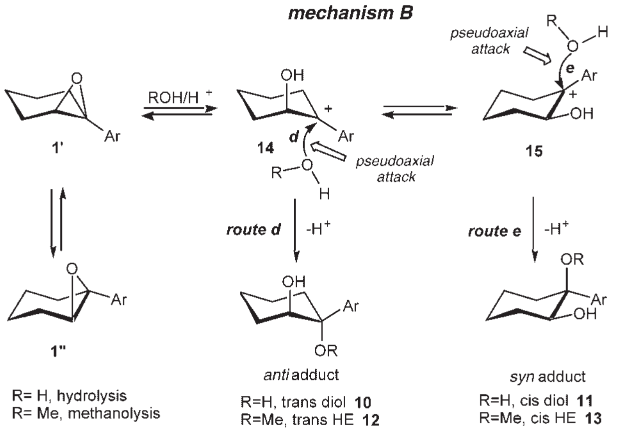
Scheme 1

opening of the oxirane ring. Evidence for the preferential reactivity of epoxides **1** through conformation **1′** has previously been obtained by examination and comparison of the chemical behavior of semi-rigid epoxide **1d** and the corresponding conformationally constrained epoxides **2d** and **3d**[4]), of discrete (not free) intermediate carbocationic species (ion–dipole pairs) with different levels of positive charge at the benzylic oxirane carbon: the intramolecular intimate ion–dipole pair **8**, in which there is an extended benzylic C—O bond, and the more carbocationic nucleophile-separated ion–dipole pair **9**. Nucleophilic attack on **8** can occur only from the back side, because the benzylic C—O bond is not broken (route ***a***), affording only the *anti* adduct (the *trans* diol **10** in the acid hydrolysis), whereas nucleophilic attack on **9** would preferentially occur by the internal nucleophile with retention of the configuration to afford the *syn* adduct (the *cis* diol **11** in the hydrolysis) (route ***b***, Scheme 1). In this rationalization, the *syn* stereoselectivity of the opening process derives exclusively from the competition between the two alternative processes: direct attack of the nucleophile on **8**, which leads to the *anti* adduct, and/or conversion of **8** into **9**, which leads to the *syn* adduct [the attack of the nucleophile internal to the ion–dipole pair **9** looks so entropically favored that an attack on species **9** by an external nucleophile, which would lead to the *anti* adduct (route ***c***, Scheme 1), can reasonably be excluded]. As a consequence, any factor, such as the ability of the substituent on the aromatic ring to stabilize a benzylic carbocationic center, favoring the isomerization process of **8** to **9**, will determine an increase in the *syn*/*anti* ratio (mechanism A, Scheme 1).[1,2]

Related studies originally carried out by the Bethesda and Baltimore groups on the opening reactions (acid hydrolysis) of the benzo-condensed epoxides **4**–**6a** led the authors to rationalize the stereoselectivity obtained with these epoxides by admitting the incursion of corresponding fully developed benzylic carbocations, then attacked by the nucleophile (water) in a preferential pseudo-axial fashion.[3]

The same authors then tried to apply the mechanism proposed for epoxides **4**–**6a** also to the results from epoxides **1a**–**j**, which had been the object of our previously described original rationalization. In this framework, the semi-rigid epoxides **1a**–**j** open in an axial fashion through conformation **1′** to give the fully developed benzylic carbocation **14** (mechanism B, Scheme 2). Nucleophilic attack on **14** can occur only through the preferential pseudo-axial pathway to give the anti adduct (the *trans* diol **10**, route ***d***). However, if the aryl substituent is sufficiently capable of stabilizing the benzylic carbocationic species, the initially formed carbocation **14** (axial OH) can isomerize to the more stable carbocation **15** (equatorial OH). Nucleophilic attack on **15** can occur also in this case *only* in a pseudo-axial fashion, to give the *syn* adduct (the *cis* diol **11**, route ***e***). As a consequence, the *syn* stereoselectivity is practically linked to the presence of **15** in the **14** $\rightleftharpoons$ **15** conformational equilibrium, with the nucleophile entering, in any case, through a pseudo-axial pathway.[3a]

