Chiral Ions in the Gas Phase, Part 7[≠]

Wagner–Meerwein Rearrangements in the Gas Phase: Deuterium Isotope Effects on Acid-Induced Dissociation of Optically Active Phenylpropanols

Maurizio Speranza* and Antonello Filippi[a]

Abstract: The deuterium isotope effects on the kinetics of H_2O loss from O-protonated (*S*)-1-phenyl-2-propanol ($\mathbf{1s}_{H^+}$) and (*S*)-2-phenyl-1-propanol ($\mathbf{2s}_{H^+}$) have been investigated in the gas phase at 750 Torr and at 25 °C. The measured primary and secondary α-D_1, β-D_1, and β'-D_3 kinetic isotope effects provide conclusive evidence on the detailed mechanism of the gas-phase dissociation of $\mathbf{1s}_{H^+}$ and $\mathbf{2s}_{H^+}$; this involves competing anchimeric assistance from all the groups adjacent to the reaction center (C_α). Their analysis, combined with that of the relevant activation parameters reported in the preceding paper, is consistent with: i) a phenyl-group participation transition state (TS) structure, which is placed rather early along the reaction coordinate and in which the partial C_α–OH_2^+ bond cleavage is coupled with a weak Ph-C_α interaction, ii) a tight TS structure for the β-hydrogen participation, in which a limited C_α–OH_2^+ bond cleavage is fully outweighed by the advanced H(D)–C_α bonding, and iii) a borderline TS structure for the β-methyl group participation in $\mathbf{2s}_{H^+}$, in which intense Me–C_α bonding is coupled with a pronounced C_α–OH_2^+ bond elongation. The values of the primary and secondary α-D_1, β-D_1, and β'-D_3 kinetic isotope effects, measured in the present gas-phase investigation, are discussed and compared with those of related gas-phase and solvolysis reactions.

Keywords: anchimeric assistance · chirality · gas-phase chemistry · kinetic isotope effects · phenonium ions

Introduction

In the preceding paper of this issue,[1] the kinetics and the mechanisms of the unimolecular H_2O loss from O-protonated (*S*)-1-phenyl-2-propanol ($\mathbf{1s}_{H^+}$) and O-protonated (*S*)-2-phenyl-1-propanol ($\mathbf{2s}_{H^+}$; Figure 1) were investigated in the gas phase, that is, under conditions excluding nucleophilic assistance by the solvent (k_S), which generally interferes with anchimeric assistance (k_Δ) in analogous β-arylalkyl solvolyses.[2–5] The results are consistent with a gas-phase unimolecular dissociation of $\mathbf{1s}_{H^+}$ and $\mathbf{2s}_{H^+}$ that is anchimerically assisted by all the groups adjacent to the leaving H_2O moiety, that is, the phenyl group and the hydrogen atom in $\mathbf{1s}_{H^+}$, and the phenyl and methyl groups, and the hydrogen atom in $\mathbf{2s}_{H^+}$. According to the relevant activation parameters of Figure 1, kinetic competition among these genuine k_Δ processes appears to be governed, in the gas phase, more by entropic than by enthalpic factors. In view of the relative stability of the $\mathbf{1s}_{H^+}$ and $\mathbf{2s}_{H^+}$ rotamers (Scheme 1), the largely different pre-exponential terms for their dissociation pathways cannot be accounted for by conformational equilibria. Rather, they must be determined by the specific features of the corresponding transition state (TS) structures and their positions along the dissociation coordinate.

The aim of the present investigation is to characterize the nature of the TS structures involved in the potential energy profiles of Figure 1. Primary and secondary kinetic isotope effects are widely recognized as being among the most reliable tools for investigating reaction mechanisms, in the sense that they provide unique and direct information about the TS structure of the reaction.[6] In this context, deuterium primary (PKIEs) and secondary kinetic effects (SKIEs) have been extensively applied in the condensed phase for establishing the mechanism of β-arylalkyl solvolysis, especially in connection with the discrimination between anchimeric-assisted (k_Δ) and solvent-assisted (k_S) reaction profiles.[4c, 6–8]

Following the same approach, the competition kinetics of the unimolecular H_2O loss from $\mathbf{1s}_{H^+}$ and $\mathbf{2s}_{H^+}$ and their deuterated analogues have been examined in the gas phase, namely, in the absence of solvent assistance (k_S), under

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[≠] Part 6: A Filippi, M. Speranza, preceding paper in this issue.

