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Aromatic Substituent Effect on the Stereoselectivity of the Gas-Phase Acid-Induced Ring Opening in 9,10-Oxides Derived from *trans*-1,2,3,4,4a,10a-Hexahydrophenanthrene

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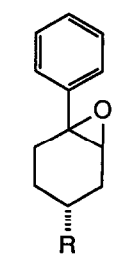
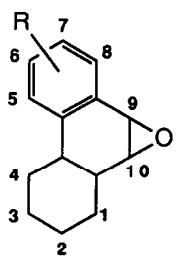
Abstract *: The effect of the aromatic ring substituents on the product distribution of the gas-phase acid-induced ring opening of benzocondensed epoxides 2a and 2b with MeOH was examined and compared with results from methanolysis. The observed syn/anti diastereoselectivity is strictly dependent on the type of the aromatic ring substituent (6-OCH_3 or 7-Br), and a very satisfactory Hammett-type linear correlation was found for both epoxides. A razionalization of the results is given.*

Arene oxides have been demonstrated to be the metabolic intermediates responsible for the carcinogenic and mutagenic activity of polycyclic aromatic hydrocarbons (PAH), due to the oxirane opening process which can lead the hydrocarbon molecule to be covalently linked to cellular biomolecules.[1] The study of the exact mechanism and an examination of all the factors influencing the stereochemistry of the oxirane ring opening process of arene oxides and of their simpler models, the 2-aryl-substituted oxiranes, can thus be of importance in understanding the more complex biological transformations.[2,3]

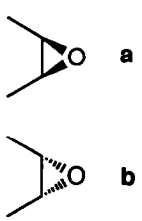
Two different types of 2-aryloxiranes were particularly taken into account as simplified models of arene oxides: the 1-arylcyclohexene oxides **1**[2] and the 9,10-oxides (**2a** and **2b**) derived from *trans*-1,2,3,4,4a,10a-hexahydrophenanthrene.[3] The substantially different stereochemistry observed in the ring opening process



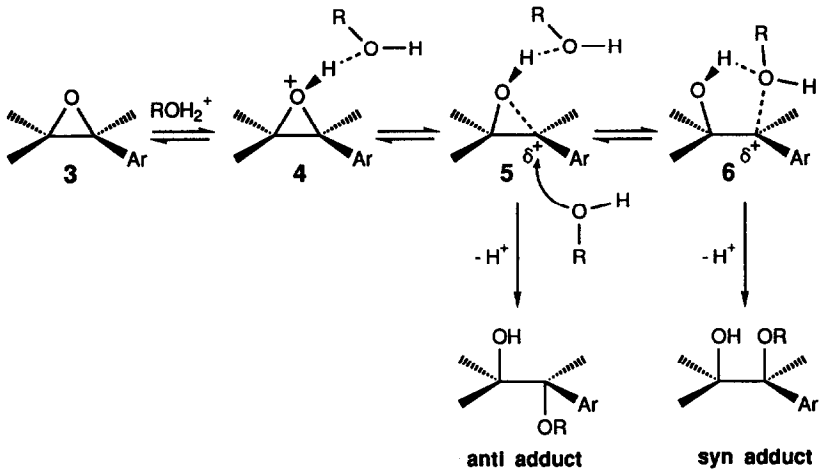
1
R= H, *t*-butyl



2a,b-Br : R= 7-Br
2a,b-H : R= H
2a,b-OCH_3 : R= 6-OCH_3

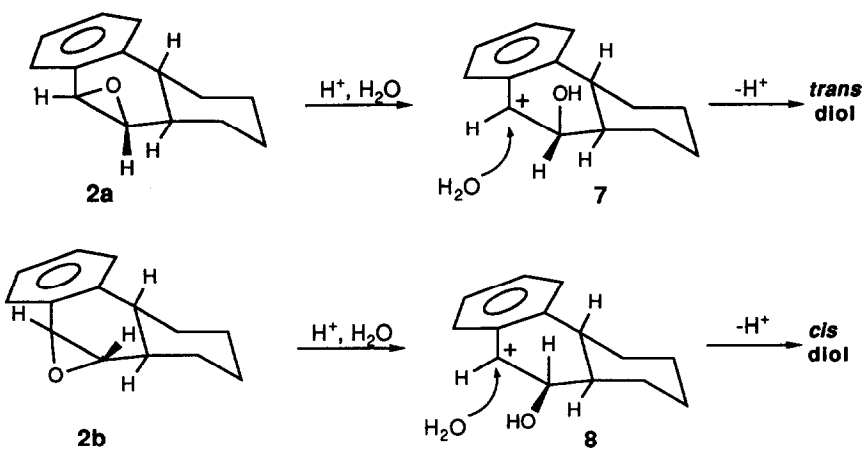


of these models under acidic conditions was explained by means of two different, independent rationalizations, which were then extended to the whole class of 2-aryloxiranes.[2,3] The first rationalization (derived from several studies on system **1**[2]) implied the incursion of different benzylic carbocationic species (ion-dipole pairs [4]) like **5** and **6** with different positive charge values at the benzylic carbon (mechanism ***A***, shown in Scheme 1 for a generic 2-aryloxirane **3**) (see below). The second alternative rationalization (derived



Scheme 1 (mechanism *A*)

from the particular stereochemistry observed in the hydrolysis of system **2**[3]) implied the incursion of fully developed benzylic carbocations such as **7** and **8**, preferentially attacked by the nucleophile in a pseudoaxial fashion (mechanism ***B***, Scheme 2).[3] Subsequent studies performed on both systems **1** and **2**,[2,5,6] under



Scheme 2 (mechanism *B*)

different operating conditions (condensed[2,5] and gas-phase[6]) showed unequivocally that mechanism ***B*** was to be ruled out because it was completely inadequate, even if attractive, to account for all the results obtained from these model systems. At the same time, mechanism ***A*** appeared to be completely operative for system **1**, and the only reasonable one for system **2**, the configuration of the epoxides and the reaction conditions being adequately taken into account.[5,6c]

