Regio- and Stereochemistry of Gas-Phase Acid-Induced Nucleophilic Substitutions on Chiral Allylic Alcohols[1]

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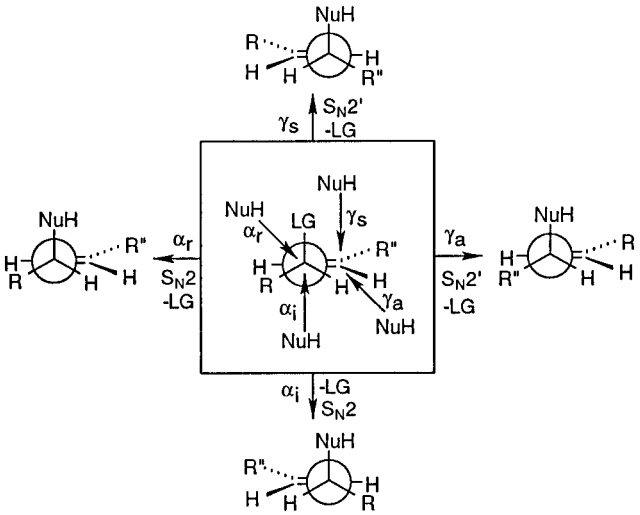
The regio- and stereochemistry of the nucleophilic attack of (*S*)-*trans*-3-hexen-2-ol (**M$_S$**) and (*S*)-*trans*-4-hexen-3-ol (**E$_S$**) on the corresponding O-protonated (L = H) and -methylated (L = CH_3) derivatives (**M$_S$L**$^+$ and **E$_S$L**$^+$) are investigated in the gas phase at 40 °C (720 Torr). The **M$_S$L**$^+$ and **E$_S$L**$^+$ intermediates are produced in the gas phase by the attack of the ionic Brønsted and Lewis acids, formed by stationary γ-radiolysis of bulk CH_3Cl, on the corresponding chiral alcohols, i.e., **M$_S$** and **E$_S$**. In these systems, firm evidence in favor of the concerted S_N2' pathway, accompanying the classical S_N2 one, is obtained by excluding the following: (i) the isomerization of **M$_S$L**$^+$ (or **E$_S$L**$^+$) before the attack by the nucleophile NuH = **M$_S$** (or **E$_S$**); (ii) the isomerization of the $(C_6H_{11})_2$-OH^+ substitution intermediates before neutralization; (iii) the intermediacy of allylic cations. The regioselectivity factors (S_N2'/S_N2 = 1.4 (**M$_S$**), 1.1 (**E$_S$**)) confirm previous experimental and theoretical evidence about the prevalence in the gas phase of the S_N2' pathway, over the competing S_N2 one. Orientation of NuH by **M$_S$L**$^+$ (or **E$_S$L**$^+$) determines the regiochemistry of the allylic substitution. When NuH approaches the oxonium intermediate from the direction syn to the leaving moiety LOH, a frontside S_N2 displacement takes places favored by preliminary proton bonding between LOH and NuH. The S_N2' reaction instead follows attack on the π-LUMO of the oxonium ion by the NuH juxtaposed anti to the leaving LOH group. Observation of a predominant *anti*-S_N2' orientation provides the first experimental basis of modern concepts pointing to Coulombic interactions as the main intrinsic factors governing the S_N2' stereochemistry and to solvation and ion pairing as the factors determining the low efficiency of S_N2' reactions and their preferred syn stereochemistry in solution.

Introduction

In the brief history of classical physical organic chemistry, few reactions have stirred the imagination of both the experimental and theoretical chemists to the extent noted with the S_N2' reaction. Bimolecular nucleophilic displacements in allylic compounds are known to proceed via four possible pathways (Scheme 1), namely, (i) the α_i-S_N2 route, where the nucleophile (NuH) attacks from the backside the C_α center of the allylic substrate displacing the nucleofuge (LG) with inversion of the C_α configuration; (ii) the α_r-S_N2 route, where NuH attacks from the frontside the C_α center of the allylic substrate displacing LG with retention of the C_α configuration; (iii) the γ_a-S_N2' route, where NuH attacks the C_γ of the allylic substrate from a direction opposite (anti) to that of LG; and (iv) the γ_s-S_N2' route, where NuH attacks the C_γ of the allylic substrate from the same direction (syn) of LG.

The existence itself of the S_N2' mechanism,[2−8] the question of its concertedness,[3,9−16] and the origin of its stereochemistry[5,15−19] have remained points of controversy since its first introduction in the late 1930s.[20−22]

