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Gas-Phase Acid-Induced Ring Opening in Diastereoisomeric 9,10-Oxides derived from *trans*-1,2,3,4,4a,10a-Hexahydrophenanthrene

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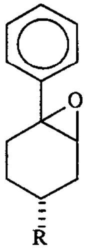
Abstract : *The stereochemical outcome of the two diastereoisomeric rigid benzocondensed epoxides* ***2a*** *and* ***2b*** *in the acid-induced nucleophilic attack by MeOH in the gas-phase was studied and compared with the corresponding results obtained with the mobile epoxides of type* ***1****. The stereochemistry of the ring opening process in these systems (****1****,* ***2a, b****) appears to be dependent on the extent of the positive charge developed at the benzylic carbon. A rationalization which implies different benzylic carbocationic species is proposed, while the hypothesis of the intermediacy of fully developed benzylic carbenium ions does not appear to be supported by the present results.*

Introduction

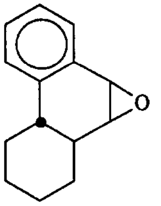
Polycyclic aromatic hydrocarbons (PAHs) are widely present in the environment as products of the incomplete combustion of organic matter. The carcinogenic and mutagenic activity displayed by some of them has been linked to their metabolic transformation into reactive benzylic epoxides (a type of arene oxides) which can alkylate cellular biomolecules such as DNA.[1] Different types of 2-aryloxiranes were selected, as a simplified model, to understand the chemical behaviour of metabolically occurring arene oxides in biological processes.[2-5]

Among them, the solvolytic ring opening reactions of 1-arylcyclohexene oxides **1** (R = H or *t*-Bu),[2] and on the diastereoisomeric 9,10-oxides derived from *trans*-1,2,3,4,4a,10a-hexahydrophenanthrene **2a** and **2b**[3a,b,4] exhibit significant and not easily reconcilable differences and two different rationalizations were independently proposed[2,4] in order to explain the stereochemical outcome from each system (**1** and **2**), no unifying mechanism being found.[2,3]