However, for a complete acceptance of mechanism ***A*** also for system **2**, it was necessary to examine the influence of the aromatic ring substituent on the stereochemical outcome of the oxirane ring opening process of diastereoisomeric epoxides **2a** and **2b** under acidic conditions, as previously done with the epoxides of type **1**.[2,6a,b] Only if a clear dependence of the syn diastereoselectivity of the opening process of epoxides **2a** and **2b** on the electronic properties of the substituent on the aromatic ring were found, together with all the other evidences,[5,6] could mechanism ***A*** be considered fully operative also in such a puzzling 2-aryloxirane system as system **2**. For these reasons, we decided to examine the stereochemistry of the gas-phase acid-induced ring opening of epoxides **2a-Br**, **2a-OCH$_3$**, **2b-Br** and **2b-OCH$_3$** with MeOH as the nucleophile, as previously done for the unsubstituted ones **2a-H** and **2b-H**.[6c] The results are reported in Tables 1 and 2. While in **2a-OCH$_3$** and **2b-OCH$_3$** a strong electrondonating group is present (the OCH$_3$ group in the "*para*" position 6), in **2a-Br** and **2b-Br** a typical electronwithdrawing one is introduced (the Br atom in the "*meta*" position 7), able to respectively stabilize or destabilize partial positive charges developing on the oxirane benzylic carbon in the course of the opening process. Gas-phase operating conditions were necessarily chosen for this study, because in these conditions both epoxides **2a** and **2b** yield mixtures of syn and anti adducts, and, furthermore, because in the dilute gas state the interference from the complicating effects of solvation, ion pairing, etc., is minimized. However, for the sake of completeness, also the methanolysis reactions (condensed phase) of epoxides **2a-Br**, **2a-OCH$_3$**, **2b-Br**, and **2b-OCH$_3$** were examined and compared with the results both from the hydrolysis[5a] (Table 3) and from the gas-phase (present work) (Tables 1 and 2).

RESULTS

Epoxides **2a-Br**, **2a-OCH$_3$**, **2b-Br** and **2b-OCH$_3$** were prepared as previously described.[5a] The reference hydroxy ethers **9-12-Br** and **9-12-OCH$_3$** were prepared following a synthetic scheme as previously utilized for the synthesis of the parent compounds **9-12-H** (Scheme 3).[5e] The acid-methanolysis of epoxides **2b-Br** and **2b-OCH$_3$**, yielded a 23:77 and a 38:62 mixture of *cis* (**9-Br**, and **9-OCH$_3$**) and *trans* hydroxy ethers (**10-Br**, and **10-OCH$_3$**), respectively, which were separated by preparative TLC. Conversely, the same reaction carried out on epoxides **2a-Br** and **2a-OCH$_3$** yielded the *trans* diaxial hydroxy ether **12-Br** and **12-OCH$_3$**, only. The remaining *cis* diastereoisomers **11-Br** and **11-OCH$_3$** were obtained by oxidation of hydroxy ethers **10-Br** and **10-OCH$_3$** to the methoxy ketones **13-Br** and **13-OCH$_3$**, respectively. The $LiAlH_4$ reduction of **13-Br** and **13-OCH$_3$** afforded a 1:9 mixture of **10-Br** and **11-Br** and a 13:87 mixture of **10-OCH$_3$** and **11-OCH$_3$**, respectively, from which pure hydroxy ethers **11-Br** and **11-OCH$_3$** were obtained by preparative TLC (**11-OCH$_3$**), or fractional crystallization (**11-Br**).

Table 1. Distribution of Products from the Gas-Phase Acid-Induced Ring Opening of Epoxides 2a.

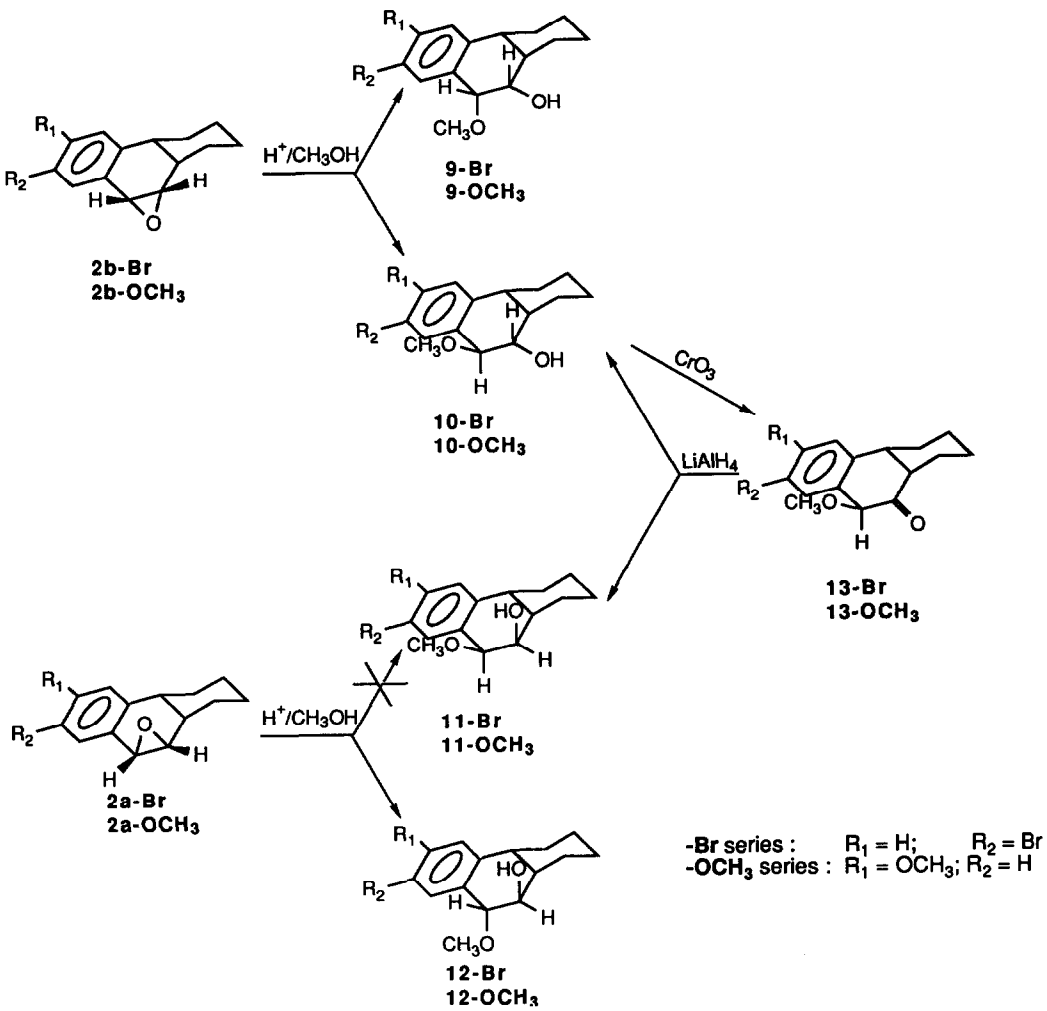
system composition (Torr)[a]				product distribution[b]				
epoxide		bulk gas	CH_3OH	*cis* **11** G	*cis* **11** %	*trans* **12** G	*trans* **12** %	total abs. yield %[c]
2a-Br	(.49)	D_2 (760)	(1.61)	.28	10.7	2.33	89.3	87
2a-H	(.37)	D_2 (760)	(1.18)	1.11	42.4	1.51	57.6	87
2a-OCH_3	(.51)	D_2 (760)	(1.61)	1.24	44.3	1.55	55.7	93
2a-Br	(.51)	D_2 (100)	(1.45)	.34	12.2	2.45	87.8	93
2a-H	(.41)	D_2 (100)	(1.39)	1.30	43.2	1.70	56.8	99
2a-OCH_3	(.47)	D_2 (100)	(1.33)	1.49	50.1	1.48	49.9	99
2a-Br	(.43)	D_2 (760)[d]	(1.41)	.06	13.0	.57	87.0	21
2a-H	(.38)	D_2 (760)[d]	(1.25)	.15	22.4	.52	77.6	22
2a-OCH_3	(.46)	D_2 (760)[d]	(1.29)	.29	37.0	.49	63.0	26