Further studies carried out in Pisa on the hydrolysis and methanolysis, both in the condensed[2,5a–c] and in the gas phase[5d,e,6a] (in the gas phase, the opening reaction with



Scheme 2

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MeOH under acidic conditions was carried out only on epoxides **4–6a**,**b**) of the conformationally restricted epoxides **2b**,**d**,**h** and **3b**,**d**,**h**, the 4-*tert*-butyl derivatives of epoxides **1b**,**d**,**h** (S_1 oxirane system)[2] and epoxides **4–6a** and their 1- and 9-methyl derivatives **4–6b** (S_2 oxirane system)[5,6] substituted on the aromatic ring with an electron-donating or electron-withdrawing group[5a,c,e,6a] definitely ruled out mechanism B as a useful rationalization in order to explain the stereoselectivity of the opening process under acid conditions of these 2-aryloxiranes (S_1 and S_2 system). At the same time, mechanism A appeared to be the *only* rationalization able to explain all the results so far obtained by both the S_1 and S_2 oxirane systems.[5e,6a] As a consequence, we considered the question definitely solved.

Recently, Whalen's group (Baltimore) found a mistake in our original study on the Hammett-type dependence of the hydrolysis of semi-rigid epoxides **1a–j**.[7] In particular, the result obtained by us in the case of the *p*-OMe derivative **1a** after 24 h in 0.2 N H_2SO_4 (95.3% *cis* diol and 4.7% *trans* diol, heterogeneous conditions)[1] was found not to be the result of the opening process but actually the result of an equilibration of the initially formed less stable trans diol **10a** into the more stable *cis* diol **11a**.[7] As a consequence, the acid hydrolysis reaction of epoxide **1a** is far less *syn* stereoselective (*cis* diol **11a**:*trans* diol **10a** ratio = 74:26) than we originally erroneously thought.[1] The consequence is that the new, correct result from the *p*-OMe derivative **1a** does not fit any more, particularly as regards the Hammett-type relationship, with the results obtained with the other semi-rigid epoxides of type **1** (we are indebted to Whalen's group for their appropriate re-checking; evidently at that time, the stability of the *cis* and *trans* diols **11a** and **10a** in the reaction conditions was not appropriately and accurately checked).

This observation led Whalen's group to state that, at least in the series made up by epoxides **1a** (*p*-OMe), **1b** (*p*-Me) and **1d** (*p*-H derivative), '... the *cis*/*trans* diol ratio from the acid-catalyzed hydrolysis ... does not depend systematically on the electron-donating ability of the *para*-substituent' and to re-propose mechanism B as an appropriate rationalization of the results.[7] As for epoxide **1j** (*p*-NO_2 derivative) and other phenylcyclohexene oxides with electron-withdrawing groups on the phenyl ring, the same authors state that '... they must react at least partially by a mechanism different than that by which **1a**,**b**,**d** react'.[7]

Once again, in spite of all the evidence collected in the past, the dependence of the *syn*/*anti* adduct ratio on the electronic properties of the substituent on the aromatic ring and, in general, the validity of mechanism A are questioned and, correspondingly, mechanism B re-proposed. Moreover, the impression is that, now, there is some confusion about the way in which epoxides **1a–j** react, to the point that each epoxide is thought to react almost independently of the others.

