Gas-Phase Acid-Induced Nucleophilic Displacement Reactions. 5. Quantitative Evaluation of Neighboring-Group Participation in Bifunctional Compounds[1]

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Abstract: A previous radiolytic study on the stereochemistry of gas-phase nucleophilic displacement on several classes of positively charged intermediates, formed from the attack of gaseous acids (CH_5^+, $C_2H_5^+$, $CH_3FCH_3^+$, etc.) on suitable substrates, is now completed with the assessment of the detailed mechanism and the relative extent of the other major reaction pathways accompanying them. The analysis of the stereoisomeric distribution of the neutral end products allows a quantitative evaluation of the gas-phase neighboring-group participation in such systems. A participating-group ability trend of OH $\gg$ Br $\geq$ Cl is found, which is appreciably dependent on the nature of the leaving group and the configuration of the starting substrate. The evaluation of the adjacent-group "effective concentrations" in these gaseous systems provides the first direct evidence for a gas-phase anchimerically assisted ionic reaction, involving a three-membered ring formation. The results obtained in the gas phase differ significantly from those concerning related solvolytic processes.

Solvent and ion-pairing effects have been recently shown to be of critical importance for all solvolytic displacement reactions,[2] particularly those involving neighboring-group participation.[3] The ability of a nucleophilic group to establish an intramolecular through-space interaction with the reaction center and the ensuing stabilization of the resulting cyclic complex are, in fact, dramatically influenced by environmental factors, such as the nucleophilicity and the solvating power of the solvent and the size and the mobility of the counterion.[2a,3,4] As a consequence, the recognition of many anchimerically assisted solvolytic displacements is frequently difficult, and a theoretical generalization of such reactions, even if unambigously ascertained in solution, is prevented by the lack of an adequate theory of liquids.[5] Hence, even the most advanced theoretical models for chain-length-dependent intramolecular processes call for the development of a suitable experimental methodology, allowing kinetic investigation of ionic displacements in the gas phase, where interference from the solvent and the counterion(s) is excluded.[6] At first sight, conventional and ion cyclotron resonance (ICR) mass spectrometry would appear as a straightforward answer to such requirements. As a matter of fact, a variety of mass spectrometric experiments aimed at clarifying the features of intramolecular ionic processes in the gas phase has been recently reported.[7] Nevertheless, the paucity of unambiguous data obtained by these techniques, which cannot provide direct information on the structure of the charged species and the neutral products involved, poses serious limitations to the solution of the problem and underlines the need of alternative gas-phase approaches.[8]

In the previous papers of this series,[1] the stereochemistry of gas-phase acid-induced bimolecular nucleophilic displacements at saturated carbon and its dependence on the presence of nucleophilic groups adjacent to the reaction center have been thoroughly investigated by a gas-phase radiolytic method. The high stereospecificity of these processes suggests application of such technique for a quantitative evaluation of the extent of neighboring-group participation in gas-phase nucleophilic displacement reactions. Our approach is based on the knowledge that inversion would occur in a nucleophilic displacement without participation (eq 1a) and on the well-supported presumption that neighboring-group participation should give net retention of configuration resulting from two inversions (eq 1b). Thus, once the mechanistic details of all the processes following GA^+ attack on RX are thoroughly examined, the stereoisomeric distribution of the neutral end products can be easily linked to the percent

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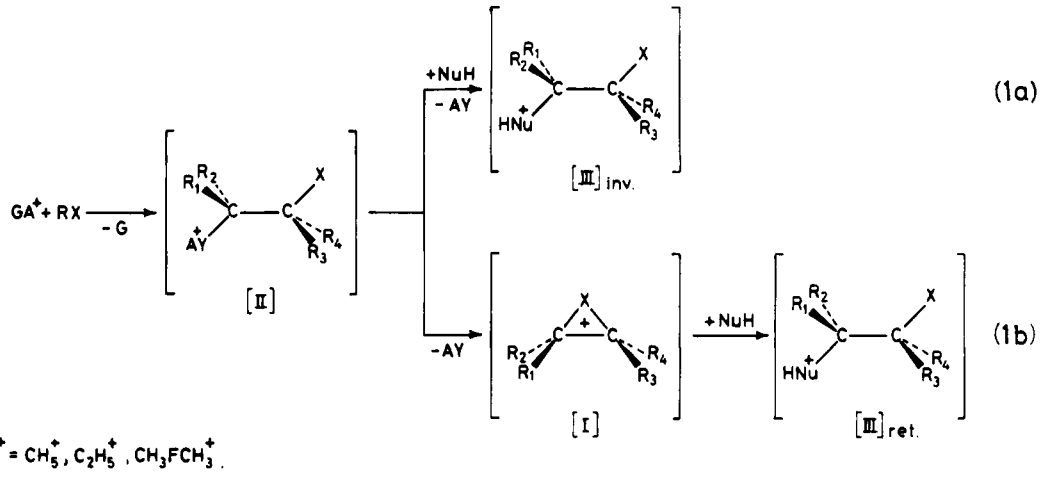


$R_1 = R_4 = H$; $R_2 = R_3 = Me$ meso or erythro forms
$R_1 = R_3 = H$; $R_2 = R_4 = Me$ *d,l* or threo forms

1, X = Y = F
2, X = Cl; Y = F
3, X = Br; Y = F
4, X = Y = Cl
5, X = Br; Y = Cl
6, X = Y = Br
7, X = OH; Y = F
8, X = OH; Y = Cl
9, X = OH; Y = Br