[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 100eV absorbed energy. [c] Total absolute yields (%) estimated from the ratio of the overall G(M) values of products to the $G(D_3^+)$ formation values (see ref.7). [d] 3 Torr of NMe_3 added to the gaseous mixture.

Table 2. Distribution of Products from the Gas-Phase Acid-Induced Ring Opening of Epoxides 2b.

system composition (Torr)[a]				product distribution[b]				
epoxide		bulk gas	CH_3OH	*cis* **9** G	*cis* **9** %	*trans* **10** G	*trans* **10** %	total abs. yield %[c]
2b-Br	(.34)	D_2 (760)	(1.18)	.59	39.9	.88	60.1	49
2b-H	(.43)	D_2 (760)	(1.18)	.97	61.4	.61	38.6	53
2b-OCH_3	(.37)	D_2 (760)	(1.20)	1.21	71.0	.50	29,0	57
2b-Br	(.46)	D_2 (100)	(1.41)	.91	32.5	1.88	67.5	93
2b-H	(.39)	D_2 (100)	(1.18)	1.20	40.7	1.75	59.3	98
2b-OCH_3	(.48)	D_2 (100)	(1.38)	1.44	49.0	1.88	51.0	98
2b-Br	(.35)	D_2 (760)[d]	(1.23)	.12	34.3	.24	65.7	12
2b-H	(.34)	D_2 (760)[d]	(1.16)	.42	80.8	.10	19.2	17
2b-OCH_3	(.55)	D_2 (760)[d]	(1.48)	.53	99.0	.02	1.0	18

[a-d] See the corresponding footnotes in Table 1.



Scheme 3

The structure and configuration of hydroxy ethers **9-12-Br** and **9-12-OCH$_3$** were determined on the basis of their method of synthesis and examination of their ^{1}H NMR and IR spectra in the 3μ range (Table 4), following the same considerations as done in the previous case of the unsubstituted derivatives **9-12-H**.[5e]

Table 3. Stereoselectivity of the Acid Solvolysis Opening Reactions of Epoxides 2a and 2b.

epoxide	methanolysis[a]		hydrolysis[b]	
	syn adduct	anti adduct	syn adduct	anti adduct
2a-Br	0[c]	100[d]	0[o]	100[p]
2a-H	0[e]	100[f]	0[o]	100[p]
2a-OCH_3	0[g]	100[h]	0[o]	100[p]
2b-Br	23[i]	77[j]	31.0[o]	69.0[p]
2b-H	28[k]	72[l]	51.4[o]	48.6[p]
2b-OCH_3	38[m]	62[n]	81.1[o]	18.9[p]

[a] 0.2N H_2SO_4 in anhydrous MeOH. [b] Aqueous 0.2N H_2SO_4-dioxane (1:1). [c] Hydroxy ether **11-Br**. [d] Hydroxy ether **12-Br**. [e] Hydroxy ether **11-H**, ref.5e. [f] Hydroxy ether **12-H**, ref. 5e. [g] Hydroxy ether **11-OCH_3**. [h] Hydroxy ether **12-OCH_3**. [i] Hydroxy ether **9-Br**. [j] Hydroxy ether **10-Br**. [k] Hydroxy ether **9-H**, ref. 5e. [l] Hydroxy ether **10-H**, ref.5e. [m] Hydroxy ether **9-OCH_3**. [n] Hydroxy ether **10-OCH_3**. [o] *cis* diol, ref. 5a. [p] *trans* diol, ref.5a.

Table 4. ^1H NMR and IR Data of Hydroxy Ethers 9-12 (Br and OCH_3).