Since we were still convinced of the more general validity of mechanism A, we thought it necessary to re-examine the stereoselectivity of the opening reactions of epoxides **1a–j** under acidic conditions, making use of MeOH as the nucleophile. MeOH was chosen because the reaction of 2-aryloxiranes with this nucleophile in the condensed phase (acid methanolysis, H_2SO_4–MeOH) is commonly a fast reaction which goes to completion in a few seconds (or minutes, at most), making it possible to reduce the possible incursion of isomerization processes of the primary reaction products. Moreover, the opening reaction with MeOH may be easily and advantageously repeated also in the gas phase, making a correlation possible between the results obtained in these two very different operating conditions, the condensed and the gas phase; this correlation could turn out to be useful in order to understand the real behavior of these oxirane systems. In fact, while the condensed phase is characterized by the presence of a large amount of the nucleophile (MeOH), used also as the solvent of the reaction and, as a consequence, it is influenced by its strong solvating effect, in the gas phase the nucleophile (MeOH) is present only in a small amount (3 equiv.) in an inert bulk gas (D_2), in the presence of a gaseous Brønsted acid (D_3^+), to the point that the oxirane opening process proceeds without any interfering effect by the polar nucleophile. Under these conditions, the reacting system made up of the oxirane, the acid (devoid of the counterion) and the nucleophile behaves like a practically isolated, non-solvated system, particularly suitable for studies of the reaction mechanism involved in the opening process.[8]

RESULTS

The reference compounds, the hydroxy ethers (HEs) **12–13a–i** were prepared by acid methanolysis (0.2 N H_2SO_4 in anhydrous MeOH) of the corresponding epoxide to give a mixture of the corresponding HEs, which were separated by preparative TLC. HEs **12–13j** were prepared as described previously.[9]

The exact regiochemistry of HEs **12–13a–j** was easily determined by simple considerations based on the regioselectivity commonly observed in the acid ring opening of these systems with a nucleophilic attack on the benzylic carbon. As for the stereochemistry inside each pair of HEs, the relative configuration was appropriately assigned by examination of the signal of proton H_a in the ^1H NMR spectra of these compounds, on the reasonable assumption that the aryl group occupies preferentially an equatorial position. In the *cis* stereoisomers **12**, H_a exhibits larger coupling constants or/and larger $W_{1/2}$ values than in the corresponding *trans* diastereoisomers **13** in accordance with its axial or equatorial nature, respectively (Scheme 3 and Experimental section).[10]

Epoxides **1a–j** were subjected to ring-opening reactions with MeOH both in the condensed and in the gas

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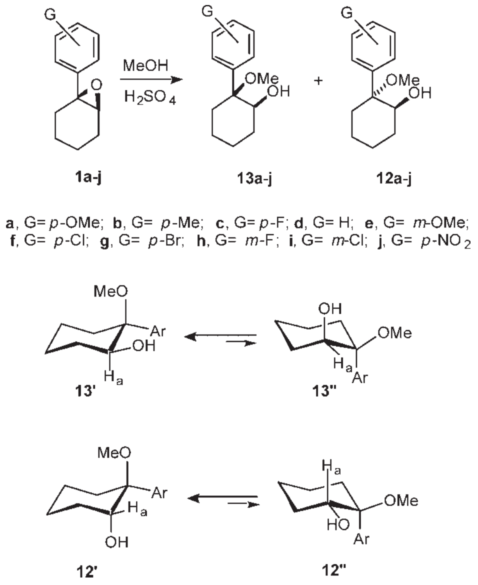


Scheme 3

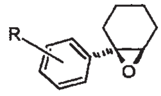
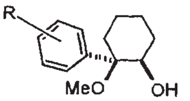
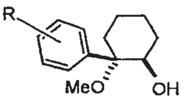
phase. The results obtained are shown in Tables 1 and 2. The reaction time utilized in the condensed phase was particularly short (10–60 s, Table 1) in order to avoid any possibility of isomerization under the reaction conditions. However, appropriate control experiments aimed to evaluate the stability of the primary reaction products, the HEs *cis* **13** and *trans* **12**, showed that they are stable under the reaction conditions used. Only the *cis p*-OMe derivative (HE **13a**) turned out to isomerize partly, and after 1 min of contact with the methanolysis solution (0.2 N H_2SO_4–MeOH) a modest, even if significant, amount (4%) of epimerization took place. Control experiments carried out also for the gas-phase operating conditions showed that addition products were completely stable under these conditions. As a consequence, the *cis*/*trans* ratio measured corresponds exactly to the stereoselectivity of the reaction, and is not the result of a subsequent epimerization process.