Scheme 1



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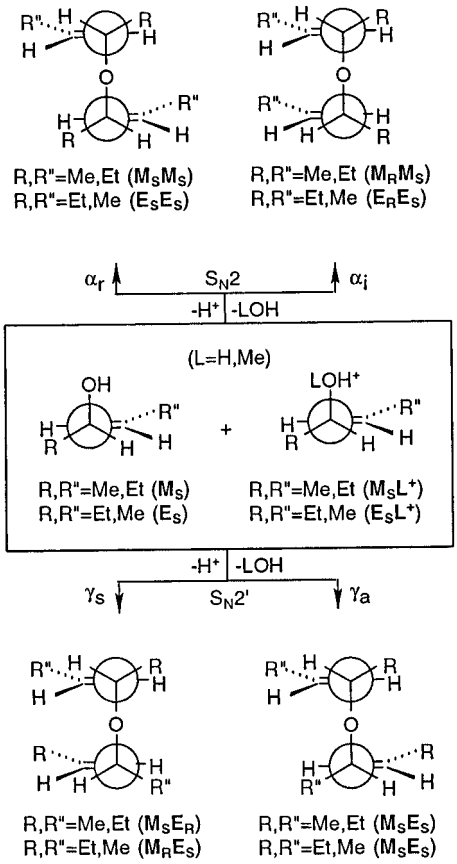
The controversy is continuously stirred up by the observation that, in solution, solvation and ion-pairing factors may profoundly affect the efficiency of the S_N2' reaction as well as that of the competing S_N2 or S_N1 processes. In this respect, Bordwell regards the concerted S_N2' reactions as a myth.[3] He cites evidence that all so-called S_N2' reactions in solution are actually either S_N1 processes followed by capture of NuH at the remote carbon of the intermediate allyl cation or nucleophilic addition−elimination processes. Carrion and Dewar[23] suggest that the predominance in solution of the S_N2 mechanism over the S_N2' one is primarily due to energy-demanding ion desolvation in the S_N2' transition structure, which mostly contributes to the building up of the relevant activation barrier, whereas the more favored S_N2 barrier is essentially determined by electronic factors. In light of these modern concepts, these and other authors conclude that there is no real reason concerted S_N2' reaction should not be feasible in the gas phase.[23−26] This indication has been followed in a recent gas-phase study of acid-induced nucleophilic substitution on some allylic alcohols that showed that the concerted S_N2' reaction actually competes with the classical S_N2 pathway in the absence of solvation and ion-pairing factors.[27−29] The same modern concepts consider restrictive any theoretical rationale of the S_N2' stereochemistry simply based on stereoelectronic factors,[30−40] since an important role may be played by Coulombic interactions between NuH and LG and among these and the reaction medium.

In this framework, we deemed it important to assess the regio- and stereochemistry of the gas-phase acid-induced nucleophilic displacement on representative allylic compounds in the gas phase, where interference from solvation and ion pairing is excluded, and to compare them with most advanced theoretical predictions that normally refer to isolated species. The experimental approach adopted, which has recently been reviewed,[41] is based upon the generation of stationary concentrations of gaseous acid catalysts by γ-radiolysis of CH_3Cl (720 Torr) and their attack on chiral allylic alcohols, i.e., the S-enantiomers of *trans*-3-hexen-2-ol (**M$_S$**) and of *trans*-4-hexen-3-ol (**E$_S$**). Attack of the gaseous acid catalysts on the oxygen of the selected alcohols generates the corresponding oxonium ion (either **M$_S$L$^+$** or **E$_S$L$^+$**), wherein the potential leaving group LOH (L = H,CH_3) may be easily displaced by the nucleophiles present in the mixture, including the allylic substrate itself (Scheme 2).

Scheme 2



Experimental Section

Materials. Methyl chloride and oxygen were high-purity gases from UCAR Specialty Gases N.V., used without further purification. The racemates of (*S*,*R*)-*trans*-3-hexen-2-ol (**M$_S$**−**M$_R$**) and (*S*,*R*)-*trans*-4-hexen-3-ol (**E$_S$**−**E$_R$**) were prepared and purified according to previously described procedures.[1a,42] The kinetic resolution of the **M$_S$**−**M$_R$** and **E$_S$**−**E$_R$** racemates was carried out by lipase-catalyzed enantioselective transesterification, using the same procedure described in a previous paper.[1a] The enantiomeric excess (ee) of the purified (*S*)-*trans*-3-hexen-2-ol (**M$_S$**) and (*S*)-*trans*-4-hexen-3-ol (**E$_S$**) was 98.5%; that of (*R*)-*trans*-3-hexen-2-ol (**M$_R$**) and (*R*)-*trans*-4-hexen-3-ol (**E$_R$**) was 99.0%. Their methyl ethers, i.e., (*S*)-*trans*-3-methoxy-4-hexene (**E$_S$Me**), (*R*)-*trans*-3-methoxy-4-hexene (**E$_R$Me**), (*S*)-*trans*-2-methoxy-3-hexene (**M$_S$Me**), and (*R*)-*trans*-2-methoxy-3-hexene (**M$_R$Me**) were synthesized from the corresponding chiral alcohols as described in the preceding paper.[1b]

Procedure. The experimental techniques used for the preparation of the gaseous mixtures and their irradiation have been already reported.[1] The irradiations were carried out at 40 °C in a 220 Gammacell from Nuclear Canada Ltd. to a dose of 2×10^4 Gy at a rate of 10^4 Gy h^{-1}, as determined by a neopentane dosimeter. Control experiments, carried out at doses ranging from 1×10^4 to 1×10^5 Gy, showed that the relative yields of products are largely independent of the dose.

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The radiolytic products were analyzed by GLC, using a Perkin-Elmer 8700 gas chromatograph equipped with a flame ionization detector (FID) on a 25-m long, 0.25 mm i.d. MEGADEX 5 (30% dimethylpentyl-β-cyclodextrin in OV 1701) fused silica column, operated at temperatures ranging from 50 to 80 °C, 3 °C min^{-1}. The products were identified by the indirect procedure described below, and their identity was checked by GLC−MS using a Hewlett-Packard 5890 A gas chomatograph in line with a HP 5970 B mass selective detector. Their yields were determined from the areas of the corresponding eluted peaks, using the internal standard (i.e., 3-methylpentan-3-ol) method and individual calibration factors to correct for the detector response. Blank experiments were carried out to ascertain the occurrence and the extent of thermal isomerization and racemization of the individual starting substrates, i.e., $\mathbf{M_S}$ and $\mathbf{E_S}$, as well as of their ethereal products at any given reaction temperature. The yields of the radiolytic products from irradiation of the selected mixtures were corrected accordingly.