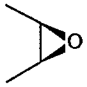
1

R = H, *t*-butyl

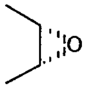


2

a

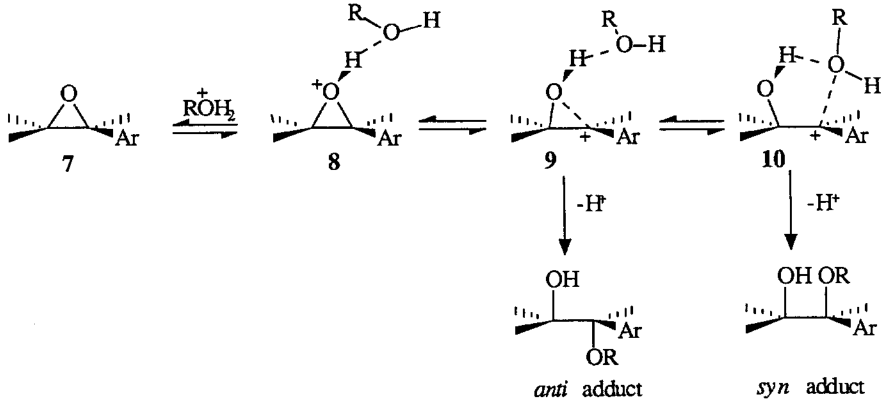


b



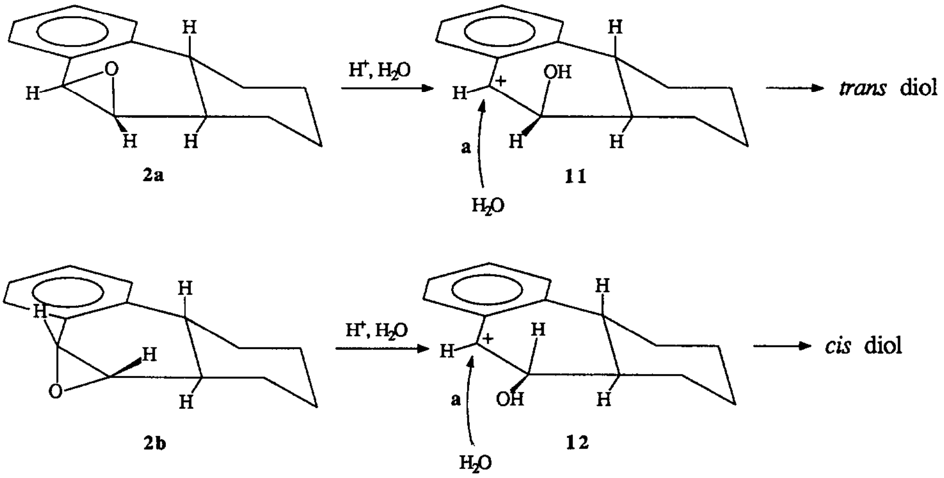
In fact, the similar diastereoselectivity of the acid-induced ring opening of epoxides of type **1** (R = H) observed in both the gaseous[5] and condensed phase[2] pointed to a mechanism which involves two different carbocationic species, the less carbocationic-like **9** and the more carbocationic-like **10** (Scheme 1, where a simplified general formula **7** is used, valid for any 2-aryl-substituted oxirane) and in which the stereochemical result is determined essentially by intrinsic electronic factors, *i.e.* by the extent of positive charge developed at the C_α benzylic carbon during the opening process. According to this rationale, the attack of the nucleophile on

SCHEME 1



the intimate ion/dipole pair **9** affords the *anti* adduct, while an internal rearrangement of **9** leads to the nucleophile/separated ion/dipole pair **10** which collapses to yield the *syn* adduct. On the contrary, the totally different stereoselectivity of the hydrolysis of epoxides **2a** (100% *trans* diol) and **2b** (mixture of *cis* and *trans* diol, see Table IV) was tentatively rationalized in terms of completely developed benzylic carbenium ions **11** (from **2a**) and **12** (from **2b**, Scheme 2), which are preferentially attacked by the nucleophile in a pseudoaxial fashion.[4]

SCHEME 2



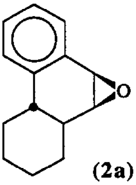
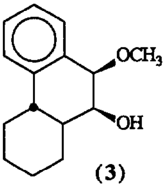
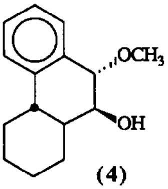
a = pseudoaxial attack

In an attempt to unify the two sets of data in a single reactivity model, we need first to verify whether environmental factors, such as solvation and ion pairing, may actually influence the stereochemical course of the acid-induced ring opening of **2a** and **2b** and, therefore, be responsible for their different behaviour with respect to epoxides of type **1**. To this purpose, we decided to undertake the study of the stereochemistry of the acid-induced nucleophilic attack on **2a** and **2b** by MeOH in the gas phase,[6] *i.e.* under conditions where the complicating effects of solvation and ion pairing are minimized. It is hoped thereby to provide a unifying reactivity model for arene oxides toward nucleophiles suitable for rationalizing the behaviour of PAHs metabolytes in biological processes.

Results

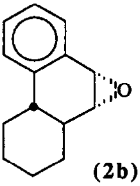
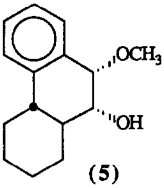
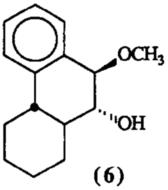
The composition of the irradiated system and the yield of the neutral end products obtained following protonation of the substrates with the gaseous Brönsted acids, generated according to well-established radiolytic techniques,[7] are given in Table I-III, which summarize the results of three sets of irradiations. Tables I and II report the relative and absolute yields of products from γ-radiolysis of gaseous mixtures containing either **2a** or **2b** as the substrate, and D_2 or CH_4 as the bulk gas, and CH_3OH and NMe_3 as additives. Table III gives data concerning competition experiments, using both **2a** and **2b** as the competing substrates.