DISCUSSION

The results obtained in the acid methanolysis of the *p*-Me, *p*-F, *p*-H, *m*-OMe, *p*-Cl, *p*-Br, *m*-F and *m*-Cl derivatives (epoxides **1b–i**) in both the condensed- and gas-phase operating conditions indicate that there is a clear dependence of the *syn* stereoselectivity of the opening process on the nature and the electronic properties, that is, on the electron-donating ability of the substituent on the aromatic ring. The highest and lowest levels of *syn* stereoselectivity are obtained in the case of the *p*-Me and *m*-Cl derivatives (epoxides **1b** and **1i**), respectively, and a satisfactory Hammett-type linear correlation was found between the diastereoselectivity of the reaction (*syn*/*anti* adduct ratio) and the Brown σ^+ constants of the substituent on the phenyl group, in accordance with Eqn (1) (Table 3). The $\rho_{syn} - \rho_{anti}$ value obtained, together with the corresponding correlation coefficient (*r*) and standard deviation (*s*) are summarized in Table 3 and plotted in Figure 1.

The only exception is given by the *p*-OMe and *p*-NO_2 derivatives (epoxides **1a** and **1j**), which afford in both the condensed and gas phase corresponding stereochemical results which do not fit the results obtained with the other epoxides as regards the Hammett-type linear correlation: epoxide **1a** affords a 61:39 (condensed phase) and 63.9:36.1 (gas phase) *syn* adduct/*anti* adduct ratio, whereas epoxide **1j** gives a completely (>99% *anti* adduct) and a practically complete *anti* stereoselective result in the condensed and gas phases (*anti* adduct:*syn* adduct = 98.2:1.8), respectively.

Table 1. Distribution of products in the methanolysis (0.2 N H_2SO_4–MeOH, condensed phase) of epoxides **1a–j**

			Product distribution (%)	
			syn adduct	*anti* adduct
				
Entry	**1** epoxide	Reaction time (s)	**13**	**12**
1	**1a**, R = *p*-OMe	10	61.0	39.0
2	**1b**, R = *p*-Me[a]	10	61.2	38.8
3	**1c**, R = *p*-F	30	41.9	58.1
4	**1d**, R = H[a]	10	38.1	61.9
5	**1e**, R = *m*-OMe	30	31.2	68.8
6	**1f**, R = *p*-Cl	30	28.3	71.7
7	**1g**, R = *p*-Br	30	26.6	73.4
8	**1h**, R = *m*-F	30	13.2	86.8
9	**1i**, R = *m*-Cl[a,b]	30	12.2	87.8
10	**1j**, R = *p*-NO_2[b]	60	<1	>99

[a] Ref. 2.

[b] Ref. 9.

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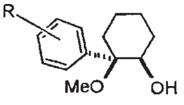
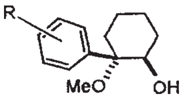
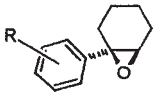
Table 2. Distribution of products in the gas-phase acid-induced ring opening with MeOH of epoxides **1a–j**

	Gas-phase system composition (Torr)[a]				Product distribution[b]				
					syn adduct  **13**		*anti* adduct  **12**		
Entry	 **1** epoxide		Bulk gas[c]	MeOH	*G*	%	*G*	%	Total absolute yield (%)[d]
1	**1a**, $R = p$-OMe	(0.98)	D_2 (760)	(3.12)	0.69	63.9	0.39	36.1	36
2	**1b**, $R = p$-Me	(1.09)	D_2 (760)	(3.14)	1.10	96.5	0.04	3.5	38
3	**1c**, $R = p$-F	(0.99)	D_2 (760)	(3.02)	0.96	94.1	0.06	5.9	34
4	**1d**, $R = H$	(1.03)	D_2 (760)	(3.10)	0.95	93.1	0.07	6.9	34
5	**1e**, $R = m$-OMe	(1.12)	D_2 (760)	(3.06)	0.80	92.0	0.07	8.0	29
6	**1f**, $R = p$-Cl	(1.07)	D_2 (760)	(3.12)	0.77	91.7	0.07	8.3	28
7	**1g**, $R = p$-Br	(1.04)	D_2 (760)	(3.08)	0.82	91.1	0.08	8.9	30
8	**1h**, $R = m$-F	(1.04)	D_2 (760)	(3.10)	0.68	87.2	0.10	12.8	26
9	**1i**, $R = m$-Cl[e]	(1.10)	D_2 (760)	(3.26)	0.80	86.0	0.13	14.0	31
10	**1j**, $R = p$-NO_2[e]	(1.07)	D_2 (760)	(3.12)	0.01	1.8	0.56	98.2	19