Identification of the Substitution Products. According to Scheme 2, the nucleophilic attack of a given allylic alcohol, e.g., $\mathbf{M_S}$, on its oxonium derivative, i.e., $\mathbf{M_SL}^+$ (or its isomeric forms, vide infra), is expected to generate predominantly two pairs of diastereomeric $(C_6H_{11})_2O$ ethers, namely $\mathbf{M_SM_S}$ (α_r), $\mathbf{M_RM_S}$ (α_i), $\mathbf{M_SE_S}$ (γ_a), and $\mathbf{M_SE_R}$ (γ_s). These products may be accompanied by minor amounts of other $(C_6H_{11})_2O$ isomers if some rearrangement takes place in their ionic precursors $(C_6H_{11})_2OH^+$ before neutralization. Thus, the $\mathbf{M_RM_R}$, $\mathbf{M_RE_S}$, and $\mathbf{M_RE_R}$ isomers may arise from partial epimerization of the ionic precursors of $\mathbf{M_RM_S}$, $\mathbf{M_SE_S}$, and $\mathbf{M_SE_R}$, respectively. They would be accompanied by $\mathbf{E_RE_S}$ and $\mathbf{E_RE_R}$, if a suprafacial 1,3-rearrangement takes place in the ionic precursors of $\mathbf{M_SE_S}$ and $\mathbf{M_SE_R}$, respectively. It should be noted that formation of the last isomer of the family, i.e., $\mathbf{E_SE_S}$, requires occurrence of both the epimerization and suprafacial 1,3-rearrangement of the direct ionic precursor of $\mathbf{M_SE_S}$. An analogous product distribution is expected, mutatis mutandis, from the nucleophilic attack of $\mathbf{E_S}$ on $\mathbf{E_SL}^+$ (or its isomeric forms, vide infra). Here, $\mathbf{E_RE_S}$ (α_i), $\mathbf{E_SE_S}$ (α_r), $\mathbf{M_SE_S}$ (γ_a), and $\mathbf{M_RE_S}$ (γ_s) are expected to be directly formed from the nucleophilic displacement. They would be accompanied by $\mathbf{E_RE_R}$, $\mathbf{M_SE_R}$, and $\mathbf{M_RE_S}$ if partial epimerization of the ionic precursors takes place and by $\mathbf{M_RM_S}$ and $\mathbf{M_RM_R}$ if they instead undergo a suprafacial 1,3-rearrangement. Again, the last isomer of the family, i.e., $\mathbf{M_SM_S}$, requires occurrence of both the epimerization and suprafacial 1,3-rearrangement of the direct ionic precursor of $\mathbf{M_SE_S}$.

In summary, 10 ethereal isomers can be conceivably produced from nucleophilic attack of the selected allylic alcohols on their oxonium derivatives. Their complete separation and unequivocal discrimination by spectroscopic techniques is virtually impossible. Thus, we resorted to an indirect method based on the analysis of the $(C_6H_{11})_2O$ product patterns from the gas-phase reaction of $\mathbf{M_S}$, $\mathbf{M_R}$, $\mathbf{E_R}$, and $\mathbf{E_S}$ (0.5 Torr) with free *exo*-1-methyl-*exo*-3-ethylallyl cations, generated at 40 °C (720 Torr) in methane by radiolytic protonation of *trans*, *trans*- or *cis*,*trans*-2,4-hexadiene (ca. 2 Torr). As observed in the preceding paper,[1b] gas-phase addition of free *exo*-1-methyl-*exo*-3-ethylallyl cations on alcohols gives rise exclusively to the corresponding trans ethers in almost equal isomeric proportions. Thus, gas-phase addition of free *exo*-1-methyl-*exo*-3-ethylallyl cations on one of the selected alcohols is expected to produce four different trans,trans ethers in comparable yields, e.g., $\mathbf{M_RM_S}$, $\mathbf{M_SM_R}$, $\mathbf{M_SE_R}$, and $\mathbf{M_SE_S}$ from the $\mathbf{M_S}$ alcohol, possibly accompanied by minor amounts of the other six trans,trans isomers. As a matter of fact, irrespective of the structure of the starting allylic alcohol, the gas-chromatographic analyses of the ethers produced from its reaction with the 1-methyl-3-ethylallyl cation are invariably characterized by the observation of only eight peaks, instead of the expected 10, arranged in two sets of four comparable signals with largely different intensity (Figure 1a−d). These product patterns suggest that two out of eight peaks are unresolved and each representative of a pair of isomeric ethers. Hence, six out of eight signals can be assigned to a single isomer. In this perspective, the following points are noted: (i) The only abundant peak observed in all systems is that labeled as 2. It necessarily contains a pair of isomeric ethers with all the possible group signatures, i.e., either (a) $\mathbf{M_RE_R} + \mathbf{M_SE_S}$, (b) $\mathbf{M_RM_S} + \mathbf{E_RE_S}$, or (c) $\mathbf{M_SE_R} + \mathbf{M_RE_S}$. {ii} Besides peak 2, the product patterns from either $\mathbf{E_R}$ and $\mathbf{E_S}$ exhibit two intense peaks labeled as 1 and 5, which must contain ethers with both group signatures. Thus, one of these peaks can be assigned to the $\mathbf{E_RE_R} + \mathbf{E_SE_S}$ enantiomeric pair and the other to the $\mathbf{E_RE_S}$ meso form. By exclusion, each of the peaks 3, 4, 6, 7, and 8 is ascribed to a single ethereal isomer. (iii) Peak 8 is attributed to $\mathbf{M_RM_S}$, since it is abundant in the product patterns from either $\mathbf{M_R}$ and $\mathbf{M_S}$. This assignment rules out the above hypothesis b at point i. (iv) Peaks 3 and 4 can be safely attributed to $\mathbf{M_RM_R}$ and $\mathbf{M_SM_S}$, respectively, since the first is abundant only in the systems with $\mathbf{M_R}$ and the latter only in those with $\mathbf{M_S}$, as the substrates. (v) Peak 6 corresponds to $\mathbf{M_RE_S}$, since it is abundant in the product patterns from either $\mathbf{M_R}$ and $\mathbf{E_S}$. Peak 7 is attributed to $\mathbf{M_SE_R}$, since it is abundant in the product patterns from either $\mathbf{M_S}$ and $\mathbf{E_R}$. These assignments rule out hypothesis c at point i, and therefore, peak 2 is attributed to the $\mathbf{M_RE_R} + \mathbf{M_SE_S}$ pair by exclusion.