	^1H NMR			IR (diluted CCl_4 solution)		
	H_9		H_{10}	stretching OH (cm^{-1})		
compound	δ(ppm)	$J_{9,10}$	δ(ppm)	OH_{free}	OH---O	OH---π
9-Br	4.13[a]	3.9	3.63[b]	-	3569	-
9-OCH_3	4.08[a]	3.8	3.50[b]	-	3566	-
10-Br	4.41[a]	8.3	3.73[b]	3615[c]	3594	-
10-OCH_3	4.38[a]	8.1	3.67[b]	3620[c]	3590	-
11-Br	4.13[a]	3.8	4.28[b]	-	3570	-
11-OCH_3	4.05[a]	3.8	4.24[b]	-	3566	-
12-Br	3.94[a]	2.7	3.89[b]	3630	-	3600
12-OCH_3	3.93[a]	2.9	3.83[b]	3630	-	3594

[a] Doublet. [b] Unresolved multiplet. [c] Shoulder.

DISCUSSION

Epoxides **2a** and **2b** behave in a completely different way when subjected to solvolysis opening reactions such as hydrolysis[5a] and methanolysis: epoxides **2a** always give a result of complete anti stereoselectivity, while epoxides **2b** afford mixtures of syn and anti adducts in ratios which depend on the type of substituent present on the aromatic ring (Table 3).[5e] As previously observed for the hydrolysis,[5a] also for the methanolysis of epoxides **2b** a very good Hammett-type linear correlation was found between the diastereoselectivity of the reaction and the σ^+ constants,[8] in accordance with equation 1.[2,5a,9,10] The ρ_{syn} -ρ_{anti} values obtained together with their correlation coefficients (r) and standard deviations (s) are summarized in Table 5, and plotted in Figure 1.

Comparison of the solvolysis data from epoxides **2b** indicates that the syn diastereoselectivity of the methanolysis is considerably lower than the hydrolysis (Table 3); moreover, interestingly, the sensitivity of the methanolysis to the type of the substituent on the aromatic ring is drastically reduced with respect to the hydrolysis reaction, as shown by the considerably different ρ_{syn} -ρ_{anti} values obtained from both reactions (Table 5 and Figure 1). These differences between hydrolysis and methanolysis have already previously observed in the opening reactions of 2-aryloxirane system **1**.[2]

Table 5. ρ_{syn} - ρ_{anti} Values Obtained for the Acid-Catalyzed Solvolysis (Condensed Phase) and Gas-Phase Acid-Induced Ring Opening of Epoxides 2a and 2b with MeOH as the Nucleophile.

$$\log \frac{[S]\,[A^\circ]}{[A]\,[S^\circ]} = (\rho_{syn} - \rho_{anti})\,\sigma^+ \qquad \text{(eq. 1)}$$

Epoxide	Reagents and reaction conditions[a]	ρ_{syn} - ρ_{anti}	Correlation coefficient (r)	Standard deviation (s)
2a	MeOH-GA$^+$	-0.52	0.992	0.015
2b	MeOH-GA$^+$	-1.90	0.998	0.023
2b	MeOH-H_2SO_4	-0.26	0.999	0.001
2b	H_2O-H_2SO_4[b]	-0.82	0.999	0.016

[a] MeOH-GA$^+$: gas-phase operating conditions; MeOH-H_2SO_4 and H_2O-H_2SO_4: condensed phase operating conditions (solvolysis). [b] Ref.5a.

The gaseous acid used in the present study (D_3^+) is formed in known yield from the γ-radiolysis of the corresponding neutral bulk gas (D_2) and thermalyzed by a large number of unreactive collisions with the parent molecules, before reacting with the selected substrate (**2a** or **2b**). Thermal D_3^+ ion may act as Brönsted acid by protonating the n-centre (the oxygen atom) of the epoxide, present in low concentration ($\leq$ 0.5 mol%) in the gaseous mixture. The excess internal energy of the protonated intermediate is dissipated

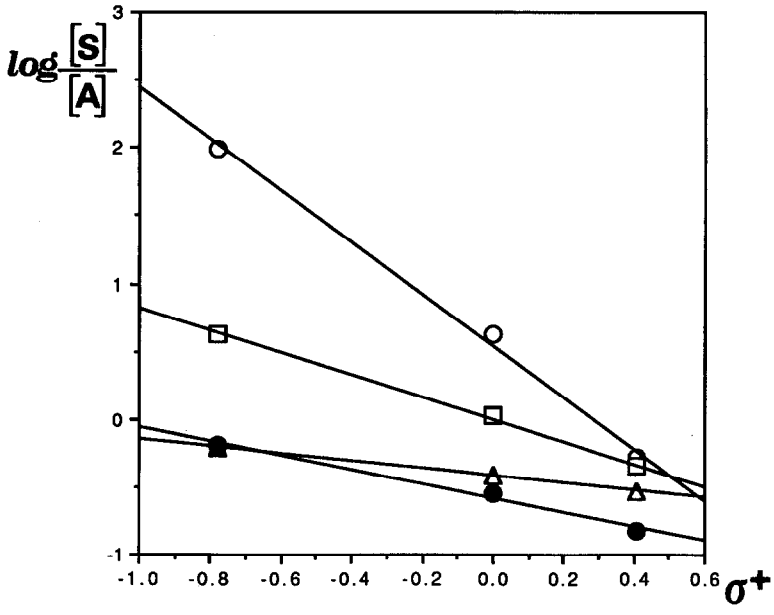


Figure 1. Hammett-Brown $\rho\sigma^+$ plot for the acid-catalyzed ring opening of epoxides **2a** and **2b** with the indicated nucleophile: ● = **2a** (gas phase, MeOH); △= **2b** (condensed phase, MeOH); ○= **2b** (gas phase, MeOH); □= **2b** (condensed phase, H_2O), ref.5a.