[a] O_2: 4 Torr (1 Torr = 133.3 Pa), 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] 3 Torr of NMe_3 added to the gaseous mixture.

[d] Total absolute yields (%) estimated from the percentage ratio of the combined *G*(M) values of products and the literature $G(GA^+)$ values.[11]

[e] See ref. 9.

Table 3. $\rho_{syn} - \rho_{anti}$ values obtained in the acid methanolysis (condensed phase) and in the gas-phase acid-induced ring opening with MeOH of epoxides **1b–i**

$$\mathrm{Log}\left(\frac{[S]\,[A°]}{[A]\,[S°]}\right) = \left(\rho_{syn} - \rho_{anti}\right)\sigma^+ \qquad (1)$$

Epoxide	Reagents and reaction conditions[a]	$\rho_{syn} - \rho_{anti}$	Correlation coefficient (*r*)	Standard deviation (*s*)
1b–i	MeOH–H_2SO_4	−1.51	0.996	0.026
1b–i	MeOH–GA^+	−0.96	0.994	0.021

[a] MeOH–H_2SO_4, condensed-phase operating conditions (methanolysis); MeOH–GA^+, gas-phase operating conditions.

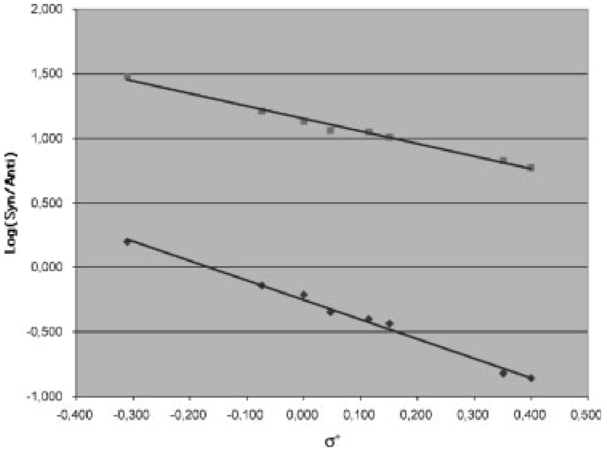
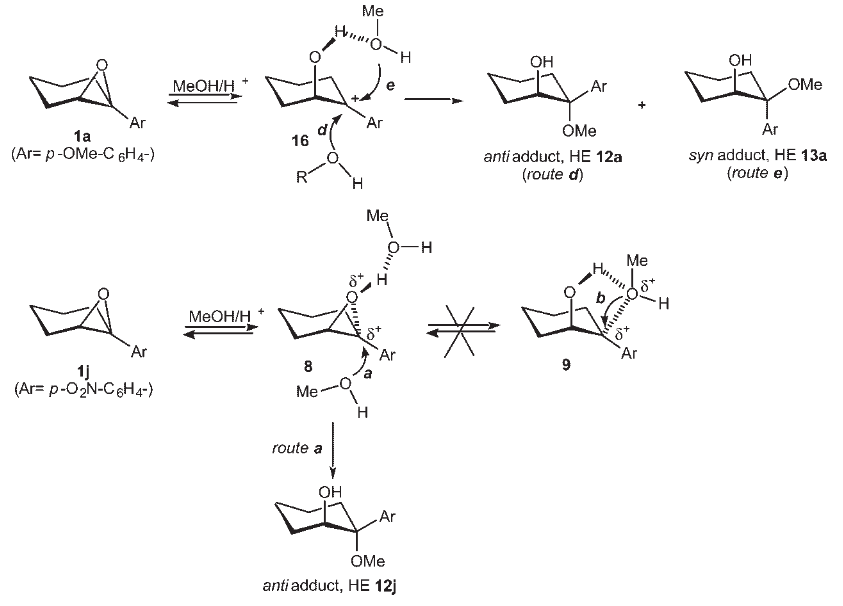