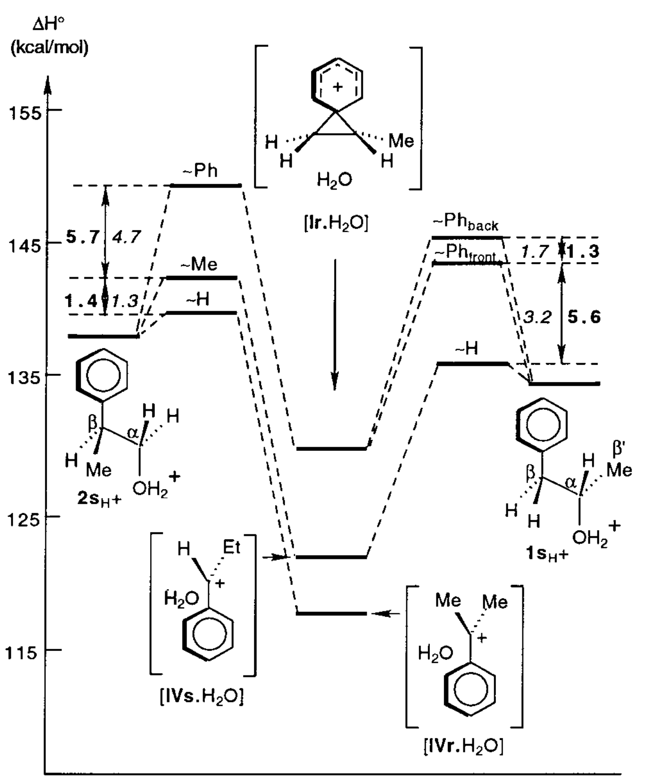
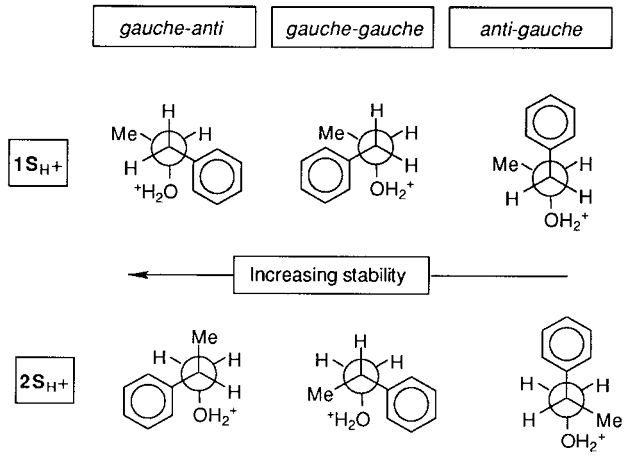


Figure 1. Energy profiles for adjacent group participations to H_2O loss in O-protonated (*S*)-1-phenyl-2-propanol (**1**s_{H^+}) and O-protonated (*S*)-2-phenyl-1-propanol (**2**s_{H^+}). The bold figures refer to the ΔE^* and the italic ones to $\Delta \log A^*$ (ref. [1]).

Abstract in Italian: *Gli effetti dell'isotopo deuterio sulla cinetica di eliminazione di H_2O in protonati all'ossigeno (S)-1-fenil-2-propanolo (**1**s_{H^+}) e (S)-2-fenil-1-propanolo (**2**s_{H^+}) sono stati studiati in fase gassosa a 750 Torr ed a 25°C. L'effetto isotopico primario e gli effetti isotopici secondari tipo α-D_1, β-D_1, e β'-D_3 forniscono un quadro conclusivo del meccanismo di dissociazione di **1**s_{H^+} e **2**s_{H^+} in fase gassosa, che procede attraverso l'assistenza anchimerica da parte di tutti i gruppi adiacenti al centro di reazione (C_α). L'analisi degli effetti isotopici, combinata con quella dei corrispondenti parametri di attivazione riportati nel lavoro precedente, indica: i) una collocazione piuttosto anticipata sulla coordinata di reazione per estato di transizione (TS) della partecipazione del gruppo fenile in cui una debole interazione fra il gruppo Ph ed il centro C_α corrisponde alla estesa rottura del legame C_α–OH_2^+; ii) una struttura compatta per lo TS della partecipazione dell'atomo di idrogeno in beta in cui una intensa interazione fra l'atomo H_β ed il centro C_α corrisponde ad una limitata rottura del legame C_α–OH_2^+; iii) una struttura intermedia per lo TS della partecipazione del gruppo Me metile in beta in cui una intensa interazione fra il gruppo Me_β ed il centro C_α corrisponde ad una pronunciata elongazione del legame C_α–OH_2^+. I valori degli effetti isotopici primario e secondari, misurati negli esperimenti in fase gassosa, sono esaminati alla luce di corrispondenti dati raccolti sia in fase gassosa che in soluzione.*