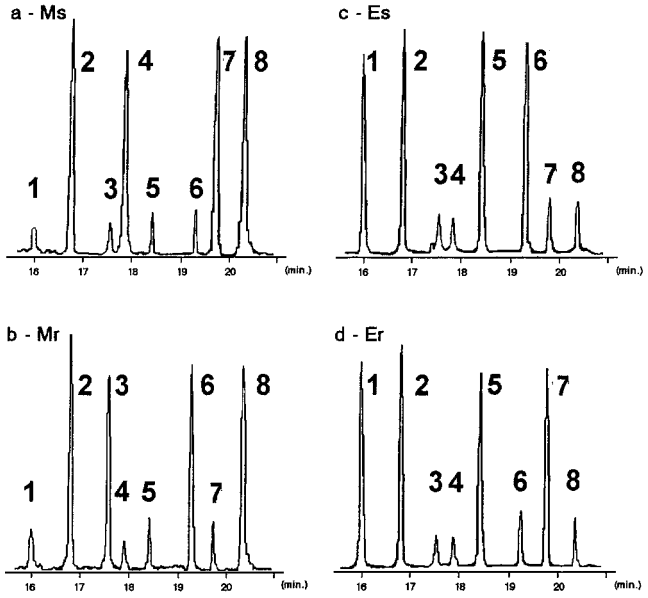


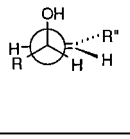
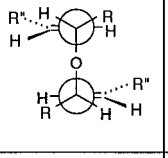
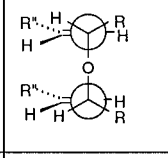
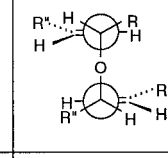
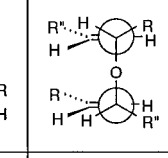
Figure 1. Gas chromatographic analyses of isomeric *trans*,*trans*-$(C_6H_{11})_2O$ ethers obtained at 40 °C and 720 Torr from the attack of free *exo*-1-methyl-*exo*-3-ethylallyl cations on $\mathbf{M_S}$ (a), $\mathbf{M_R}$ (b), $\mathbf{E_S}$ (c), and $\mathbf{E_R}$ (d) (peak numbering as in the text).

On the grounds of these assignments, it is noted that, under the used analytical conditions, the homochiral diastereomers are eluted ca. 2.5−3.0 min before the corresponding heterochiral forms. This is true for the homochiral enantiomers $\mathbf{M_RM_R}$ (peak 3) and $\mathbf{M_SM_S}$ (peak 4) eluted before the heterochiral meso form $\mathbf{M_RM_S}$ (peak 8) and for the homochiral enantiomeric pair $\mathbf{M_RE_R} + \mathbf{M_SE_S}$ (peak 2) relative to the heterochiral enantiomeric pair $\mathbf{M_RE_S}$ (peak 6) and $\mathbf{M_SE_R}$ (peak 7). This trend is consistent with the well-recognized performances of the gas-chromatographic column employed in the present study. On these grounds, peak 1 is attributed to the homochiral enantiomeric pair $\mathbf{E_RE_R} + \mathbf{E_SE_S}$ and peak 5 to the heterochiral meso form $\mathbf{E_RE_S}$. Further evidence in favor of this assignment will be provided below.

Results

Gas-phase γ-radiolysis of gaseous mixtures containing CH_3Cl, as the bulk gas, together with traces of the selected allylic alcohol (either $\mathbf{M_S}$ or $\mathbf{E_S}$) and of oxygen, used as a thermal radical scavenger, yields three sets of

Table 1. Relative Yields of the $(C_6H_{11})_2O$ Ethers from the Gas-Phase Attack of $(CH_3)_2Cl^+$ Ions on M_S and E_S at 313 K

Substrate (R,R")[a]	Product Distribution[b]			
				
M_S(R,R"=Me,Et)	M_SM_S(0.28)	M_RM_S(0.14)	M_SE_S(0.45)	M_SE_R(0.13)
E_S(R,R"=Et,Me)	E_SE_S(0.39)	E_RE_S(0.09)	M_SE_S(0.44)	M_RE_S(0.08)

a) CH_3Cl: 720 torr; O_2: 4 torr; M_S or E_S: 0.5-1.5 torr; added H_2O: 0-2 torr. Radiation dose: 2×10^4 Gy (dose rate: 1×10^4 Gy h^{-1}); b) Expressed as the ratio between each given $(C_6H_{11})_2O$ isomer and the combined yield of all recovered $(C_6H_{11})_2O$ isomers. The reported isomers account for ca.85% of the $(C_6H_{11})_2O$ family (see text). Each value is the average of several determinations, with an uncertainty level of ca.5%.

ethereal products, namely the expected $(C_6H_{11})_2O$ substitution products and the methoxy and chloromethoxy derivatives of the allylic substrate. Other conceivable products, such as the cis isomers of the above ethers and the isomers of the starting alcohol, were not found among the products despite a specific search. The absolute yields of the recovered products, expressed as the number of molecules M produced per 100 eV of energy absorbed by the gaseous mixture (G(M) values), were measured at 40 °C and for a total dose of 2×10^4 Gy (dose rate: 1×10^4 Gy h^{-1}). For both starting substrates, the overall G(M) of the $(C_6H_{11})_2O$ ethers ranges around 0.5, that of the methoxyhexenes around 1, and that of the chloromethoxyhexenes around 3. A drastic decrease of these G(M) values (>90%) is observed when the irradiated mixtures contain 0.4 mol % of the very strong $(C_2H_5)_3N$ base.