Table I. Product Yields from the Gas-Phase Attack of $C_nH_5^+$ (n = 1, 2) Ions on 3-Halobutan-2-ols

system composition[a]			$G_{(M)} \times 10^2$ values of products[b]					
			2,3-epoxybutanes			2,3-butanediols		total absolute
substrate (torr)	torr of H_2O	torr of NH_3	trans	cis	butanone	meso	*d,l*	yields, %[c]
erythro-**7** (2.0)	2.2		90.4	7.2	122.7	2.4	0.9	80
threo-**7** (2.0)	2.1		11.2	86.0	123.3	0.6	2.1	80
erythro-**8** (2.0)	1.9		42.4	5.2	110.0	0.3	n.d.[d]	56
erythro-**8** (1.6)		0.9	79.4	7.2	99.0	n.d.	n.d.	66
erythro-**8** (2.3)		3.0	76.3	14.9	41.6	n.d.	n.d.	47
erythro-**8** (1.4)		10.0	37.9	5.9	15.7	n.d.	n.d.	21
threo-**8** (2.0)	1.9		4.0	39.0	119.5	n.d.	0.4	58
threo-**8** (2.0)		0.9	5.2	33.2	43.7	n.d.	n.d.	29
threo-**8** (1.5)		3.0	4.0	16.5	23.9	n.d.	n.d.	16
threo-**8** (1.6)		10.0	2.2[e]	17.7[e]	11.7	n.d.	n.d.	11
erythro-**9** (1.9)	1.8		n.d.	n.d.	36.6	n.d.	n.d.	13
threo-**9** (2.0)	1.9		n.d.	n.d.	35.6	n.d.	n.d.	13

[a] CH_4, 760 torr; O_2, 4 torr. Radiation dose, 4.8 Mrad (dose rate, 0.35 Mrad h^{-1}). [b] $G_{(M)}$ values as the number of molecules of M produced per 100 eV of absorbed energy. Standard deviation of data ca. 10%. [c] Total absolute yields estimated by using $G_{(CH_5^+)} = 1.9 \pm 0.2$ and $G_{(C_2H_5^+)} = 0.9 \pm 0.2$ (ref 10). [d] n.d. = below detection limit ($G_{(M)} < 1 \times 10^{-4}$). [e] Reference 11.

of reaction proceedings via the cyclic intermediate [I] and, therefore, to the extent of adjacent group (X) participation to the NuH-to-AY displacement process (eq 1).

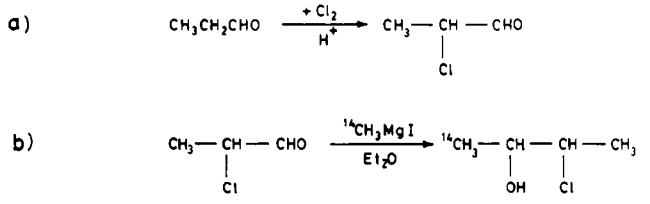
In this paper, the previous study[1] is consolidated in an overall picture concerning the general mechanism and the relative extent of the major reaction pathways following gas-phase acid (GA^+) attack on bifunctional compounds (RX = **1–9**), in the presence of different external nucleophile (NuH). We hope thereby to estimate the extent of neighboring-group participation to gas-phase nucleophilic displacements and, by comparing the gas-phase results with the available solution data, its dependence on the reaction environment.

Experimental Section

The GA^+ acids ($C_nH_5^+$, with n = 1, 2, and $CH_3FCH_3^+$) were obtained by irradiating, with the ^{60}Co γ-radiation, the corresponding parent gas (CH_4 and, respectively, CH_3F) containing a trace amount of the bifunctional substrate, in the presence of the external nucleophile (NuH), and O_2, as a thermal radical scavenger. Typical experimental conditions were: CH_4 (or CH_3F), 760 torr; substrate (**1-9**), 1–2 torr; NuH = H_2O, 1–2 torr; O_2, 4 torr; radiation dose, 4.8 Mrad; dose rate, 0.35 Mrad h^{-1}; irradiation temperature, 37.5 °C.

Full experimental details of the techniques used for the synthesis and purification of the reagents, the preparation and irradiation of the gaseous samples, and the gas chromatographic analysis of the irradiated mixtures, including a complete account of the columns employed, have been reported in the preceding papers.[1b,d]

A few experiments have been carried out with the use of *cis*- and *trans*-2,3-epoxybutanes (**10**) (Fluka A.G.) and *erythro*- and *threo*-1-^{14}C-3-chlorobutan-2-ols (**8***) as the substrate. Compounds **8*** have been prepared in good yields according to the following sequence:[9]



Their purification was obtained by preparative GLC (4-m 20% Tricresylphosphate on Chromosorb W 60–80 mesh, T_c = 80 °C) and their identity checked by NMR analysis. All the starting compounds were

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Table II. Product Yields from the Gas-Phase Attack of $C_nH_5^+$ (n = 1, 2) Ions on 2,3-Dihalobutanes

system composition[a]		$G_{(M)} \times 10^2$ values of products[b]						
		$CH_3CHXCHNuCH_3$						total absolute yield,[c] %
substrate (torr)	nucleophile NuH (torr)	X	Nu	threo	erythro	butanone	THF	
meso-**1** (1.0)	H_2O (2.1)	F	OH	n.d.[d]	n.d.	93.4		33
d,l-**1** (0.7)	H_2O (1.2)	F	OH	n.d.	n.d.	105.0		37
erythro-**2** (1.0)	H_2O (2.2)	F	OH	1.9	0.9	41.2		26
		Cl	OH	3.3	26.6			
threo-**2** (1.1)	H_2O (2.3)	F	OH	1.7	2.0	72.0		37
		Cl	OH	24.7	5.4			
erythro-**3** (0.8)	H_2O (1.6)	F	OH	3.4	2.4	40.6		17
threo-**3** (0.7)	H_2O (1.3)	F	OH	1.6	3.5	83.4		31
meso-**4** (0.8)	H_2O (2.1)	Cl	OH	5.0	56.3	58.0		43
d,l-**4** (0.9)	H_2O (2.0)	Cl	OH	51.1	5.7	59.5		41
erythro-**5** (0.4)	H_2O (1.3)	Cl	OH	3.5	16.8	97.8		44
		Br	OH	0.3	0.4			
threo-**5** (0.4)	H_2O (0.5)	Cl	OH	3.8	1.6	115.0		45
meso-**6** (0.2)	H_2O (1.5)	Br	OH	n.d.	n.d.	19.8		7
d,l-**6** (0.1)	H_2O (0.7)	Br	OH	n.d.	n.d.	21.6		8
erythro-**5** (0.5)	1,4-Br_2-C_4H_8 (0.7)	Br	Br	1.0	9.1			4
threo-**5** (0.8)	1,4-Br_2-C_4H_8 (0.7)	Br	Br	10.4	0.4			4
erythro-**5** (0.5)	1,4-$(OH)_2$-C_4H_8 (0.5)	Cl	OH	8.5	35.5	11.1	10.1	27
		Br	OH	1.4	7.8			
threo-**5** (1.0)	1,4-$(OH)_2$-C_4H_8 (0.6)	Cl	OH	13.5	2.0	0.8	1.3	8
		Br	OH	3.3	1.0			
meso-**6** (1.0)	1,4-$(OH)_2$-C_4H_8 (0.7)	Br	OH	0.3	1.9	1.0	3.6	2
d,l-**6** (1.0)	1,4-$(OH)_2$-C_4H_8 (0.7)	Br	OH	2.1	1.3	1.3	7.5	4

[a] See footnote *a* of Table I. [b] See footnote *b* of Table I. [c] See footnote *c* of Table I. [d] See footnote *d* of Table I.