Scheme 1. Order of stability of the conformers of O-protonated (*S*)-1-phenyl-2-propanol and (*S*)-2-phenyl-1-propanol.

experimental conditions as those outlined in the preceding paper, with the only exception of the use of $CH_3{}^{16}OH$, instead of $CH_3{}^{18}OH$, as the external nucleophile.[1] Thereby we hoped to elucidate the nature of the TS structures involved in the neighboring-group assistance in the H_2O loss and their sensitivity to environmental effects by comparing the gas-phase deuterium PKIEs and SKIEs with those measured in analogous solvolysis processes.

Experimental Section

Materials: Methane and oxygen were high purity gases from Matheson and were used without further purification. (*S*)-1-phenyl-2-propanol (**1s**) and its *R*-enantiomer (**1r**), (*S*)-2-phenyl-1-propanol (**2s**) and its *R*-enantiomer (**2r**), (*S*)- and (*R*)-1-phenyl-1-propanol, and 2-phenyl-2-propanol were research grade chemicals from Aldrich. The (*R,R*)/(*S,S*)-racemate of 1-phenyl-1-deutero-2-propanol (**1β***) was synthesized, together with the (*R,S*)/(*S,R*) racemate of 1-phenyl-2-deutero-1-propanol, by reaction of *trans*-β-methyl-styrene with $LiAlD_4$ and subsequent oxidation with hydrogen peroxide.[9] The same procedure was employed to prepare the (*R*)/(*S*)-racemate of 2-phenyl-2-deutero-1-propanol (**2β**) from α-methyl-styrene. The (*R*)/(*S*)-racemate of 1-phenyl-2-deutero-2-propanol (**1α**) was prepared by $LiAlD_4$ reduction of phenylacetone. The same reaction with the (*R*)/(*S*)-racemate of 2-phenylpropionaldehyde yields the mixture of the (*R,R*)/(*S,S*)- and (*R,S*)/(*S,R*)-racemates of 2-phenyl-1-deutero-1-propanol (**2α**). The (*R*)/(*S*)-racemate of 1-phenyl-3,3,3-trideutero-2-propanol (**1βββ**) was synthesized by treating phenylacetaldehyde with CD_3MgI. The deuterium content of these labeled alcohols was determined by NMR spectroscopy and GLC–MS analysis. All of them display a D content exceeding 98%. The equimolar mixture of both (*R,R*)/(*S,S*)- and (*R,S*)/(*S,R*)-racemates of 1-phenyl-1-deutero-2-propanol (**1β**) was obtained, together with the unlabeled product (***rac*-1**) and minor amounts of the (*R*)/(*S*) racemate of 1-phenyl-1,1-dideutero-2-propanol (**1ββ**), by D_2O exchange of phenylacetone in dioxane/pyridine solutions and subsequent $LiAlH_4$ reduction of the variously deuterated ketones.[8a] NMR and GLC–MS analyses are consistent with a [***rac*-1**]:[**1β**]:[**1ββ**] = 4.8:3.2:1.0 distribution. The methyl ethers of the above alcohols were synthesized by the dimethyl sulfate method, and their configurations were assigned according to the starting alcohol.[10] In this way, (*S*)- (**3s**) and (*R*)-1-phenyl-2-methoxypropane (**3r**) were obtained from **1s** and **1r**, respectively, (*S*)- (**4s**) and (*R*)-2-phenyl-1-methoxypropane (**4r**) from **2s** and **2r**, respectively, (*S*)- (**5s**) and (*R*)-1-phenyl-1-methoxypropane (**5r**) from (*S*)- and (*R*)-1-phenyl-1-propanol, respectively, and 2-phenyl-2-methoxypropane (**6**) from 2-phenyl-2-propanol. In the same way, all the isomers of 1-phenyl-2-deutero-2-methoxypropane (**3α**), 1-phenyl-1-deutero-2-methoxypropane (**3β**), 1-phenyl-1,1-dideutero-2-methoxypropane (**3ββ**), and 1-phenyl-3,3,3-trideutero-2-

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Table 1. Characteristic mass spectrometric peaks of the radiolytic products.