Figure 1. Hammett–Brown ρ^+ for the acid-catalyzed ring opening of epoxides **1b–i** with MeOH in the condensed phase (◆) and in the gas phase (ν)

The results obtained with epoxides **1b–i** appear to be nicely consistent with our rationalization (mechanism A), reported in Scheme 1, in which the *syn*/*anti* stereoselectivity depends on the equilibrium between the two alternative pathways (routes ***a*** and ***b***, Scheme 1) involving the two carbocationic-like species **8** and **9**, modulated by the aryl substituent, as discussed above. An increased electron-donating ability of the aryl substituent favors the isomerization of **8** to **9** with the consequent formation of increased amounts of *syn* adduct.

In principle, the results obtained in the acid methanolysis of epoxides **1b–i** are compatible also with mechanism B. However, this mechanism appears to be less appropriate to rationalize the results on the basis of previous unequivocal evidences obtained with the conformationally constrained epoxides **2–3b**,**c**,**h**.[2] Moreover, mechanism B, which implies a preferential pseudoaxial attack of the nucleophile on a fully developed



Scheme 4

carbocation, would not be able to rationalize why the *p*-OMe derivative (epoxide **1a**) affords *syn* stereoselectivity (61 and 63.9%) similar to or decidedly lower than that of the *p*-Me derivative (epoxide **1b**) both in the condensed and in the gas phase (61.2 and 96.5%), respectively.

In the framework of mechanism A, also the behavior of the *p*-OMe- and *p*-NO_2-substituted epoxides **1a** and **1j**, apparently difficult to rationalize, can be simply and easily explained as the result of an extremization of the mechanism itself, due to the particular nature of the substituent on the phenyl group. In the case of the *p*-OMe derivative **1a**, the strong conjugative electron-donating ability of the methoxy group, together with the associated stabilizing effect on a benzylic carbocation, determines the incursion of an S_N1-type mechanism with the formation of a completely developed carbocationic species such as **16** (Scheme 4). Subsequent nucleophilic attack by the nucleophile (MeOH) can reasonably occur, almost indifferently, on both the diastereotopic faces (routes ***d*** and ***e***, Scheme 4), to give the unstereoselective results observed both in the condensed and in the gas phase [*syn* adduct (HE **13**):*anti* adduct (HE **12**) ratio = 61:39 and 64:36, respectively]. The only slight preference for the syn adduct (route ***e***) could be simply the consequence of a directing effect of the OH group through a hydrogen bond with the nucleophile, as shown in structure **16** (Scheme 4). (In our opinion, obtaining, in the case of epoxides **1a** and **1j**, almost the same stereoselectivity in the condensed and in gas phase gives confirmation of the incursion of the same mechanism, an S_N1 process in the case of **1a** and an S_N2 process in the case of **1j**, under both operating reaction conditions.)

On its own, in epoxide **1j**, the strong electron-withdrawing effect of the *p*-NO_2 substituent group and the associated destabilizing effect on a developing benzylic carbocation do not allow any partitioning between the two carbocationic species **8** and **9** (mechanism A, Schemes 1 and 4). As a consequence, in this case only the less carbocationic species **8** can be formed and subsequently nucleophilically attacked by the MeOH necessarily in an *anti* fashion, because the benzylic oxirane C—O bond is not broken, to give the completely (condensed phase) or almost completely (gas phase) *anti* stereoselective result observed in both the reaction conditions, through a typical S_N2 or borderline-S_N2 mechanism (route ***a***, Scheme 4). In this way, a completely *anti* stereoselective result is obtained (see the comment at the end of the previous paragraph).