Table I

SYSTEM COMPOSITION (Torr) [a]			PRODUCT DISTRIBUTION [b]				
SUBSTRATE	BULK GAS	CH_3OH	*SYN* ADDUCT		*ANTI* ADDUCT		TOTAL ABS. YIELD[c]
 (2a)			 (3)		 (4)		%
			G	% rel	G	% rel	
(.38)	D_2 (760)[d]	(1.25)	.15	22.4	.52	77.6	22
(.37)	D_2 (760)	(1.18)	1.11	42.4	1.51	57.6	87
(.41)	D_2 (100)	(1.39)	1.30	43.2	1.70	56.8	100
(.32)	CH_4 (760)[d]	(1.11)	.03	17.6	.14	82.4	6
(.34)	CH_4 (760)	(1.07)	.23	24.0	.73	76.0	34
(.26)	CH_4 (100)	(.93)	1.06	38.0	1.73	62.0	100

a) O_2: 4 Torr, Radiation dose 1.5×10^4 Gy (dose rate: 1×10^4 Gy h^{-1}). b) G values expressed as the number of molecules produced per 100 eV absorbed energy. c) Total absolute yields estimated from the ratio of the overall G (M) values of products to the G (D_3^+) and G ($C_nH_5^+$) formation values.[8] d) 3 Torr of NMe_3 added to the gaseous mixture.

Table II

SYSTEM COMPOSITION (Torr) [a]			PRODUCT DISTRIBUTION [b]				
SUBSTRATE	BULK GAS	CH_3OH	*SYN* ADDUCT		*ANTI* ADDUCT		TOTAL ABS. YIELD[c]
 (2b)			 (5)		 (6)		%
			G	% rel	G	% rel	
(.34)	D_2 (760)[d]	(1.16)	.42	80.8	.10	19.2	17
(.43)	D_2 (760)	(1.18)	.97	61.4	.61	38.6	53
(.39)	D_2 (100)	(1.18)	1.20	40.7	1.75	59.3	98
(.32)	CH_4 (760)[d]	(.95)	.08	72.7	.03	27.3	4
(.34)	CH_4 (760)	(1.13)	.54	58.7	.38	41.3	33
(.30)	CH_4 (100)	(.95)	1.47	52.5	1.33	47.5	100

a) - d) see Table I

Table III

SYSTEM COMPOSITION (Torr) [a]				PRODUCT DISTRIBUTION [b]								
2a	2b	BULK GAS	CH_3OH	3		4		5		6		TOTAL ABS. YIELD[c]
				G	% rel	G	% rel	G	% rel	G	% rel	%
(.32)	(.34)	CH_4(760)[e]	(.98)	.04	8.9	.11	25.5	.25	55.5	.05	11.1	16

a-d) see Table I
e) 5 Torr of NMe_3 added to the gaseous mixture.

Table IV

STEREOSELECTIVITY OF THE ACID SOLVOLYSIS OPENING REACTIONS OF EPOXIDES **2a** AND **2b**.

EPOXIDE	Reaction conditions[f]	*SYN* ADDUCT	*ANTI* ADDUCT
2a	A	0	100
2a	B	0	100
2a	C	0[g]	100[h]
2b	A	51.4	48.6
2b	B	76	24
2b	C	28[i]	72[l]

f) A: aqueous 0.2N H_2SO_4-Dioxane (1:1)[3a]; B: 10^{-3}M $HClO_4$ in Dioxane: H_2O (1:9), containing 0.1M $NaClO_4$[4]; C: 0.2N H_2SO_4 in anhydrous MeOH[3d]. g) *cis*-Hydroxyether **3**. h) *trans*-hydroxyether **4**. i) *cis*-hydroxyether **5**. l) *trans*-hydroxyether **6**.

Analysis of Table II shows that, irrespective of the bulk gas used, the relative yield of the *syn* adduct increases at high pressure and in the presence of trimethylamine. The *syn/anti* selectivity ratio is slightly greater in deuterium than in methane, under comparable experimental conditions.

The opposite trend is observed in the case of the epoxide **2a** (Table I) for which formation of the corresponding *syn* hydroxyether reaches a minimum at 760 Torr in the presence of trimethylamine. Here, the *syn/anti* selectivity ratios tend to increase to ~40/60 (methane) and ~45/55 (deuterium) at low pressure conditions.

Table III shows that **2b** is almost twice as reactive as **2a** in 760 Ttorr CH_4 and in the presence of 5 Torr of NMe_3.

For each set of experiments, the G-values always increase as the pressure is lowered and substantially fall in the presence of 3 Torr of NMe_3.