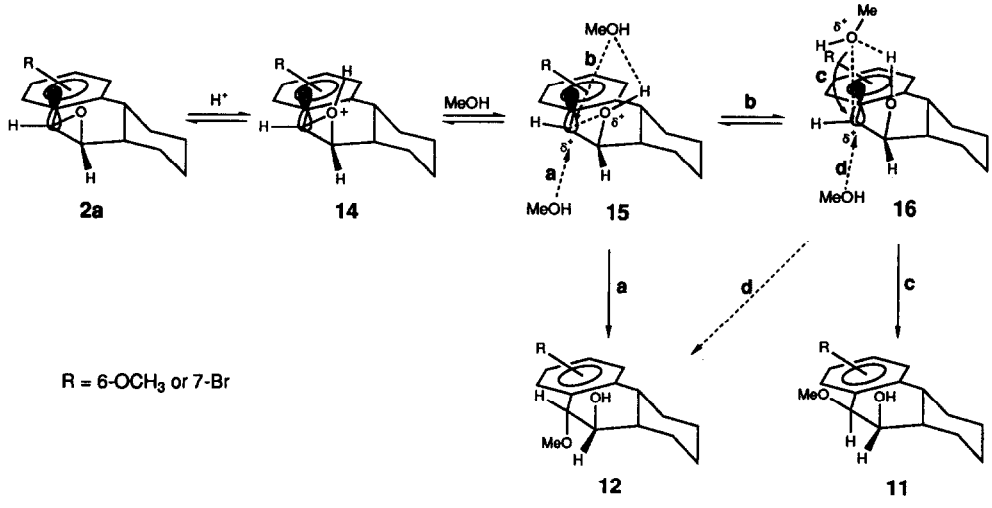
by unreactive impacts with the bath-gas molecules to an extent increasing with the total pressure of the mixture. Furthermore, the charged intermediates are rapidly trapped by suitable nucleophile (MeOH) and converted into neutral end products. The presence of an efficient thermal radical scavenger, such as oxygen, favors the ionic reaction pattern, whose role is testified by the marked effect of a powerfull ion trap, such as NMe_3, on the overall product yields (Tables 1 and 2).

In the gas-phase acid-induced ring opening conditions with MeOH as the nucleophile, both epoxides **2a** and **2b** afford mixtures of syn and anti adducts, whose compositions are typically affected by the different experimental gaseous conditions. In particular, under long-lived excited-ion conditions, i.e. at low pressure and in the absence of a base, almost equal amounts of the syn and anti adducts are formed. Instead, at high pressure and in the presence of NMe_3 (3 Torr), namely at low ion lifetimes,[6c] the opening reactions of epoxides **2b** are more syn stereoselective than the corresponding reactions of epoxides **2a** (Tables 1 and 2). However, complete regioselectivity is observed for all the epoxides **2a** and **2b**, under all the experimental conditions adopted, thus indicating the development of a significant positive charge at the benzylic carbon during the ring opening process. Focusing the attention on low ion lifetime gaseous conditions, the syn/anti diastereoselectivity observed for epoxides **2a** and **2b** turns out to be strictly dependent on the type of substituent present on the aromatic ring, the larger amounts of syn adduct being obtained with the 6-OCH_3 derivatives and the lower ones with the 7-Br derivatives (Tables 1 and 2). Moreover, under these conditions, a very satisfactory Hammett-type linear correlation was found both for **2a** and **2b**, as found for **2b** in the condensed phase (Table 5, and Figure 1). To our knowledge, this is the first example of an Hammett-type

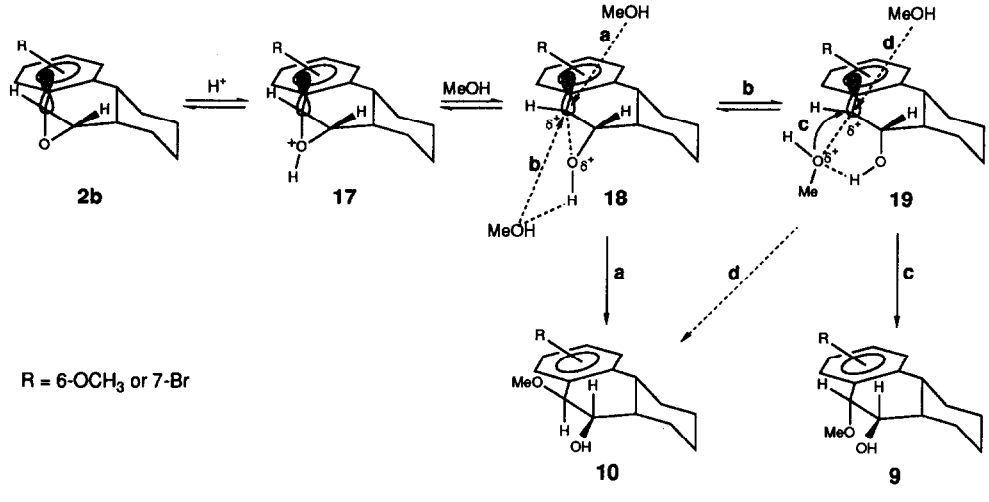
linear correlation found in the gas-phase for the acid-induced oxirane ring opening . The opening reactions of epoxides **2b** in the gas-phase are more syn stereoselective than the corresponding reactions of the same epoxides in the condensed phase (Tables 2 and 3). This indicates that opening processes in the gas-phase possess a higher carbocationic character than when the same reactions are carried out in the condensed phase. As a consequence, the ρ_{syn} -ρ_{anti} value (which is a measure of the dependence of the opening process of a 2-aryloxirane system on the aromatic ring substituent)[2,5a,10] for the gas-phase operating conditions, had to be more negative than the corresponding value from the condensed phase opening conditions, as actually found (Table 5). The Hammett-type linear correlation found for **2a** in the gas-phase opening conditions indicates, for this substrate and for this reaction, a sensitivity to the electronic effects of the aromatic substituent which, although lower than that found for **2b** in the same conditions, is significantly higher than that found for **2b** in the condensed phase (Tables 5 and Figure 1). Unfortunately, the result of complete anti stereoselectivity, constantly found for **2a** in the condensed phase, prevents its utilization in a more effective comparison with the other results from epoxides **2a** (gas-phase) and **2b** (gas- and condensed-phase).