As a consequence of the extremization of mechanism A, as observed in the cases of the *p*-OMe (completely S_N1) and *p*-NO_2 derivatives (completely S_N2), the results obtained with these epoxides cannot fit the results obtained with the other substrates in which, on the contrary, there is a constant partitioning of the reaction pathways between the two intermediate species **8** and **9**, appropriately modulated by the electronic properties of the substituent on the aromatic ring.

The results obtained in the gas phase constitute another example of the particular behavior of epoxides **1a**–**j** in acid-catalyzed ring opening reactions (see above). In these conditions, the opening reactions of epoxides **1b**–**i** are more *syn* stereoselective than the corresponding reactions carried out in the condensed phase (Tables 1 and 2). In accordance with mechanism A, the decidedly lower amount of nucleophilic molecules (MeOH), which characterizes the gas-phase operating conditions, favors the isomerization of the less carbocationic species **8** to the more carbocationic species **9**, thus determining a marked increase in the *syn* stereoselectivity, as correctly observed. (If mechanism B, implying fully developed

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intermediate carbocations, were operating, the *syn* stereoselectivity should turn out to be independent on the amount of the nucleophile added, contrary to the experimental result from the gas phase.) On its own, the increased carbocationic character of the opening process determined by the gas phase operating conditions causes an appropriate reduction in the sensitivity of the diastereoselectivity of the opening reaction to the electronic effect of the substituent on the aromatic ring. As a consequence, the $\rho_{syn} - \rho_{anti}$ value of the reaction with MeOH is lower in the gas-phase operating conditions than in the condensed phase, as shown in Table 3 and Fig. 1.

CONCLUSIONS

The examination of the opening reactions with MeOH under acidic conditions of 1-aryl-1,2-epoxycyclohexanes **1a–j** bearing different substituents on the aromatic ring has demonstrated that the stereochemical outcome of the opening reaction depends directly on the nature and the electronic properties of the aryl group, to the point that a nice Hammett-type linear correlation is found between the *syn* stereoselectivity and the Brown σ^+ of the substituent present on the aromatic ring. On the basis of the present and previously reported results, the ion–dipole pair mechanism (mechanism A), based on the incursion of two discrete carbocationic equilibrating species, appears to be adequate to rationalize all the results. Only in the case of epoxides **1a** and **1j**, which bear a strong electron-donating (*p*-OMe) and a strong electron-withdrawing group (*p*-NO_2), respectively, must a different and opposite behavior be admitted in order to rationalize the results obtained with these epoxides, not in linear correlation with the results obtained with the other corresponding epoxides. In the case of the *p*-OMe derivative, the opening process proceeds through a fully developed benzylic carbocation by means of an S_N1 mechanism, whereas the *p*-NO_2 derivative reacts through an almost exclusive S_N2 process. The behaviors of epoxides **1a** and **1j** are not something apart, but constitute the extreme points with respect to the general mechanism proposed.

In conclusion, not different mechanisms in order to rationalize the results obtained in very similar substrates, but only a different modulation of the same mechanism, in which the substrates bearing substituent groups characterized by very strong electron-donating or electron-withdrawing properties, constitute the extreme points.

EXPERIMENTAL

Reactions in the condensed phase

General. Melting-points were determined on a Kofler apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were determined with a Bruker AC-200 spectrometer on $CDCl_3$ solutions using tetramethylsilane as the internal standard. Routine IR spectra were taken on paraffin oil mulls with a Mattson 3000 FTIR spectrophotometer. All reactions were followed by TLC on Alugram SIL G/UV_{254} silica gel sheets (Macherey–Nagel) with detection by UV spectrophotometry or with 0.5% phosphomolybdic acid solution in 95% EtOH. Preparative TLC were performed on 2.0 or 0.5 mm Macherey–Nagel DC-Fertigplatten UV_{254} silica gel plates. GLC analyses of mixtures of HEs **12** and **13** were performed on a Hewlett-Packard 5890 series II gas chromatograph unit (flame ionization detector). Epoxides **1a–j**[12] and HEs **12–13j**[9] were prepared as described previously.