Discussion

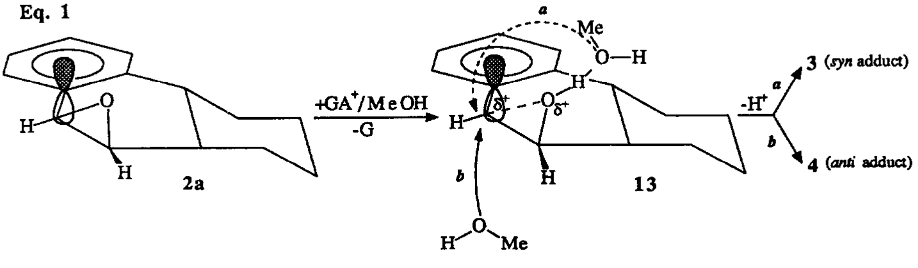
γ-radiolysis of gaseous deuterium and methane produces known yields of powerful gaseous acids D_3^+ and $C_nH_5^+$ (n = 1, 2) respectively. In view of the proton affinities[9] of their conjugated bases, D_3^+ is a stronger Brönsted acid relative to $C_nH_5^+$ and therefore it is expected to convey a greater excitation energy on their protonated derivatives of **2a** and **2b** relative to those from $C_nH_5^+$. These are free from their anionic counterparts which are represented by far removed electrons. The absence of solvent and counterion around the protonated intermediates which are primarily generated by interaction with such ions in dilute gas phase can effectively make the reaction pathways virtually unaffected by the complicating effects typical of condensed phase reactions namely solvation, ion-pairing, catalysts etc. Furthermore, the excess internal energy of the protonated intermediates is dissipated by unreactive collisions with the bath-gas molecules to an extent increasing with the total pressure of the mixture. The protonated intermediates may undergo substitution or neutralization by the nucleophiles present in the mixture, e.g. CH_3OH or NMe_3, to yield eventually the neutral end products. The sharp decrease of the reaction products by addition of 3 Torr of a base such NMe_3, demonstrates their ionic origin, independently ensured by the presence of O_2, an effective radical scavenger.

Inspection of Tables I and II reveals a significantly different isomeric distribution of products in both deuterium and methane as a function of the experimental conditions. In particular, under long-lived excited-ion conditions, *i.e.* at low pressure and in the absence of base, almost equal amounts of the *syn* and *anti* products are formed. Instead, at high pressure and in the presence of NMe_3 (3 Torr), namely at low ion lifetimes, epoxide **2a** yields predominantly the *anti* adduct (> 77.6%), whereas **2b** gives rise essentially to the *syn* isomer (> 72.7%). In the meantime, complete regiospecificity is observed for both substrates under all experimental conditions adopted, pointing to the development of significant positive charge at the C_α benzylic carbon of both *O*-protonated **2a** and **2b** isomers. At low bath-gas pressure and in the absence of added base, the *O*-protonated intermediates from either **2a** or **2b**, excited by their formation process, are able to unimolecularly fragment the C_α-O bond yielding the fully developed carbocations **11** and **12** of Scheme 2, which, in the gas phase, may undergo equally efficient attack by MeOH on both sides of the quasi-planar C_α^+ centre, as demonstrated by the formation of both the *syn* and the *anti* adduct from both substrates **2a** and **2b** under these conditions (Tables I and II). At high pressures and in the presence of NMe_3, unimolecular C_α-O bond fragmentation is efficiently prevented by collisional stabilization of the excited *O*-protonated derivatives of **2a** and **2b**, the first undergoing preferentially a backside displacement by MeOH (Table I) while the latter a predominantly frontside MeOH attack (Table II).