Table III. Product Yields from the Gas-Phase Attack of $CH_3FCH_3^+$ Ions on 2,3-Dihalobutanes

system composition[a]		$G_{(M)} \times 10^2$ values of products[b]				
		3-X-butan-2-ols				total product yield ($G_{(M)} \times 10^2$)
substrate (torr)	torr of H_2O	X	threo	erythro	butanone	
meso-**1** (1.2)	2.3	F	0.2	n.d.[c]	7.0	7.2
d,l-**1** (1.2)	2.4	F	n.d.	0.1	13.5	13.6
erythro-**2** (1.8)	3.8	F	5.1	3.5	24.9	35.2
		Cl	0.7	1.0		
threo-**2** (1.7)	3.6	F	0.4	1.6	24.8	27.7
		Cl	0.7	0.2		
erythro-**3** (0.7)	1.4	F	2.7	1.0	4.6	8.3
threo-**3** (0.7)	1.6	F	0.3	2.2	5.2	7.7
meso-**4** (0.6)	1.4	Cl	2.7	10.1	5.2	18.0
d,l-**4** (0.8)	2.2	Cl	15.2	1.7	7.0	23.9
erythro-**5** (0.6)	1.1	Cl	3.1	8.7	9.1	21.1
		Br	0.07	0.09		
threo-**5** (0.2)	0.5	Cl	3.8	0.6	11.5	16.2
		Br	0.2	0.08		
meso-**6** (0.2)	1.4	Br	0.2	0.3	8.0	8.5
dl-**6** (0.3)	1.3	Br	1.0	0.8	10.5	12.3

[a] CH_3F, 760 torr; O_2, 4 torr. Radiation dose, 4.8 Mrad (dose rate, 0.35 Mrad h^{-1}). [b] See footnote *b* of Table I. [c] See footnote *d* of Table I.

repeatedly purified and their purity checked by GLC, using flame ionization detection (FID).

Results and Discussion

Table I reports the $G_{(M)}$ values and the isomeric distribution of the products from the 3-halobutan-2-ols (**7–9**) undergoing gas-phase attack of the radiolytically produced $C_nH_5^+$ (n = 1, 2) acids, in the presence of H_2O or NH_3 as the external base. The results concerning the irradiation of the gaseous samples with 2,3-dihalobutanes (**1–6**), as the substrates, and CH_4 or CH_3F, as the batch gas, are illustrated in Tables II and III, respectively. Table I and II summarize also the total absolute yields of products, expressed by the ratio of their overall $G_{(M)}$ value to the known $G_{(CH_5^+)}$ and $G_{(C_2H_5^+)}$ values of the ionic reactants from the γ-radiolysis of CH_4 under comparable conditions.[10] Taking into account that all the experiments require the presence of relatively high concentrations of an external nucleophile (H_2O, NH_3, etc.) in the gaseous samples, competing with the substrate for the GA^+ acid(s), the reported absolute yields indicate that the product distribution of the tables accounts for the major reaction pathways occurring in the irradiated mixtures.[12] Other minor products not reported in the tables, such as low molecular weight alkanes or olefins, amount to a few percent of the overall product yield and are mainly traced to direct radiolysis of the batch gas (blank runs on (CH_4 or CH_3F)/(H_2O or NH_3)/O_2 mixtures) or to acid-induced secondary reactions on the selected substrates, namely unimolecular fragmentation and base-catalyzed elimination processes. As pointed out in the preceding paper, the relative yields of the fragmentation products (low molecular weight alkanes and C_2–C_3 olefins) are higher in the CH_4 systems with fluorinated substrates (**1**, **2**, and **3**), whereas the highest yields of elimination

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(11) In Table II of ref 1b, these figures were erroneously higher, even though still within the uncertainty range (ca. 10%).

(12) The relatively low product yields obtained in the systems with **6** or **9**, as the substrate, are ascribed to the exceedingly high stability of bromonium ions in the gas phase (see preceding paper).

Table IV. Product Yields from the Gas-Phase Attack of Gaseous Acids on 2,3-Epoxybutanes

system composition[a]				$G_{(M)} \times 10^2$ values of products[b]			
				2,3-butanediols			total absolute
substrate (torr)	batch gas (torr)	GA^+ acids	torr of H_2O	meso	*d,l*	butanone	yield, %[c]
trans-**10** (0.7)	CH_4 (760)	$C_nH_5^+$	2.5	30.0	0.7	23.4	20
cis-**10** (1.4)	CH_4 (760)	$C_nH_5^+$	3.6	0.7	26.7	52.4	30
trans-**10** (0.9)	C_3H_8 (760)	*i*-$C_3H_7^+$	3.0	14.9	0.8	0.8	6
cis-**10** (1.4)	C_3H_8 (760)	*i*-$C_3H_7^+$	3.7	0.9	29.8	4.3	12

[a] O_2, 4 torr. Radiation dose, 4.8 Mrad (dose rate, 0.35 Mrad h^{-1}). [b] See footnote *b* of Table I. [c] See footnote *c* of Table I. Total absolute yields estimated for the last two entries by using $G_{(i\text{-}C_3H_7^+)} \simeq 3.0$ (ref 20).

products (substituted C_4 olefins) are recovered from the CH_4 samples with **8** and NH_3, which acts as an efficient deprotonating agent.