Preparation of HE 12a–i and 13a–i

General procedure. A solution of the epoxide (0.20 g) in 0.2 N H_2SO_4 in MeOH (20 ml) was stirred at room temperature for 1 h. Dilution with saturated aqueous $NaHCO_3$, extraction with diethyl ether and evaporation of the washed (water) ether extracts afforded a crude product which was subjected to preparative TLC (8:2 hexane–AcOEt was used as the eluent). Extraction of the two most intense bands afforded the corresponding HEs *cis* **13** and *trans* **12**.

Acid methanolysis of epoxides 1a–j

General procedure. A solution of the epoxide (0.050 g) in thermostated (25 °C) 0.2 N H_2SO_4 in anhydrous MeOH (5.0 ml) was stirred at 25 °C during the time reported in Table 1, quenched with saturated aqueous $NaHCO_3$ and extracted with diethyl ether. Evaporation of the washed (water) ether extracts yielded mixtures consisting of the corresponding HEs **12** and **13**, which were analyzed by GLC (Table 1). The values in Table 1 are the averages of at least three measurements done on at least two different runs for each point.

Stability of HE 12a–j and 13a–j under the methanolysis reaction conditions

General procedure. A solution of the HE (0.020 g) in thermostated (25 °C) 0.2 N H_2SO_4 in anhydrous MeOH (2.0 ml) was stirred at 25 °C during the time reported in Table 1 for the reaction of the corresponding epoxide. Dilution with saturated aqueous $NaHCO_3$, extraction with diethyl ether and evaporation of the washed ether extracts afforded a crude product, which was analyzed by GLC. HEs **12–13a–j** turned out to be completely stable under the exact reaction conditions used. In the case of *cis* HE **13a** (*p*-OMe), slight epimerization (4%) was observed after 60 s of contact with the 0.2 N H_2SO_4–MeOH solution.

Reactions in the gas phase

Materials. Oxygen and trimethylamine were high-purity gases from Matheson Gas Products Inc., deuterium

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(99.98%) was purchased from Aldrich and all were used without further purification. The purity of starting arylcyclohexene oxides, with special regard to the absence of their substituted derivatives, was checked by analytical gas chromatography on the same columns as employed for the analysis of the products from radiolytic experiments.

Procedure. The samples were prepared by introducing fragile ampoules, containing weighed amounts of selected arylcyclohexene oxide (**1a**–**j**) and MeOH, 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 (D_2, O_2 and NMe_3) 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 broken and the gaseous components allowed to mix before being subjected to irradiation. The gaseous mixtures were submitted to irradiation at a constant temperature (37.5 °C) in a ^{60}Co 220 Gammacell from Nuclear Canada Ltd (dose, 1.5×10^4 Gy; dose rate, 1×10^4 Gy h^{-1}, determined with a Fricke dosimeter). Control experiments, carried out at doses ranging from 1×10^4 to 1×10^5 Gy, showed that the relative yields of products are largely independent of the dose. In order to verify the stability of the opening reaction products, the HEs **12**–**13a**–**j** were placed with the gaseous members (D_2, O_2, MeOH and NMe_3) in Pyrex bulbs and irradiated under the same experimental conditions as adopted for the reactions of the corresponding epoxides **1a**–**j** (37.5 °C; dose, 1.5×10^4 Gy). In all cases, the HEs **12**–**13a**–**j** were recovered unchanged and no trace of isomerization products was detected.

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 anhydrous diethyl ether. Satisfactory agreement between the results of the gaseous mixture and the ether 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 50 m × 0.31 mm i.d. Ultra1 cross-linked methylsilicone fused-silica capillary column, heated from 60 to 200 °C at 5 °C min^{-1}; (ii) a 30 m × 0.32 mm i.d. Supelcowax 10 fused-silica capillary column, operating at 180 °C. The identity of the products was further confirmed by GLC–MS, using a Hewlett-Packard Model 5971A 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 Table 2 are the averages of at least three measurements taken on at least two different runs for each point.

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