Table 1 reports the relative distribution of the major $(C_6H_{11})_2O$ ethers formed from either $\mathbf{M_S}$ or $\mathbf{E_S}$), whose combined G(M) value accounts for over 85% of all the $(C_6H_{11})_2O$ ethers recovered. The remaining 15% is equally distributed among the other $(C_6H_{11})_2O$ isomers. The assignment of the structures of Table 1 to the recovered products is based on the identification procedure illustrated in the previous section. In this connection, comparison of the product pattern from $\mathbf{E_S}$ with that from $\mathbf{M_S}$ further corroborates the assignment of peak 1 of Figure 1 to the homochiral enantiomeric pair $\mathbf{E_RE_R} + \mathbf{E_SE_S}$ and peak 5 to the heterochiral meso form $\mathbf{E_RE_S}$.

It should be noted that the relative distribution of all the $(C_6H_{11})_2O$ ethereal products is not appreciably affected by trebling the concentration of the allylic substrate or by adding to the gaseous mixtures up to 0.3 mol % of H_2O (see footnote a in Table 1).

Discussion

Origin of the Ethereal Products. Since we are interested in evaluating the relative extent of the substitution pathways of Scheme 2 from the $(C_6H_{11})_2O$ product patterns of Table 1, it is crucial to determine (i) the origin of the $\mathbf{M_SL^+}$ (or $\mathbf{E_SL^+}$) intermediates involved in the substitution reaction, (ii) their tendency to fragment or to isomerize before nucleophilic attack by the $\mathbf{M_S}$ (or $\mathbf{E_S}$) neutral, and (iii) the propensity of the ensuing $(C_6H_{11})_2OH^+$ substitution intermediates to rearrange before neutralization under the experimental conditions adopted.

Concerning point i, the low concentration of the allylic substrate (0.07−0.21 mol %) diluted with a large excess of CH_3Cl, excludes direct radiolysis of the starting compound as a significant route to the ethereal products. Occurrence of possible free-radical pathways in the irradiated samples is strongly inhibited by the presence of an efficient thermal radical scavenger, such as oxygen, which does not interfere with the competing ionic processes and whose role is testified by the marked depressing effect of ca. 0.4 mol % of the powerful ion trap $(C_2H_5)_3N$ (PA = 232.3 kcal mol^{-1})[43] on the alkylated product yields.

As pointed out in the preceding paper,[1b] ionization of the bulk CH_3Cl gas leads to the formation of $(CH_3)_2Cl^+$ and CH_2Cl^+ as the final ionic species completely unreactive toward the CH_3Cl molecules.[44−50] Thermal $(CH_3)_2Cl^+$ ($\Delta H_f°$ = 184 kcal mol^{-1})[43,51,52] behaves as a pure Lewis acid with a distinct affinity for all the n-type nucleophiles present in the gaseous mixture.[53−58] The allylic substrate (either $\mathbf{M_S}$ or $\mathbf{E_S}$) is the n-type nucleophile deliberately added to the gaseous systems, which, however, also contain H_2O as an ubiquitous impurity either initially introduced in the mixture together with its bulk components or formed from its radiolysis. The average stationary concentration of H_2O in the radiolytic systems is estimated to be approximately twice as large as that of

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Table 2. Gas-Phase Intramolecular Racemization and Isomerization of the Primary Oxonium Intermediates at 40 °C and 720 Torr

	rate constants[a] ($k_{rearr} \times 10^{-6}$ s^{-1})			relative distribution of isomeric structures $\%_{rearr}$[c]			
oxonium intermediate	k_{rac}	k_{iso}	τ[b] ($\times 10^8$ s)	$\mathbf{M_RL}^+$	$\mathbf{M_SL}^+$	$\mathbf{E_RL}^+$	$\mathbf{E_SL}^+$
$\mathbf{M_SL}^+$ (L = Me)	1.8	2.9	1.6	2.8	92.6	2.3	2.3
$\mathbf{E_SL}^+$ (L = Me)	1.9	3.4	1.7	2.8	2.8	3.1	91.3
$\mathbf{M_SL}^+$ (L = H)	1.8	1.2	1.5	2.7	95.5	0.9	0.9
$\mathbf{E_SL}^+$ (L = H)	1.8	1.2	1.6	1.0	1.0	2.9	95.1

[a] Reference 1a,b. Rearrangement of $\mathbf{M_SH}^+$ is estimated by using the racemization and isomerization rate constants measured for $\mathbf{E_SH}^+$ (ref 1a). [b] Oxonium ion lifetime, τ, calculated from the reciprocal of the first-order collision constant between the oxonium ion and its allylic alcohol precursor (see text). [c] $\%_{rearr} = 100(1 - e^{-k_{rearr}\tau})$.

the allylic substrate.[1a,b] Thus, taking into account the relatively high diffusion rate of H_2O in the gaseous medium, a significant fraction of the radiolytic $(CH_3)_2Cl^+$ ions, instead of attacking the allylic alcohol yielding the corresponding O-methylated derivative (either $\mathbf{M_SMe}^+$ or $\mathbf{E_SMe}^+$),[59] is trapped by H_2O, giving rise to $CH_3OH_2^+$. This ion is able to transfer a proton to the allylic alcohol yielding the O-protonated derivative (either $\mathbf{M_SH}^+$ or $\mathbf{E_SH}^+$).[59] It is concluded that the $(C_6H_{11})_2O$ products of Table 1 may arise from the nucleophilic attack of the allylic substrate on two different ionic intermediates, namely $\mathbf{M_SL}^+$ (or $\mathbf{E_SL}^+$) (L = H, CH_3; Scheme 2), formed in the gaseous mixtures in proportions depending upon the relative concentration of their alcoholic precursor and of H_2O.[59]