The ionic nature of the products reported in Tables I–III is demonstrated by the dependence of their $G_{(M)}$ values upon the concentration of a powerful ion interceptor, such as NH_3, in the irradiated mixture (see Figure 1). Inspection of Tables I–III reveals that relatively high yields of butanone are invariably formed in all systems, together with comparable amounts of the substituted derivatives of **7–9** (epoxybutanes and glycols) and **1–6** (halohydrins), whose formation mechanism has been discussed in detail in the preceding papers.[1b,d] The only obvious exception to such behavior is represented by those runs on bromochlorobutanes (**5**) with 1,4-dibromobutane, as the external nucleophile, in CH_4. In this case, the only source of oxygen atoms is the O_2 molecules, which clearly do not intervene in the butanone formation process.

Several factors seem to play a role in determining the efficiency of the butanone formation from **1–9**, including the nature of both the GA^+ acid and the leaving halogen (Y), and the configuration of the starting substrate. Thus, the relative butanone yield increases with the exothermicity of the GA^+ acid attack on the substrate ($CH_5^+ > CH_3FCH_3^+$)[13] and according to the leaving-group order AF > ACl > ABr. Furthermore, threo or *d,l* forms of the compounds **1–9** give higher yields of butanone, if compared to those from the corresponding erythro or meso isomers.

Butanone Formation Mechanism. From a general standpoint, at least two different mechanistic pathways for butanone formation can be conceived, whose occurrence is strictly related to the nature of either the selected substrate or the added nucleophile. Thus, butanone formation from 2,3-dihalobutanes (**1–6**) (Tables II and III) requires attack of the external oxygenated nucleophile (H_2O or 1,4-dihydroxybutane) on some suitable intermediate from the GA^+ attack on the dihalogenated compound (eq 2a). In fact,

$$GA^+ + RX \xrightarrow[-G]{} [RXA]^+ \xrightarrow{+H_2O} CH_3CH_2COCH_3 \cdot \quad (2a)$$

$$GA^+ + RX \xrightarrow[-G]{} [RXA]^+ \longrightarrow CH_3CH_2COCH_3 + \quad (2b)$$

in the presence of a nucleophile containing no oxygen, such as 1,4-dibromobutane, no detectable formation of butanone is observed. On the other hand, butanone is easily formed from the attack of $C_nH_5^+$ ions on 3-halobutan-2-ols (**7–9**)(Table I), even in the absence of H_2O (runs with NH_3). Hence, an additional route to the carbonyl product is required, presumably involving isomerization of some oxygenated intermediate from the GA^+ attack on the alcoholic substrate (eq 2b). Even when occurring in the presence of H_2O, the intramolecular mechanism 2b seems to be favored over the intermolecular one (eq 2a), as suggested by the relatively small decrease of butanone yield from **8** observed when 1.9 torr of H_2O are replaced by 0.9 torr of NH_3, as the external nucleophile. Notably, a much more evident decrease is observed for the *threo*-**8** than for the erythro isomer, indicating a more efficient occurrence of process 2b for the latter under these conditions. The same configurational effect observed in the butanone formation characterizes as well the cyclization reaction [II] → [I] (eq 1b), which gives the corresponding 2,3-epoxybutanes,[1a] suggesting therefore that a common intermediate could be involved in both processes. In this view, a detailed mechanism common to reactions 2a and 2b may be envisioned as follows.[14]

The butene X-onium ion [I], from fast intramolecular X-to-AY displacement within the intermediate [II], easily isomerizes to the open-chain X-onium ion [IV] by 1,2-hydride ion transfer, e.g., eq 3a. According to the nature of X, intermediate [IV] can either directly lose a proton to a suitable base B (X = OH, eq 3b)[15] or,

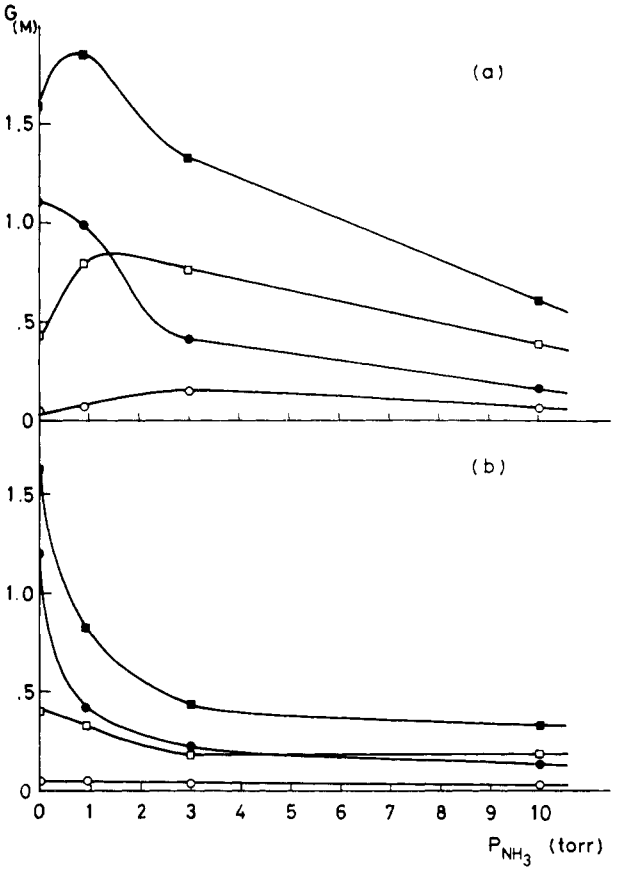
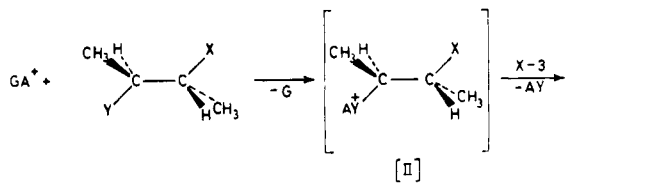


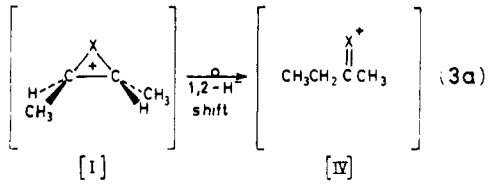
Figure 1. Overall (■) and individual (□, inverted 2,3-epoxybutane; ○, retained 2,3-epoxybutane; ●, butanone) $G_{(M)}$ values from *erythro*- (a) and *threo*-3-chlorobutan-2-ol (**8**) (b) in CH_4 as a function of the partial pressure (P_{NH_3}) of the added NH_3.