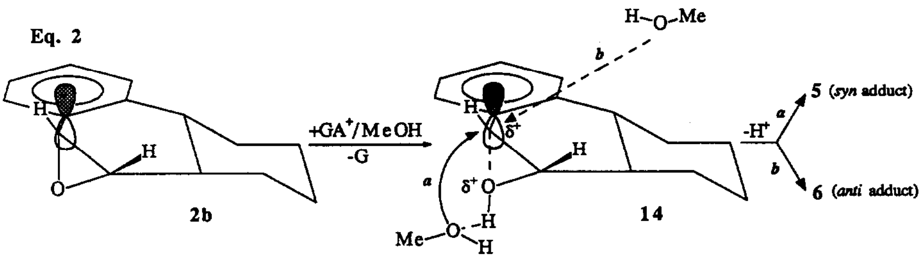
The opening reactions of **2a** and **2b** in the gas-phase, with MeOH as the nucleophile (Tables I and II), are significantly more *syn*-stereoselective than the corresponding reactions carried out in the condensed-phase (reaction conditions C, Table IV). This observation, besides being of remarkable importance in the case of **2a**, because of the complete *anti*-stereoselectivity constantly found for this epoxide, and also for some its derivatives,[3a] in the condensed-phase solvolysis reactions,[3a] offers some useful insight into the mechanistic problem involved with this kind of 2-aryloxiranes.[2,4] In fact, if a preferential pseudoaxial attack of the nucleophile (MeOH, in this case) on completely developed benzylic carbenium ions was operating as shown in Scheme 2, it would be difficult to explain why this pathway becomes more important for **2b** (increased amount of the *syn* adduct, the *cis* hydroxyether **5**) and contemporary less important for **2a** (decreased amount of the *anti* adduct, the *trans* hydroxyether **4**) on passing from condensed- to gas-phase operating conditions (Tables I,II and IV). On the contrary, a mechanism of the type shown in Scheme 1,[2,5] appears to be more suitable in order to rationalize the different *syn* stereoselectivity found for **2a** and **2b** under different operating conditions (gas- and condensed-phase). Following this rationale (Scheme 1), the largely lower amount of nucleophilic molecules, as present in the gas-phase compared to the ones present in the condensed-phase reaction conditions, while reducing the amount of a backside attack on the species **9** which would give the *anti* adduct, favours the isomerization channel of the species **9** to the species **10** which leads to the *syn* adduct. As a consequence an increased *syn* stereoselectivity under gas-phase with respect to condensed-phase acid induced ring opening, has to be expected for both **2a** and **2b** as experimentally found.

In the framework of the reactivity model for 2-aryl-oxiranes as shown in Scheme 1, the substantially different stereochemical results from **2a** and **2b**, both in the gas- and in the condensed-phase (the opening reactions of **2b** are always more *syn* stereoselective than the corresponding ones of **2a**, Tables I,II and IV) is attributable to a more intense location of the positive charge at the benzylic C_α carbon of *O*-protonated **2b** with respect to **2a** (structure **14** and **13**, respectively, Scheme 3). Within the assumption of a similar geometry for either **2a** and **2b** and their *O*-protonated counterparts (**13** and **14**, respectively), this difference can be attributed to the fact that, while the pseudoaxial C_α-O bond of epoxide **2b** is nearly parallel to the *p*-orbitals of the benzene ring π-system, the corresponding C_α-O bond in **2a** is largely far from such parallelism. As a consequence, in *O*-protonated **2b**, extensive C_α-O bond rupture is allowed by the favourable locked conformation of the aromatic moiety which can maximize its stabilizing conjugative effect toward the developing positive charge. The same stabilizing factors cannot be fully operative in *O*-protonated **2a**, owing to an unfavourable mutual position for conjugation between the aromatic π-system and the developing empty C_α p-orbital (Scheme 3).