Any reasonable rationalization able to explain the chemical behavior of epoxides **2a** and **2b** has primarily to justify the following points: 1) the effect of the aromatic ring substituent on the stereoselectivity of the opening reaction, 2) the decisive influence of the reaction conditions on the stereoselectivity and 3) the lower syn stereoselectivity of epoxides **2a** with respect to epoxides **2b** under all experimental conditions. Our proposed rationalization, which is an application of mechanism ***A*** (Scheme 1) to epoxides **2a** and **2b**, is shown in Schemes 4 (for epoxide **2a**) and 5 (for epoxide **2b**). Following this rationale, epoxides **2a** and **2b**, after protonation to give the protonated epoxides **14** and **17**, lead to the intimate ion-dipole pairs **15** and **18**, respectively. Intermediates **15** and **18** can follow two distinct routes: they can be directly attacked by the nucleophilic MeOH to give the anti adducts (the *trans* hydroxy ethers **12** from **15**, and **10** from **18**) (*route a*), or they can isomerize to more carbocationic structures like the solvent-separated ion-dipole pairs **16** (from **15**) and **19** (from **18**) (*route b*). Ion-dipole pairs **16** and **19** will then collapse almost entirely to the syn adducts, the *cis* hydroxy ethers **11** and **9**, respectively, under an entropically favored process (*route c*). In this mechanistic setting, any substituent present on the aromatic ring, able to stabilize (like the 6-OCH_3 group) or to destabilize (like the 7-Br group) a partial positive charge on the benzylic carbon, should favor or disfavor the isomerization pathway (*route b*), leading to larger or lower amounts of syn adducts, respectively, as experimentally found (point 1). In the case of epoxides **2b**, the isomerization pathway is constitutionally favored by the very favorable orientation, almost parallelism, of the π orbitals of the aryl group (only one shown in Schemes 4 and 5) and the benzylic oxirane C-O bond which is to be broken in the opening process. In **2a**, the breaking benzylic oxirane C-O bond is by and large far from such a parallelism with the π orbitals of the aromatic system. In this situation, where the aromatic ring cannot exert its stabilizing effect completely on the incipient benzylic carbocationic species, the isomerization pathway (*route b*) is followed to a much lower extent. As a consequence, lower amounts of syn adducts are always to be expected from epoxides **2a**, as experimentally found (point 3).

Into this framework of fundamental structural differences between epoxides **2a** and **2b**, the different operative conditions (condensed or gas-phase conditions) have to be inserted. Large amounts of nucleophilic molecules (MeOH), as found in the condensed phase reaction conditions, make the attack of the nucleophile on species **15** from epoxide **2a** and **18** from epoxide **2b**, giving the anti adducts (*route a*), highly



Scheme 4



Scheme 5

competitive compared with the isomerization step which would lead to the syn adducts (*routes b-c*). Actually, in these conditions, epoxides **2b** give prevailing amounts of anti adducts, indicating a considerably slower isomerization pathway, while, due to their intrinsic difficulty to follow the isomerization process (see above), epoxides **2a** give a result of complete anti stereoselectivity, whatever substituent is present on the aromatic ring. In the gas-phase operating conditions, only a limited amount of nucleophilic molecules is present; in these conditions intermediates **15** and **18** can evolve to the more carbocationic structures **16** and **19** (*route b*), respectively, to an extent which depends on the structure of the epoxide and on the nature of the aromatic substituent, to give corresponding stereochemical results (Tables 1 and 2) (point 2).

In conclusion, the 2-aryloxirane system of epoxides **2a** and **2b** shows a chemical behavior which is closely linked to that of epoxides **1**,[2] with only some puzzling "apparent" differences which must be attributable to their particular constrained structure, and which do not justify any independent rationalization.[3]

EXPERIMENTAL

For general experimental procedures see ref. 5e. Epoxides **2a,b-H**,[3] **2a,b-Br**[5a] and **2a,b-OCH$_3$**[5a] and unsubstituted hydroxy ethers **9-12-H**[5e] were prepared as previously described. All preparative and semipreparative TLC separations were performed with a 1:1 mixture of petroleum ether and ether as the eluant.

Acid-Catalyzed Methanolysis of Epoxides 2a-Br and 2a-OCH$_3$. A solution of epoxide **2a-Br** (0.10 g) in 0.2 N H_2SO_4 in anhydrous MeOH (10 ml) was stirred at r.t. for 5 min. Dilution with saturated aqueous $NaHCO_3$ solution, extraction with ether and evaporation of the washed (water) ether extracts afforded a solid residue (0.095 g) consisting of hydroxy ether **12-Br** (^{1}H NMR and GC) which was recrystallized from hexane to give pure *(4aβ,9a,10β)-7-bromo*-t-*9-methoxy*-trans-*1,2,3,4,4a,10a-hexahydrophenanthren*-r-*10-ol* (**12-Br**) (0.050 g), as a solid, m.p. 138-139°C; IR, see Table 4; ^{1}H NMR δ 7.12-7.36 (m,3H), 3.46 (s,3H), and see Table 4. Anal.Calcd for $C_{15}H_{19}BrO_2$: C, 57.89; H, 6.15. Found: C, 57.61; H, 6.24.

The same reaction carried out on epoxide **2a-OCH$_3$** (0.070 g) in 0.2 N H_2SO_4 in anhydrous MeOH (7 ml) for 1 min at r.t. afforded a crude solid residue (0.065 g) consisting of hydroxy ether **12-OCH$_3$** which was recrystallized from hexane to give pure *(4aβ,9a,10β)-6*,t-*9-dimethoxy*-trans-*1,2,3,4,4a,10a-hexahydrophenanthren*-r-*10-ol* (**12-OCH$_3$**) (0.040 g), as a solid, m.p. 124-125.5 °C; IR, see Table 4; ^{1}H NMR δ 7.13 (m,1H), 6.80 (m,1H), 6.68 (m,1H), 3.70 (s,3H), 3.38 (s,3H), and see Table 4. Anal.Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.41; H, 8.74.