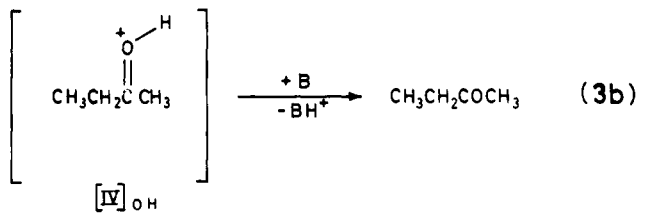
(13) Protonation by CH_5^+ ($\Delta H°_f$ = 221 kcal mol^{-1}: Chupka, W. A.; Berkowitz, J. A. *J. Chem. Phys.* **1971**, *54*, 4256–4259. Jelus, B. L.; Murray, R. K., Jr.; Munson, B. *J. Am. Chem. Soc.* **1975**, *97*, 2362–2365) and $C_2H_5^+$ ($\Delta H°_f$ = 215 ± 1 kcal mol^{-1}: Baer, T. *J. Am. Chem. Soc.* **1980**, *102*, 2482–2483) on the n centers of the selected substrates is computed to release 40–60 kcal mol^{-1} and 0–30 kcal mol^{-1}, respectively. Condensation of $C_2H_5^+$ is exothermic for ca. 20–40 kcal mol^{-1}. The exothermicity of the $CH_3FCH_3^+$-ion ($\Delta H°_f$ = 161 ± 8 kcal mol^{-1}: Beauchamp, J. L.; Holtz, D.; Woodgate, S. D.; Patt, S. L. *J. Am. Chem. Soc.* **1972**, *94*, 2798–2807) attack on the used compounds is calculated to range from 10 to 35 kcal mol^{-1}.

(14) Alexander, E. R.; Dittmer, D. C. *J. Am. Chem. Soc.* **1951**, *73*, 1665–1668.

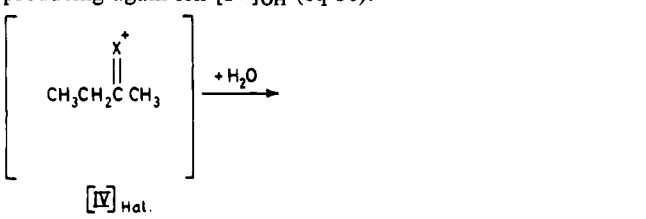
(15) Suitable bases B, either deliberately added to the system (NH_3, H_2O, etc.) or formed from its radiolysis, are present in the irradiated mixtures. The basic centers of the glass walls of the bulb can behave as good proton acceptors too.



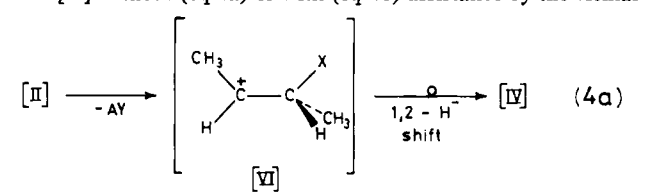




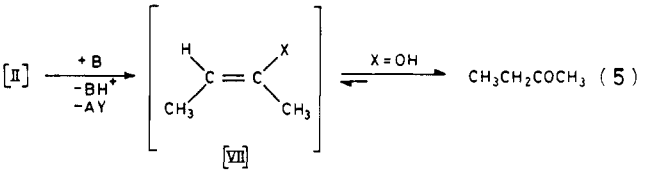
if X = halogen, undergo attack by the external nucleophile (e.g., H_2O), giving [V], which readily eliminates a HX molecule,[7f] producing again ion $[IV]_{OH}$ (eq 3c).



However, several other mechanisms for butanone formation can be envisaged, either involving intermediate [IV] or leading directly to the neutral ketone. In fact, another conceivable route to [IV] could proceed via direct elimination of the AY moiety from [II] without (eq 4a) or with (eq 4b) assistance by the vicinal



hydrogen atom. Isomerization of [VI] to [IV] has been calculated to be energetically allowed.[16] Finally, another direct route to neutral butanone from the halobutanols **7–9** could be the simple base-induced AY elimination (eq 5) from intermediates [II]. This



possibility cannot be included among the conceivable routes to the formation of butanone from dihalobutanes **1–6**, since it would simply lead to the neutral haloolefin [VII]. The mechanism 3–5 outlined are all energetically allowed[17] and, therefore, each of them must be considered as a reasonable candidate for the formation of butanone. Perhaps path 4b is less likely, as it would require a stereouncontrolled H-3 participation in [II] much faster than the competing attack of the more nucleophilic n-type group (X) on the adjacent reaction center (a X-3 process).

Several experiments have been designed to discriminate among mechanisms 3–5. Thus, the highly exothermic protonation by $C_nH_5^+$ ions of the oxygen atom of *trans*- and *cis*-2,3-epoxybutanes (**10** in Tables IV)[18] is found to induce extensive isomerization of the corresponding excited intermediates [I] (X = OH) with formation of relatively high yields of butanone. The efficiency of this process is of course dependent on the excitation energy of the intermediate ion [I]. In fact, only poor yields of butanone are formed from **10**, when the milder $i\text{-}C_3H_7^+$ acid,[19] generated from γ-radiolysis of propane,[20] is used instead of $C_nH_5^+$ as protonating agent. Furthermore, inspection of Table IV reveals that the extent of [I] isomerization is also dependent on the configuration of the starting epoxide. In fact, the cis epoxide invariably gives significantly higher yields of butanone, if compared to those from the trans isomer, suggesting that the presence of two eclipsed methyl groups in the *cis*-[I] favors its isomerization to the butanone precursor.[7p] This result parallels that observed in the butanone formation from 3-halobutan-2-ols (threo > erythro, Table I). Taking into account that GA^+ acid attack on the haloalcohols gives the corresponding cyclic intermediates [I] (X = OH; threo alcohol → *cis*-[I]; erythro alcohol → *trans*-[I]),[1b] structurally identical with those arising from protonation of the proper 2,3-epoxybutane, the similar marked dependence of the butanone yield on the configuration of the starting substrate (either a 2,3-epoxybutane or a 3-halobutan-2-ol) provides circumstantial evidence for the formation of butanone via mechanism 3.