SCHEME 3

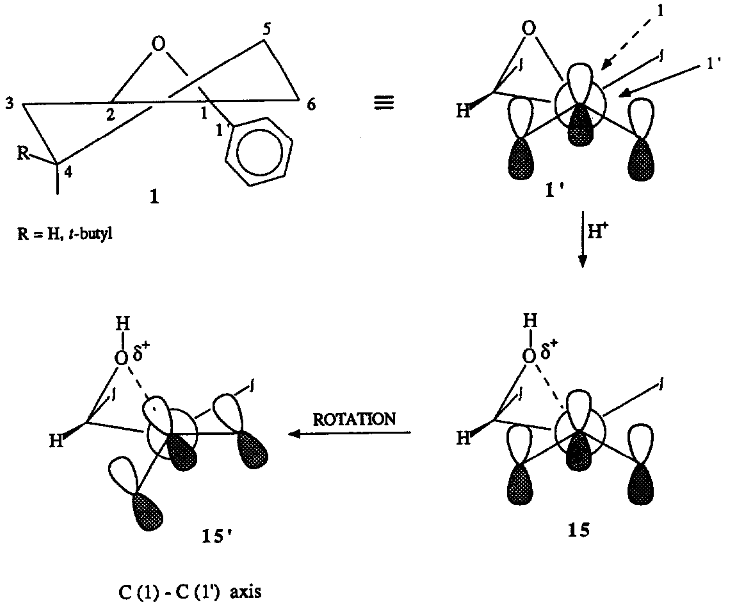


Eq. 2



If one considers that the same favourable conformation of *O*-protonated **2b** (structure **14**, Scheme 3) can be readily attained by *O*-protonated 2-aryl-oxirane of type **1** (as shown in the conformation **15'**, Scheme 4), by simple and sterically unhindered rotation around the C(1)–C(1') axis of the protonated epoxide **15**, derived from epoxide **1** assumed to react in its almost bisected conformation **1'**[10] (Scheme 4), it is immediately evident that the same rationale can account for the predominant frontside nucleophilic attack of MeOH observed for both substrates, **2b** and **1**(R = H)[5a] in the gas-phase.

SCHEME 4



In both intermediates **14**, from **2b** (Scheme 3), and **15'** from **1** (Scheme 4) extensive conjugative effects with the aromatic π-system promote development of a sufficient degree of positive charge at the C_α centre, so that any proton-bound adduct with the incoming MeOH nucleophile can readily isomerize to the entropically-favoured structure **10** (Scheme 1), precursor of the *syn* adduct. In the case of **14**, this process, which leads to the *cis* hydroxyether **5**, is simply represented as the route ***a*** in Scheme 3, equation 2. In the case of *O*-protonated **2a**, the unfavourable conformation of the ring π-system with the C_α-O bond does not allow location of a sufficient positive charge at the benzylic C_α centre. As a consequence, the isomerization channel (route ***a***, equation 1 of Scheme 3), affording the *cis* hydroxyether **3**, is slowed down enough to be overcome by the attack of an external MeOH molecule, which takes place predominantly at the unshielded side of the protonated species **13** yielding the *trans* hydroxyether **4** (route ***b***, equation 1 of Scheme 3).

On these grounds, it can be concluded that intrinsic structural and electronic features of epoxides of type **1** and **2** determine the stereochemistry of their acid-induced ring opening reactions as a response of the extent of positive charge developed at their benzylic C_α centres: extensive charge location at C_α promotes *syn* substitution (**1** and **2b**), while *anti* attack is favoured when such location is prevented (**2a**). However, when low amount of nucleophile molecules are present (gas-phase reaction conditions) an increase of the *syn* addition is observed in both the systems **1**[5a] and **2**, to indicate that the attacking direction of the nucleophile is governed by the nature of the benzylic carbocationic species involved in the process, than preferentially pseudoaxially driven.[4]

Experimental Section

Epoxides **2a** and **2b**,[4,5] and reference hydroxyether derivatives **3-6**[3d] were prepared as previously described.

The reagents and additives were introduced into carefully evacuated and outgassed 260-mL Pyrex bulbs, which are filled with the appropriate bulk gas (D_2 and CH_4) and sealed off.

The irradiations were carried out at 37.5 °C in a 220 Gammacell (Nuclear Canada Ltd.) to a total dose of $1.5 \cdot 10^4$ Gy at a dose rate of *ca.* 10^4 Gy·h^{-1}, as determined by a Fricke dosimeter.

The analyses of the irradiated mixtures were carried out on a Hewlett-Packard Model 5730A gas chromatograph equipped with a FID detector on the following columns: (1) 30 m x 0.32 mm Supelcowax 10 capillary column, operated at 230 °C, and (2) 25 m x 0.20 mm Carbowax 20M ULTRA performance capillary column, operated at 160 °C.

The products were identified by comparison of their retention volumes with those of authentic samples and their identity confirmed by GLC-MS (Hewlett-Packard Model 5988A).

The yields were measured from the area of the corresponding elution peaks, by using individual calibration factors.

Acknowledgment

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