Acid-Catalyzed Methanolysis of Epoxides 2b-Br and 2b-OCH$_3$. As described above for the corresponding reaction of **2a-Br**, treatment of epoxide **2b-Br** (0.30 g) with 0.2 N H_2SO_4 in anhydrous MeOH (30 ml) afforded a crude solid reaction mixture (0.30 g) consisting of a 23:77 mixture of hydroxy ethers **9-Br** and **10-Br** (GC) which was subjected to preparative TLC. Extraction of the faster moving

band yielded pure *(4aβ,9α,10α)-7-bromo*-c-*9-methoxy*-trans-*1,2,3,4,4a,10a-hexahydrophenanthren*-r-*10-ol* (**9-Br**) (0.040 g), as a solid, m.p. 89-90°C (after recrystallization from hexane); IR, see Table 4; ^{1}H NMR δ 7.40-7.45 (m,2H), 7.20-7.26 (m,1H), 3.54 (s,3H), and see Table 4. Anal.Calcd for $C_{15}H_{19}BrO_2$: C, 57.89; H, 6.15. Found: C, 57.55; H, 6.01.

Extraction of the slower moving band afforded pure *(4aβ,9β,10α)-7-bromo*-t-*9-methoxy*-trans-*1,2,3,4,4a,10a-hexahydrophenanthren*-r-*10-ol* (**10-Br**) (0.12 g) as a solid, m.p. 143-144 °C (after recrystallization from hexane); IR, see Table 4; ^{1}H NMR δ 7.56 (m,1H), 7.32 (m,1H), 7.13 (m,1H), 3.48 (s,3H) and see Table 4. Anal.Calcd for $C_{15}H_{19}BrO_2$: C, 57.89; H, 6.15. Found: C, 57.79; H, 6.35. Alternatively, hydroxy ether **10-Br** can be separated pure by fractional crystallization (hexane) of the crude solid methanolysis reaction mixture of epoxide **2b-Br**.

The same reaction carried out on epoxide **2b-OCH$_3$** (0.34 g) in 0.2 N H_2SO_4 in anhydrous MeOH (34 ml) for 1 min at r.t. afforded a crude solid residue (0.34 g) consisting of a 38:62 mixture of hydroxy ethers **9-OCH$_3$** and **10-OCH$_3$**, which was subjected to preparative TLC. Extraction of the faster moving band afforded pure *(4aβ,9α,10α)-6,*c-*9-dimethoxy*-trans-*1,2,3,4,4a,10a-hexahydrophenanthren*-r-*10-ol* (**9-OCH$_3$**) (0.060 g), as a solid, m.p. 93-94°C (after recrystallization from hexane); IR, see Table 4; ^{1}H NMR δ 7.15 (m,1H), 6.83 (m,1H), 6.69 (m,1H), 3.73 (s,3H), 3.40 (s,3H), and see Table 4. Anal.Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.32; H, 8.54.

Extraction of the slower moving band afforded pure *(4aβ,9β,10α)-6*-t-*9-dimethoxy*-trans-*1,2,3,4,4a,10a-hexahydrophenanthren*-r-*10-ol* (**10-OCH$_3$**) (0.10 g), as a solid, m.p. 131-132°C (after recrystallization from hexane); IR, see Table 4; ^{1}H NMR δ 7.28 (m,1H), 6.72 (m,2H), 3.73 (s, 3H), 3.33 (s,3H), and see Table 4. Anal.Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.18; H, 8.21.

Synthesis of Hydroxy Ethers 11-Br and 11-OCH$_3$. A solution of *trans* hydroxy ether **10-Br** (0.338 g, 1.08 mmol) in acetone distilled over $KMnO_4$ (10 ml) was treated with 8N CrO_3 in a 1:1 H_2SO_4/H_2O solution (0.27 ml). After 5 min at r.t., dilution with water, extraction with ether, and evaporation of the washed (saturated aqueous $NaHCO_3$ solution and water) ether extracts afforded an oily residue (0.27 g) essentially consisting of pure quite unstable *(4aβ,9β)-9-methoxy*-trans-*1,2,3,4,4a,10a-hexahydro-10(9H)-phenanthrenone* (**13-Br**); IR 1720 cm^{-1} (C=O); ^{1}H NMR δ 7.08-7.50 (m,3H), 4.58 (s,1H), and 3.37 (s,3H). Anal.Calcd for $C_{15}H_{17}BrO_2$: C, 58.27; H, 5.54. Found: C, 58.51; H, 5.44.

Analogous treatment of *trans* hydroxy ether **10-OCH$_3$** (0.11 g, 0.42 mmol) with 8N CrO_3 (0.12 ml) afforded an oily residue (0.080 g) consisting of pure quite unstable *(4aβ,9β)-6,9-dimethoxy*-trans-*1,2,3,4,4a,10a-hexahydro-10(9H)-phenanthrenone* (**13-OCH$_3$**); IR 1720 cm^{-1} (C=O); ^{1}H NMR δ 6.76-7.30 (m,3H), 4.49 (s,1H), 3.72 (s,3H), 3.27 (s,3H). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74.Found: C, 73.95; H, 7.59. Ketones **13-Br** and **13-OCH$_3$** were used in the next step without any further purification.

A solution of ketone **13-Br** (0.27 g) in anhydrous ether (50 ml) was treated with $LiAlH_4$ (0.20 g). After 2 h stirring at r.t., usual workup yielded a solid residue (0.23 g) consisting of a 10:90 mixture of hydroxy ethers **10-Br** and **11-Br** (GC and ^{1}H NMR). Fractional crystallization from hexane afforded pure

(4aβ,9β,10β)-c-9-methoxy-trans-*1,2,3,4,4a,10a-hexahydrophenanthren*-r-*10-ol* (**11-Br**) (0.080 g), as a solid, m.p. 107-108°C; IR, see Table 4; ^{1}H NMR δ 7.66 (m,1H), 7.34 (m,1H), 7.16 (m,1H), 3.62 (s,3H), and see Table 4. Anal.Calcd for $C_{15}H_{19}BrO_2$: C, 57.89; H, 6.15. Found: C, 57.95; H, 6.47.