Concerning point ii, previous studies[1a,b] indicate that, at 40 °C and 720 Torr, fast collisional quenching of the $\mathbf{M_SL}^+$ (or $\mathbf{E_SL}^+$) intermediate of Scheme 2 hinders its unimolecular dissociation to the free 1-methyl-3-ethylallyl cation and LOH (L = H, CH_3).[59] This is demonstrated by the marked difference between the product patterns of Figure 1 and the relevant product distributions of Table 1. However, by the time τ of its first encounter with $\mathbf{M_S}$ (or $\mathbf{E_S}$), thermalized $\mathbf{M_SL}^+$ (or $\mathbf{E_SL}^+$) may undergo partial unimolecular racemization and regioisomerization via independent pathways.[1a,b] The collision time τ is taken as the reciprocal of $k_{rctn} = k_{coll}[\mathbf{M_S}$ (or $\mathbf{E_S}$)], where k_{coll} is the collision rate constant between $\mathbf{M_SL}^+$ (or $\mathbf{E_SL}^+$) and $\mathbf{M_S}$ (or $\mathbf{E_S}$) at 40 °C as estimated by Su and Chesnavitch's trajectory calculation method.[60] The extent of racemization and regioisomerization at 40 °C and 720 Torr of $\mathbf{M_SL}^+$ (or $\mathbf{E_SL}^+$) by the time τ of its first encounter with $\mathbf{M_S}$ (or $\mathbf{E_S}$) is reported in Table 2. Within the reasonable assumption that the nucleophilic displacements of Scheme 2 take place with high efficiency on all the isomeric oxonium intermediates, the oxonium ion isomeric distribution of Table 2 indicates that the $(C_6H_{11})_2O$ products of Table 1 predominantly arise from the attack of $\mathbf{M_S}$ (or $\mathbf{E_S}$) on the primary $\mathbf{M_SL}^+$ (or $\mathbf{E_SL}^+$) intermediates.[61] Incidentally, the lack of any significant rearrangement in the $\mathbf{M_SL}^+$ (or $\mathbf{E_SL}^+$) intermediate (Table 2), coupled with the different product distributions of Table 1, exclude the conceivable hypothesis that substitution paths of Scheme 2 involve terbody $[C_6H_{11}^+ \cdot CH_3OH \cdot ROH]$ complexes.[62]

Reaction Mechanism and Orientation. In light of the above considerations, several mechanistic hypotheses can be advanced for the formation of the $(C_6H_{11})_2O$ products of Table 1, which may arise from the following: (a) a single substitution mechanism for all substrates (either S_N2 or S_N2'; Scheme 2), followed by extensive rearrangement of the ensuing $(C_6H_{11})_2OH^+$ intermediates (point iii of the previous section); {b) different mechanistic pathways, depending upon the nature of the leaving LOH group, e.g., the S_N2 route with LOH=CH_3OH and the S_N2' one with LOH=H_2O; (c) the occurrence of competing S_N2 and the S_N2' pathways for all substrates.

Concerning hypothesis a, if only a single mechanism, e.g., S_N2, were operative on $\mathbf{M_SL}^+$ (or $\mathbf{E_SL}^+$) (L = H, CH_3), the abundant formation of the $\mathbf{M_SE_S}$ ether from $\mathbf{E_S}$ would be explained only by assuming extensive rearrangement of the primary S_N2 oxonium intermediate, i.e., the O-protonated $\mathbf{E_SE_S}$, prior to its neutralization. In this frame, extensive isomerization of the O-protonated $\mathbf{E_SE_S}$ would eventually lead to either the $\mathbf{M_SE_S}$ + $\mathbf{M_RE_S}$ diastereomeric pair, if involving the intracomplex motion of one of its $\mathbf{E_S}$ moieties around the 1-methyl-3-ethylallyl cation residue, or the $\mathbf{M_RE_S}$ isomer, if involving the 1,3-suprafacial shift of one of its $\mathbf{E_S}$ groups.[1a,b] The small yield of the $\mathbf{M_RE_S}$ product from $\mathbf{E_S}$ denotes the poor tendency of the O-protonated $\mathbf{E_SE_S}$ intermediate to rearrange intramolecularly (point iii), thus pointing to the $\mathbf{M_SE_S}$ product as mainly arising from the S_N2' mechanism (hypothesis c). A similar reasoning excludes that the products of Table 1 arise exclusively from the S_N2' reaction. In fact, in this case, the abundant formation of the $\mathbf{E_SE_S}$ ether from $\mathbf{E_S}$ would be explained only by assuming extensive rearrangement of the primary S_N2' oxonium intermediate, i.e., the O-protonated $\mathbf{M_SE_S}$, prior to its neutralization. In this frame, extensive isomerization of the O-protonated $\mathbf{M_SE_S}$ would eventually lead to either the $\mathbf{E_SE_S}$ + $\mathbf{E_RE_S}$ diastereomeric pair, if involving the intracomplex motion of its $\mathbf{E_S}$ moiety around the 1-methyl-3-ethylallyl cation residue, or the $\mathbf{E_RE_S}$ isomer, if involving the 1,3-suprafacial shift of its

(59) As pointed out in previous studies (ref 1), the conceivable intracluster CH_3OH-to-H_2O displacement in the ion−neutral complex between the O-protonated allylic alcohol and CH_3OH ($\Delta H°$ = ca. 9 kcal mol^{-1}) (refs 43, 51, and 52), arising from the exothermic $CH_3OH_2^+$ protonation of the allylic substrate ($\Delta H°$ = ca. 23 kcal mol^{-1}) (ref 43), is a rather inefficient process. On the grounds of the standard heats of formation of the $\mathbf{M_S}$ and $\mathbf{E_S}$ alcohols ($\Delta H_f°$ = ca. −49 kcal mol^{-1}) and of their methyl ethers ($\Delta H_f°$ = ca. −44 kcal mol^{-1}), estimated according to the group additivity method (Benson, S. W. *Thermochemical Kinetics*; Wiley: New York, 1968), O-methylation of $\mathbf{M_S}$ and $\mathbf{E_S}$ by $(CH_3)_2Cl^+$ is calculated to be ca. 42 kcal mol^{-1} exothermic.