The predominance of mechanism 3 over the alternative routes 4 and 5 to butanone from halobutanols can be demonstrated by using labeled compounds, such as *erythro*- or *threo*-1-^{14}C-3-chlorobutan-2-ol (**8***), as the substrate. Among the proposed butanone formation mechanisms, in fact, only mechanism 3 requires the intermediacy of the symmetrical oxonium ion [I], whose occurrence is therefore testified by the complete equilibration of the ^{14}C label over the terminal methyl groups of the ^{14}C-butanone formed from **8***. Alternatively, only 1-^{14}C-butan-2-one is expected to be produced from **8*** by mechanisms 4 and 5, on account of the fact that only asymmetric intermediates are involved in such processes. Therefore, gaseous mixtures containing **8*** (2.6 torr, specific activity 216 μCi mmol^{-1}) in CH_4 were irradiated in the presence of H_2O (2 torr) and O_2 (4 torr). The radioactive products were diluted with inactive butanone, purified by preparative gas chromatography (specific activity of the purified butanone 0.135

(16) Hehre, W. J.; Hiberty, P. C. *J. Am. Chem. Soc.* **1974**, *96*, 2665–2677.

(17) In agreement with thermochemical calculations on molecules structurally related to those of the present study, all the proposed reactions (reactions 3–5), following formation of [II], are energetically allowed, except for sequence 4a, whose first step, when occurring from methylated [II]'s ($GA^+ = CH_3FCH_3^+$), can be endothermic for several kcal mol^{-1} (cf. ref 1b, 1d, 7f, and 7i).

(18) Proton affinities (PA) of *cis*- and *trans*-2,3-epoxybutanes are not reported in the literature. However, taking into account the contribution of the two methyl groups to the gas-phase basicity of an oxyrane ring (PA(oxyrane) = 185–186 kcal mol^{-1}: Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1975**, *97*, 4137–4139. Staley, R. H.; Cordeman, R. R.; Foster, M. S.; Beauchamp, J. L. *Ibid.* **1974**, *96*, 1260–1261), the proton affinity of **10** is computed to range around 193–195 kcal mol^{-1} (cf.: Yamdagni, R.; Kebarle, P. *Ibid.* **1976**, *98*, 1320–1324. Wolf, J. F.; Staley, R. H.; Koppel, I.; Taagepera, M.; Mc Iver, R. I., Jr.; Beauchamp, J. L.; Taft, R. W. *Ibid.* **1977**, *99*, 5417–5429) and, therefore, the exothermicity of the $C_nH_5^+$ protonation of **10** is calculated to release approximately 66 (n = 1) or 32 (n = 2) kcal mol^{-1}.

(19) Proton affinity of propene C_3H_6 is 183 kcal mol^{-1}, whereas that of C_2H_4 is only 159 kcal mol^{-1} (Houle, F. A.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1979**, *101*, 4067–4074). PA(CH_4) = 127 kcal mol^{-1} (ref 13).

(20) Lias, S. G.; Rebbert, R. E.; Ausloos, P. *J. Am. Chem. Soc.* **1970**, *92*, 6430–6440.

Scheme I

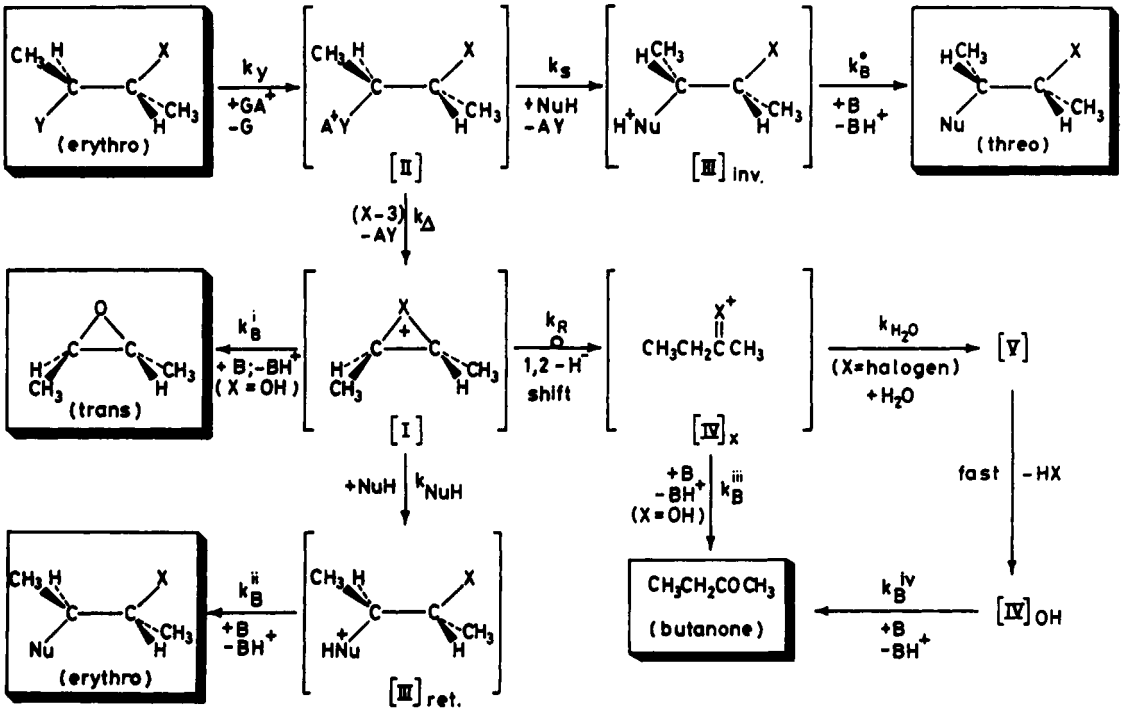
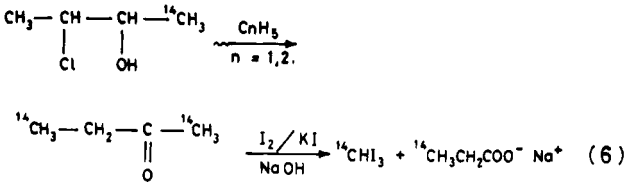