Isotopomer	Symbol[a]	*m*/*z* (parent)	*m*/*z* (fragment)
1-Phenyl-2-methoxypropanes (**3**):			
$PhCH_2CH(CH_3)OMe$	***rac*-3**	150 ($[PhCH_2CH(CH_3)OMe]^{\cdot+}$)	59 ($[MeOCHCH_3]^+$)
$PhCH_2CD(CH_3)OMe$	***3α***	151 ($[PhCH_2CD(CH_3)OMe]^{\cdot+}$)	60 ($[MeOCDCH_3]^+$)
$PhCHDCH(CH_3)OMe$	***3β***	151 ($[PhCHDCH(CH_3)OMe]^{\cdot+}$)	59 ($[MeOCHCH_3]^+$)
$PhCD_2CH(CH_3)OMe$	***3ββ***	152 ($[PhCD_2CH(CH_3)OMe]^{\cdot+}$)	59 ($[MeOCHCH_3]^+$)
$PhCH_2CH(CD_3)OMe$	***3βββ***	153 ($[PhCH_2CH(CD_3)OMe]^{\cdot+}$)	62 ($[MeOCHCD_3]^+$)
1-Phenyl-1-methoxypropanes (**5**):			
$PhCH(OMe)CH_2CH_3$	***rac*-5**	150 ($[PhCH(OMe)CH_2CH_3]^{\cdot+}$)	121 ($[PhCH(OMe)]^+$)
$PhCD(OMe)CH_2CH_3$	***5α***	151 ($[PhCD(OMe)CH_2CH_3]^{\cdot+}$)	122 ($[PhCD(OMe)]^+$)
$PhCH(OMe)CHDCH_3$	***5β***	151 ($[PhCH(OMe)CHDCH_3]^{\cdot+}$)	121 ($[PhCH(OMe)]^+$)
$PhCD(OMe)CHDCH_3$	***5αβ***	152 ($[PhCD(OMe)CHDCH_3]^{\cdot+}$)	122 ($[PhCD(OMe)]^+$)
$PhCH(OMe)CH_2CD_3$	***5γγγ***	153 ($[PhCH(OMe)CH_2CD_3]^{\cdot+}$)	121 ($[PhCH(OMe)]^+$)
2-Phenyl-2-methoxypropanes (**6**):			
$PhC(CH_3)_2OMe$	**6**		135 ($[PhC(CH_3)OMe]^+$)
$PhC(CH_3)(CH_2D)OMe$	***6β***		136 ($[PhC(CH_2D)OMe]^+$) 135 ($[PhC(CH_3)OMe]^+$)

[a] The greek letter denotes the position of the label relative to the methoxy group.

methoxypropane (***3βββ***) were synthesized from ***1α***, ***1β***, ***1ββ***, and ***1βββ***, respectively. All the isomers of 2-phenyl-1-deutero-1-methoxypropane (***4α***) and of 2-phenyl-2-deutero-1-methoxypropane (***4β***) were prepared from ***2α*** and ***2β***, respectively. Finally, the 1-phenyl-2-deutero-1-methoxypropanes (***5β***) were produced from the (*R*,*S*)/(*S*,*R*) racemate of 1-phenyl-2-deutero-1-propanol. All the alcoholic and the ethereal compounds were purified by preparative GLC on a 2 m long, 4 mm inner diameter, stainless steel column packed with 10% SP-1000 on 100-120 Supelcoport, at 180 °C. Their final purity exceeded 99.95%. The identity of the above alcohols and of their methyl ethers was verified by NMR spectroscopy and their purity assayed by GLC and GLC–MS on the same columns employed for the analysis of the irradiated mixtures.