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(61) Even considering the partial racemization and regioisomerization at 40 °C and 720 Torr of $\mathbf{M_SL}^+$ (or $\mathbf{E_SL}^+$) by the time of its encounter with $\mathbf{M_S}$ (or $\mathbf{E_S}$) (Table 2), the ether distribution of Table 1 is accounted for by the following competing nucleophilic pathways. With $\mathbf{M_S}$: $S_N2' = 58\%$ ($\gamma_a = 47\%$; $\gamma_s = 11\%$); $S_N2 = 42\%$ ($\alpha_r = 29\%$; $\alpha_i = 13\%$). With $\mathbf{E_S}$: $S_N2' = 53\%$ ($\gamma_a = 47\%$; $\gamma_s = 6\%$); $S_N2 = 47\%$ ($\alpha_r = 40\%$; $\alpha_i = 7\%$). These regio- and stereochemistry factors differ from those directly obtained from the figures of Table 1 by a value that falls within the measurement uncertainty level (ca. 5%) and, therefore, can be considered as coinciding.

(62) For examples of gas-phase terbody complexes, see: Audier, H. E.; Berthomieu, D.; Leblanc, D.; McMahon, T. B.; Morton, T. H. *Int. J. Mass Spectrom. Ion Proc.* **1992**, *117*, 327.

$\mathbf{E_S}$ group.[1a,b] Besides, rearrangement of the O-protonated $\mathbf{M_SE_S}$ would also lead to the $\mathbf{M_SM_S} + \mathbf{M_RM_S}$ diastereomeric pair, if involving the intracomplex motion of its $\mathbf{M_S}$ moieties around the 1-methyl-3-ethylallyl cation residue, or the $\mathbf{M_RM_S}$ isomer, if involving the 1,3-suprafacial shift of its $\mathbf{M_S}$ group.[1a,b] The small yields of the $\mathbf{E_RE_S}$, $\mathbf{M_SM_S}$, and $\mathbf{M_RM_S}$ products from $\mathbf{E_S}$ denotes the low propensity of the S_N2' O-protonated $\mathbf{M_SE_S}$ intermediate to rearrange (point iii), thus pointing to the $\mathbf{E_SE_S}$ product as mainly arising from the S_N2 mechanism (hypothesis c). Similar conclusions also apply to the nucleophilic displacement mechanisms operative in the systems with $\mathbf{M_S}$, as the allylic substrate. It is concluded that no significant intramolecular rearrangement takes place in the primary $(C_6H_{11})_2OH^+$ substitution intermediates before neutralization (point iii), thus ruling out the mechanistic hypothesis a as responsible for the product patterns of Table 1.

Concerning hypothesis b, the insensitivity of the $(C_6H_{11})_2O$ pattern of Table 1 by a ca. 6-fold variation of the [$\mathbf{M_S}$ (or $\mathbf{E_S}$)]/[H_2O] ratio in the irradiated mixtures suggests that the isomeric distribution of their $(C_6H_{11})_2$-OH^+ precursors does not depend appreciably on the stationary [$\mathbf{M_SMe}^+$ (or $\mathbf{E_SMe}^+$)]/[$\mathbf{M_SH}^+$ (or $\mathbf{E_SH}^+$)] ratio and that, therefore, the displacement takes place with a similar regio- and stereochemistry on both $\mathbf{M_SL}^+$ (or $\mathbf{E_SL}^+$) (L = H, CH_3), irrespective of the nature of the LOH leaving group (hypothesis c). It is therefore concluded that the $(C_6H_{11})_2O$ isomeric distribution of Table 1 essentially reflects the relative extent of the four competing substitution pathways reported in Scheme 2.[61] Accordingly, the figures in Table 1 reveal that, in the gas phase, nucleophilic substitution by $\mathbf{M_S}$ (or $\mathbf{E_S}$) on $\mathbf{M_SL}^+$ (or $\mathbf{E_SL}^+$) (L = H, CH_3) proceeds by a concerted S_N2' mechanism (58%, with $\mathbf{M_S}$; 52%, with $\mathbf{E_S}$) slightly prevailing over the classical S_N2 reaction (42%, with $\mathbf{M_S}$; 48%, with $\mathbf{E_S}$). This regioselectivity compares well with that measured in the acid-promoted nucleophilic substitution by CH_3OH on strictly related allylic alcohols (54−57% S_N2'; 43−46% S_N2) under comparable experimental conditions.[28] Besides, in all cases investigated, the S_N2 reaction predominantly proceeds via retention of the configuration of the C_α center ($\alpha_r/\alpha_i = 2.1$, with $\mathbf{M_S}$; 4.2, with $\mathbf{E_S}$), whereas the S_N2' reaction displays a distinct anti stereoselectivity ($\gamma_a/\gamma_s = 3.4$, with $\mathbf{M_S}$; 5.5, with $\mathbf{E_S}$).