Table V. Effective Concentration of Reactive Adjacent Groups in Gas-Phase Acid-Induced Nucleophilic Displacement Reactions

substrate	GA^+ acids	leaving group, AY	adjacent group, X	NuH ($\times 10^4$) (mol L^{-1})	$k_\Delta/k_s \times 10^4$, mol L^{-1}
erythro-7	$C_nH_5^+$	AF	OH	H_2O (1.2)	287
threo-7	$C_nH_5^+$	AF	OH	H_2O (1.2)	423
erythro-8	$C_nH_5^+$	ACl	OH	H_2O (1.0)	>15000
threo-8	$C_nH_5^+$	ACl	OH	H_2O (1.0)	>15000
erythro-5	$C_nH_5^+$	ACl	Br	1,4-Br_2-C_4H_8 (0.35)	3
threo-5	$C_nH_5^+$	ACl	Br	1,4-Br_2-C_4H_8 (0.35)	9
meso-4	$C_nH_5^+$	ACl	Cl	H_2O (1.2)	27
d,l-4	$C_nH_5^+$	ACl	Cl	H_2O (1.1)	21
meso-4	$CH_3FCH_3^+$	ACl	Cl	H_2O (0.8)	5
d,l-4	$CH_3FCH_3^+$	ACl	Cl	H_2O (1.3)	17
meso-6	$CH_3FCH_3^+$	ABr	Br	H_2O (0.7)	29
d,l-6	$CH_3FCH_3^+$	ABr	Br	H_2O (0.65)	9
meso-6	$C_nH_5^+$	ABr	Br	1,4-$(OH)_2$-C_4H_8 (0.35)	3
d,l-6	$C_nH_5^+$	ABr	Br	1,4-$(OH)_2$-C_4H_8 (0.35)	1

μCi mmol^{-1}), and the ketone degraded by the well-known iodoform reaction (eq 6). The radioactivity was found to be equally dis-



(6)

tributed between $^{14}CHI_3$ and $^{14}CH_3CH_2COOH$ (specific activity 0.067 μCi mmol^{-1}). It is concluded that mechanism 3 is the only significant route to butanone from the halobutanol mixtures. Unfortunately, similar direct evidence cannot be provided for the butanone formation mechanism from dihalobutanes **1–6**. However, the strict correspondence between the stereoisomeric distribution of the substituted products and the absolute yield of butanone reported in Tables I and II strongly suggests that predominance of the sequence 3a–c in the formation of butanone from dihalobutanes **1–6** in the mixtures containing oxygenated nucleophiles (e.g., H_2O) as well.

Effective Concentration. According to the general conclusions reached in the previous papers of this series[1] and in the light of the present results, the general reaction pattern responsible for the formation of the products is outlined in Scheme I. Kinetic treatment of the GA^+ acid induced reaction network of Scheme I, by application of the steady-state approximation for the transients [II], [I], [IV], and [III], leads to the following equation:

$$\frac{k_\Delta}{k_s} = \frac{G_{(butanone)} \cdot G_{(erythro)} \cdot G_{(trans)}}{G_{(threo)}} [NuH] \cdot \frac{G_\Delta}{G_{(threo)}} [NuH] \quad (7)$$

The ratio k_Δ/k_s has the dimensions of mole liter^{-1}. Following classical definitions for solution neighboring-group-participation processes,[6,21] this ratio is defined as the "effective concentration" of the reactive end X of the intermediate [II] in the particular reaction volume about the reaction center C-$^+$YA, relative to the concentration of the external nucleophile NuH within the same volume. This term represents the actual "reduced" intramolecular reactivity within [II], once it is referred to a proper intermolecular model, namely to the inherent reactivity of the two reacting moieties of the bifunctional species regarded as if they were not

(21) (a) Stoll, M.; Rouvé, A. *Helv. Chim. acta* **1934**, *17*, 1289. (b) Morawetz, H. *Pure Appl. Chem.* **1974**, *38*, 267. (c) Morawetz, H.; Goodman, N. *Macromolecules* **1970**, *3*, 699. (d) Galli, C.; Illuminati, G.; Mandolini, L. *J. Am. Chem. soc.* **1973**, *95*, 8374–8379. (e) Illuminati, G.; Mandolini, L.; Masci, B. *Ibid.* **1977**, *99*, 6308–6312.

connected by a molecular chain. Only in a few instances were reasonably good kinetic models for the intermolecular analogue (k_s) of the neighboring-group-participation reaction (k_Δ) available in the present study. The relevant effective concentration data are reported in the first part of Table V, together with those relative to less cogent reaction pairs. Mere inspection of the reported figures shows the significant participation of an OH group adjacent to the reaction center C-$^+$YA of [II], which, in the gas phase, turns out to be several orders of magnitude greater than that pertaining to a halogen atom (Cl or Br). The qualitative trend obtained for neighboring-group participation is OH $\gg$ Br $\geq$ Cl. The extent of participation is also appreciably dependent on both the leaving-group ability of the AY moiety and the configuration of the intermediate [II], while no significant dependence on the strength of the GA^+ acid is found.

In this connection, an effective OH-group concentration ranging from 3×10^{-2} (**7**) to over 1.5 mol L^{-1} (**8**) corresponds to a cyclization frequency within their intermediates [II] significantly higher than the rotation period of a C–C bond ($>10^{11}$ s^{-1}) at room temperature, if a high efficiency for the reaction between [II] and the external nucleophile is assumed ($k_s > 10^{-12}$ cm^3 $molecule^{-1}$ s^{-1}).[22] In this view, comparison of the effective concentrations pertaining to **7** and **8** indicates a less efficient HO-3 participation in **7** than in **8**, in spite of the fact that GA^+ attack on their halogen induces formation of a partial positive charge on the adjacent C center increasing in the order Cl < F,[23] which should rather favor OH participation in the intermediate [II] from **7**. On the other hand, independent atmospheric-pressure radiolytic as well as low-pressure mass-spectrometric experiments demonstrated that AF is a much better leaving group than ACl in the gas phase.[1b,c,7i,p,24] Thus, taking into account the relatively high cyclization frequency in [II], a plausible explanation for such effect can be found in a C-$^+$FA dissociation rate in fluorinated [II] of the same order of magnitude of both its cyclization frequency and its C–C rotation period, whereas in the chlorinated [II] from **8**, the C–$^+$ClA bond does not dissociate unless by intervention of the vicinal OH group. This represents direct evidence for an anchimerically assisted displacement reaction in the gas phase, while, for the other systems examined by the present investigation, a cyclization process without significant C-$^+$YA dissociation rate enhancement is observed.