Analogous treatment of ketone **13-OCH$_3$** (0.080 g) with $LiAlH_4$ (0.10 g) in anhydrous ether (10 ml) afforded a crude solid residue (0.060 g) consisting of a 13:87 mixture of hydroxy ethers **10-OCH$_3$** and **11-OCH$_3$** (GC and ^{1}H NMR) which was subjected to semipreparative TLC. Extraction of the most intense bands (the faster moving band contained **11-OCH$_3$**) afforded pure **10-OCH$_3$** and *(4aβ,9β,10β)-6,c-9-dimethoxy*-trans-*1,2,3,4,4a,10a-hexahydrophenanthren*-r-*10-ol* (**11-OCH$_3$**) as a solid, m.p.108-109 °C (after recrystallization from hexane); IR, see Table 4; ^{1}H NMR δ 7.37 (m,1H), 6.76 (m,1H), 6.71 (m,1H), 3.72 (s,3H), 3.54 (s,3H). Anal.Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.29; H, 8.78.

Methanolysis of Epoxides 2a and 2b Under Standard Conditions. A thermostatted (25°C) 0.2 N H_2SO_4-anhydrous MeOH solution (5 ml) was added to the epoxides (0.050 g) kept at the same temperature. After 5 min, in the case of **2a,b-Br**, or 1 min, in the case of **2a,b-OCH$_3$**, stirring at 25°C, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution and extracted with ether. Evaporation of the washed (water) ether extracts afforded crude residues which were analyzed by GC to give the results as reported in Table 3. Experiments were carried out in order to check that the reaction products are stable under the opening reaction conditions used. The values given in Table 3 are the average of at least three measurements taken on at least two different runs for each point.

Radiolytic Experiments. The gaseous samples were prepared by conventional techniques, using a greaseless vacuum line and enclosed into carefully outgassed 500 ml Pyrex bulbs, each equipped with a break-seal tip. The bulbs were filled with the required amount of bulk gas (D_2), and sealed-off. The irradiations were carried out at 37.5°C in a 220 gammacell (Nuclear Canada Ltd), to a dose of 1.5×10^4 Gy at a rate of 10^4 Gy h^{-1}, as determined by a neopentane dosimeter. The analysis of the irradiated mixtures was performed with a Hewlett-Packard 5890/II gas chromatograph equipped with a flame ionization detector> The following columns were employed: (i) a 30 m x 0.32 mm (i.d.) Supelcowax capillary column, operated at 180 C; (ii) a 25 m x 0.2 mm (i.d.) Carbovax 20 M ULTRA performance capillary column operated at 160°C. The products were identified by comparison of their retention volumes with those of authentic samples and were confirmed by GC/MS, using a Hewlett-Packard 5982 A quadrupole mass-spectrometer. The yields of the products were deduced from the areas of the corresponding elution peaks, using the internal standard calibration method. The results obtained are reported in the Tables 1 and 2. The values given in Tables 1 and 2 are the average of at least three measurements taken on at least two diffrent runs for each point.

References and Notes

1. *Polycyclic Hydrocarbons and Carcinogenesis*, Harvey, R.G., Ed., ACS Symposium Series n. 283, 1985, and references therein.
2. Crotti,P.; Dell'Omodarme,G.; Ferretti,M.; Macchia,F. *J.Am.Chem.Soc.* **1987**, *109*, 1463-1469 and references therein.

3. Sayer,J.M.; Yagi,H.; Silverton,J.V.; Friedman,S.L.; Whalen,D.L.; Jerina,D.M. *J.Am.Chem.Soc.* **1982**, *104*, 1972-1978 and references therein.
4. Sneen.R.A.; Felt,G.R.; Dickason,W.C. *J.Am.Chem.Soc.* **1973**, *95*, 638-639.
5. a) Chini,M.; Crotti,P.; Ferretti,M.; Macchia,F. *Tetrahedron* **1988**, *44*, 2001-2014; b) Chini,M.; Crotti,P.; Macchia,F. *Gazz.Chim.Ital.* **1988**, *118*, 827-836; c) *J.Org.Chem.* **1989**, *54*, 3930-3936; d) Chini, M.; Crotti,P. *Gazz.Chim.Ital.* **1990**, *120*, 733-739; e) *ibid* . **1991**, *121*, 197-204.
6. a) Crotti,P.; Macchia,F.; Pizzabiocca,A.; Renzi,G.; Speranza,M. *Tetrahedron Lett.* **1987**, *28*, 3393-3396; b) Cecchi,P.; Pizzabiocca,A.; Renzi,G.; Chini,M.; Crotti,P.; Macchia,F.; Speranza,M.*Tetrahedron* **1989**, *45*, 4227-4234; c) Cecchi,P.; Pizzabiocca, A.; Renzi,G.; Chini,M.; Crotti,P; Speranza,M. *Tetrahedron* **1991**, *47*, 4683-4692.
7. a) Weiss,J.; Bernestein, W. *Radiat.Res.* **1957**, *6*, 603-610; b) Ausloos,P.; Lias,S.G.; Gorden Jr.,R. *J.Chem.Phys.* **1963**, *39*, 3341-3348.
8. Brown,H.C.; Okamoto,Y. *J.Am.Chem.Soc.* **1958**, *80*, 4979-4987.
9. Equation 1 can be obtained[2,10] by term by term subtraction of the Hammett equation relative to the formation of the anti adduct (A) from the one relative to the syn adduct (S), under the very likely assumption that the two parallel reactions follow the same kinetic equation and therefore the rate ratios k_{syn}/k_{anti} can be equated to the concentration ratios [S]/[A]. This type of correlation affords the difference $\rho_{syn} - \rho_{anti}$.
10. Battistini,C.; Balsamo,A.; Berti,G.; Crotti,P.; Macchia,B.; Macchia,F. *J.Chem.Soc.Chem.Commun.* **1974**, 712-713.

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