Comparison with Theoretical Predictions. The present gas-phase results provide the first experimental evidence of the intrinsic factors governing the S_N2' stereochemistry. According to the most recent theoretical papers dealing with this matter,[23−26] the S_N2' stereochemistry is influenced by both electronic factors and by Coulombic interactions in the transition structure. Stereoelectronic factors long enjoyed considerable importance among theoretical chemists, who explained the syn preference, frequently observed in solution, in terms of the "aromaticity" of the cyclic syn transition structure,[30−38] prevented in the open anti transition structure. Additional, if minor, stabilization of the syn transition structure, relative to the *anti* one, derives from the lack of the inversion of the central C atom in the *syn*-S_N2' reaction, which instead is operative in the *anti*-S_N2' attack.[26,39] In this context, stereoelectronic factors satisfactorily accounted for the preferred syn stereochemistry often observed in solution, so that no other arguments were considered by theoreticians. A more comprehensive evaluation of the factors governing the S_N2' stereochemistry was due to Yates et al. who,[40] on the basis of ab initio calculations, first pointed out that, in the isolated state, the S_N2' stereochemistry may be controlled by nonbonded attractions and electrostatic interactions. They concluded that the anti mode of substitution should be favored in the S_N2' transition structures with NuH and LG bearing the same charge, whereas the syn mode of substitution should prevail in the S_N2' transition structures with NuH and LG bearing opposite charges. Along this line, Bach et al.[24] and Park et al.[25] pointed out that the *syn*-S_N2' route (γ_s in Scheme 1) should be the least favored of the four possible pathways when NuH = halide ion attacks 3-halogenopropene, whereas it should become the preferred reaction path with NuH = NH_3.[24] These indications find a first experimental foundation in the marked anti stereoselectivity observed in the present gas-phase S_N2' reactions. Accordingly, the main intrinsic factor governing the stereochemistry of the gas-phase S_N2' reaction investigated is identified in the destabilizing repulsive interactions in the transition structure between the positively charged NuH and LG moieties and not in the much less important stereoelectronic factors. Hence, the experimental evidence supports Bach et al.'s conclusion[24] that "the theoretical rationale resulting in an infatuation with a preferential *syn*-S_N2' is unfounded" and Park et al.'s recommendation[25] that "explicit consideration of nonbonded interactions, ion pairing, and solvation effects is essential for an adequate explanation of the preferred *syn*-S_N2' stereochemistry in solution".

Concerning the gas-phase S_N2 reaction, the results of Table 1 are consistent with an S_N2 process taking place with predominant retention of the configuration of the C_α center (α_r in Scheme 1), in contrast with the widely accepted notion that these processes must involve inversion of the configuration of the reaction center.[55,56,63−69] As pointed out in related gaseous systems,[1a,b,70] this behavior is due to the considerable C_α−O bond cleavage in the oxonium intermediate, e.g., $\mathbf{M_SL}^+$, and to the consequent location of a significant fraction of the positive charge over the C_α and C_γ centers of the allylic moiety. This effect is further enhanced in the proton-bonded complex between the oxonium intermediate and NuH. In it, the large fraction of positive charge developed in the allylic moiety of the oxonium intermediate and the high local concentration of NuH allows the occurrence of the intracomplex frontside NuH-to-LOH ligand-switching reaction, well before the attack by an external NuH molecule. Intracomplex frontside NuH-to-LOH ligand switching at C_α supersedes any conceivable intracomplex backside diplacement, since the energy-demanding rupture of the proton bond is required in the latter case.[1c] This view is further corroborated by the observation that the α_r/α_i ratio is twice as large in the proton-bound

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[$\mathbf{E_S}\mathbf{L}^{+\bullet}\mathbf{E_S}$] adduct ($\alpha_r/\alpha_i = 4.2$) than in the [$\mathbf{M_S}\mathbf{L}^{+\bullet}\mathbf{M_S}$] one ($\alpha_r/\alpha_i = 2.1$). In fact, this observation conforms to the expectation that the efficiency of the frontside NuH-to-LOH ligand switching increases with the fraction of positive charge at the C_α reaction center, namely from [$\mathbf{M_S}\mathbf{L}^{+\bullet}\mathbf{M_S}$] to [$\mathbf{E_S}\mathbf{L}^{+\bullet}\mathbf{E_S}$]. That the NuH-to-LOH ligand switching involves predominantly the C_α center of the oxonium substrate, and not its C_γ atom, it is demonstrated by the large yield difference between the retained S_N2 products and the syn S_N2' ones (Table 1). Thus, occurrence of the S_N2 reaction in these systems is determined by preliminary proton bonding between the NuH and the LG. Instead, direct interaction between the nucleophile and the π-LUMO of the oxonium intermediate promotes the S_N2' reaction, whose stereochemistry is mainly determined by repulsive Coulombic interaction in the transition structure.

Conclusions

(A) The present results confirm previous experimental[27−29] and theoretical[23−25] indications that concerted acid-induced S_N2' reactions are feasible in the gas phase and efficiently compete with the classical S_N2 processes. Competition between the S_N2 and S_N2' is essentially determined by the orienting properties of the oxonium intermediate toward the incoming nucleophile. Thus, the S_N2' reaction is governed by preliminary interaction of NuH with the π-LUMO of the oxonium intermediate, whereas the S_N2 process involves preliminary proton bonding between the two reactants.

(B) The experimental evidence indicates that the transition structure of the concerted S_N2' reaction investigated is characterized by a preferred anti juxtaposition between the positively charged NuH and LG moieties. The competing S_N2 reaction proceeds through a NuH-to-LG ligand-switching reaction with formation of the retained product.

(C) The experimental results confirm previous theoretical predictions that, in the gas phase, stereoelectronic factors play a very minor role in determining the S_N2' stereochemistry.[23−26] The preferred anti stereochemistry is determined almost exclusively by the absence, in the relevant transition structure, of the repulsive Coulombic interactions between the positively charged NuH and LG moieties, which are instead operative in the *syn*-S_N2' transition structure. Since preliminary proton bonding between NuH and the oxonium intermediate mainly promotes the occurrence of the S_N2 reaction, it has no influence on the S_N2' stereochemistry.[23−25]

(D) The present experiments demonstrate that, in solution, the low rates of S_N2' reactions and their preferred syn stereochemistry are a consequence of solvation and ion pairing effects and that any basic treatment of these reactions without explicit consideration of these environmental effects is meaningless.

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