Comparison with Related Solution Chemistry Data. While extensive evidence supports the occurrence of displacement reactions in solution via adjacent hydroxy-group or halogen-atom participation, identification of anchimerically assisted HO-3 or halogen-3 processes is often controversial. Only in a few instances, in fact, could product analysis,[25] supported by adequate kinetic data,[26] provide firm an indication of anchimeric assisted reactions involving three-membered-ring formation. Most of the difficulties encountered in these cases arise from the fact that the increase in rate associated with hydroxy- and halogen-atom participation is not very great because often the solvent is itself comparatively basic and nucleophilic, and the displacement rate is quite high even in the absence of participation by the neighboring group. In addition, the inductive effect of the participating group in a position adjacent to the leaving one may play a role whose extent and direction on the reaction rate can be dramatically influenced by the nature and the solvating power of the medium. As a consequence, no definite participating-group ability order is available in solvolytic processes, since it is strongly dependent on environmental factors. However, extensive solvolytic studies on vicinal-group participation reactions occurring in systems strictly related to those of the present investigation lead to a participation ability order of Br > OH > Cl.[27] This trend does not find any correspondence with that observed in the gas phase (OH $\gg$ Br $\geq$ Cl), which instead appears to parallel the relative gas phase nucleophilicities (e.g., methyl cation affinities) of related compounds containing the corresponding group (e.g., CH_3OH > CH_3Br > CH_3Cl).[28] These findings would indicate that, in the absence of solvent, counterion, etc., the efficiency of a vicinal-group participation process is strictly related to the nucleophilicity of the moiety adjacent to the reaction site, whereas the influence of other factors, such as the strain energy developed in the transition state, seems to play a minor role. This observation, while pointing out the solvent leveling effects on the inherent nucleophilic properties of the adjacent groups in solvolytic reactions, suggests the early character of the transition state in gas-phase neighboring-group participation, which finds a general counterpart in the role of electrostatic interactions in most gas-phase ion–molecule reactions.

Conclusions

A stereochemical approach has been adopted for the kinetic investigation of acid-induced nucleophilic displacement processes involving vicinal group participation in the gas phase, where interference from environmental factors is excluded. A OH $\gg$ Br $\geq$ Cl participation ability order is measured in the gas phase, which does not correspond to that observed in analogous solvolytic process, but rather qualitatively follows the relative gas-phase nucleophilicity scale of the neutral precursor. The results obtained on three-membered-ring closure reactions could provide a base for a comprehensive kinetic investigation on gas-phase anchimerically assisted substitutions, whose comparison with related solvolytic processes could allow a rationalization of the medium effects involved and promote development of quantitative theoretical models for cyclization reactions in the condensed phase.

Acknowledgment. The authors are grateful to F. Cacace and A. P. Wolf for stimulating discussions on the subject of this paper.

(22) Acid-induced nucleophilic displacement reactions are very efficient processes in the gas phase, with rates ranging from over 10^{-9} to 10^{-11} cm^3 $molecule^{-1}$ s^{-1} (cf.: Beauchamp, J. L.; Holtz, D.; Woodgate, S. D.; Patt, S. L. *J. Am. Chem. Soc.* **1972**, *94*, 2798–2807. Holtz, D.; Beauchamp, J. L. *Nature (London) Phys. Sci.* **1971**, *231*, 204–208).

(23) Speranza, M.; Pepe, N.; Cipollini, R. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1179–1186 and references therein.

(24) (a) Speranza, M.; Cacace, F *J. Am. Chem. Soc.* **1977**, *99*, 3051–3055. (b) Cacace, F.; Speranza, M. *Ibid.* **1976**, *98*, 7299–7304. (c) Speranza, M.; Sefcik, M. D.; Henis, J. M. S.; Gaspar, P. P. *Ibid.* **1977**, *99*, 5583–5589. (d) Jardine, I.; Fenselau, C. *Ibid.* **1976**, *98*, 5086–5089.

(25) (a) Peterson, P. E.; Coffey, J. F. *Ibid.* **1971**, *93*, 5208–5213. (b) Peterson, P. E. *Acc. Chem. Res.* **1971**, *4*, 407–413. (c) Masuda, S.; Segi, M.; Nakajima, T.; Suga, S. *J. Chem. Soc., Chem. Commun.* **1980**, 86–87.

(26) (a) Blandamer, M. J.; Golinkin, H. S.; Robertson, R. E. *J. Am. Chem. Soc.* **1969**, *91*, 2678–2683. (b) Lown, J. W.; Joshua, A. V. *Can. J. Chem.* **1977**, *55*, 122–140.

(27) (a) Winstein, S.; Lucas, H. J. *J. Am. Chem. Soc.* **1939**, *61*, 1576–1581. (b) *Ibid.* **1939**, *61*, 2845–2848. (c) Lucas, H. J.; Garner, H. K. *Ibid.* **1950**, *72*, 2145–2150. (d) Lucas, H. J.; Gould, C. W., Jr. *Ibid.* **1941**, *63*, 2541–2551. (e) De La Mare, P. B. D.; Naylor, P. G.; Williams, D. L. H. *J. Chem. Soc.* **1962**, 443–449. (f) *Ibid.* **1963**, 3429–3436. (g) Winstein, S.; Goodman, L. *J. Am. Chem. Soc.* **1954**, *76*, 4368–4372. (h) *Ibid.* **1954**, *76*, 4373–4378.

(28) Methyl cation affinities (MCA) as defined by: Holtz, D.; Beauchamp, J. L.; Woodgate, S. D. *J. Am. Chem. Soc.* **1970**, *92*, 7484–7487. MCA(CH_3OH) = 80 kcal mol^{-1}; MCA(CH_3Br) = 56 kcal mol^{-1}; MCA(CH_3Cl) = 51 kcal mol^{-1} (Sharma, D. K. S.; Kebarle, P. *Ibid.* **1978**, *100*, 5826–5830. Beauchamp, J. L.; Holtz, D.; Woodgate, S. D.; Patt, S. L. *Ibid.* **1972**, *94*, 2798–2807).