Procedure: The experimental techniques used for the preparation of the gaseous mixtures and their irradiation are described in the preceding paper.[1] The irradiations were carried out at 25 °C in ^{60}Co γ source to a dose of 2×10^4 Gy at a rate of 1×10^4 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. The radiolytic products were analyzed by GLC, with a Perkin–Elmer 8700 gas chromatograph equipped with a flame ionization detector, on a 25 m long, 0.25 mm inner diameter, MEGADEX DACTBS-β (30% diacetyl-*tert*-butylsilyl-β-cyclodextrin in OV1701) fused silica column operated at temperatures ranging from 40 to 170 °C, 4 °C min^{-1}. The products were identified by comparison of their retention volumes with those of authentic standard compounds and their identity confirmed by GLC–MS, with a Hewlett–Packard 5890A gas chromatograph in line with an HP 5970B mass spectrometer (GC-MS). Their yields were determined from the areas of the corresponding eluted peaks, by use of the internal standard (i.e. benzyl alcohol) method and individual calibration factors to correct for the detector response. Blank experiments were carried out to exclude the occurrence of thermal isomerization and racemization of the starting alcohols and the corresponding methyl ethers within the temperature range investigated.

Results

As described in the preceding paper,[1] γ irradiation at room temperature of gaseous CH_4 (750 Torr) mixtures containing alcohol **1s**, as the substrate, O_2 (4 Torr), as a thermal radical scavenger, and $CH_3{}^{16}OH$ (ca. 3 Torr), as an external nucleophile, yields the (*S*)-1-phenyl-2-methoxypropanes (**3s**) and the racemate of 1-phenyl-1-methoxypropane (***rac*-5**) as predominant products. If the starting alcohol is **2s**, the major products are (*S*)-1-phenyl-2-methoxypropanes (**3s**), the racemate of 1-phenyl-1-methoxypropane (***rac*-5**), and 2-phenyl-2-methoxypropane (**6**).

The presence and the specific position of the deuterium label in the radiolytic ethers, obtained from mixtures containing the deuterated isotopomers of the same starting alcohols, are determined from their 70 eV MS fragmentation patterns, which are dominated by C_α–C_β bond fission. The ionic fragments used for these purposes are listed in Table 1.

Table 2 displays the relative abundance of the characteristic mass spectrometric signals (Table 1) of isotopomeric ethers **3** and **5**, obtained from γ irradiation of mixtures of alcohol **1s** and its deuterated isotopomers as the starting substrates. Table 3 shows the relative abundance of the characteristic mass-spectrometric fragments (Table 1) of isotopomeric ethers **3**, **5**, and **6**, recovered from mixtures with alcohol **2s** and its deuterated isotopomers as the starting compounds. The figures in the tables represent mean ratios obtained from many mass spectrometric measurements with several separate irradiations carried out under the same experimental conditions, whose reproducibility is expressed by the uncertainty level quoted.

Table 2. Relative abundance of characteristic mass spectrometric fragments of the products from the gas-phase attack of $C_nH_5{}^+$ ($n = 1, 2$) ions on **1s** and its deuterated isotopomers.

System composition [Torr][a]			Products	Peak intensity ratios[b]
H-substrate	D-substrate	$CH_3{}^{16}OH$		
1s, 0.140	***1α***, 0.140	1.23	**3**	$\chi = [59]/[60] = 1.11$
			5	$\gamma = [150]/[151] = 1.09$
1s, 0.130	***1β****, 0.136	1.23	**3**	$\phi = [59]_S/[59]_R = 2.33$
			5	$\delta = [121]/[122] = 2.96$
			5	$\gamma = [150]/[151] = 1.46$
***rac*-1**, 0.144	***1β***, 0.096	1.12	**5**	$\delta = [121]/[122] = 2.60$
	1ββ, 0.030		**5**	$\gamma = [150]/[151] = 1.68$
			5	$\eta = [152]/[151] = 0.28$
1s, 0.116	***1βββ***, 0.120	1.23	**3**	$\rho = [59]/[62] = 1.03$
			5	$\sigma = [150]/[153] = 1.04$

[a] $T = 25$ °C; CH_4: 750 Torr; O_2: 4 Torr; radiation dose 2×10^4 Gy (dose rate: 1×10^4 Gy h^{-1}). [b] Standard deviation: ≈3%.

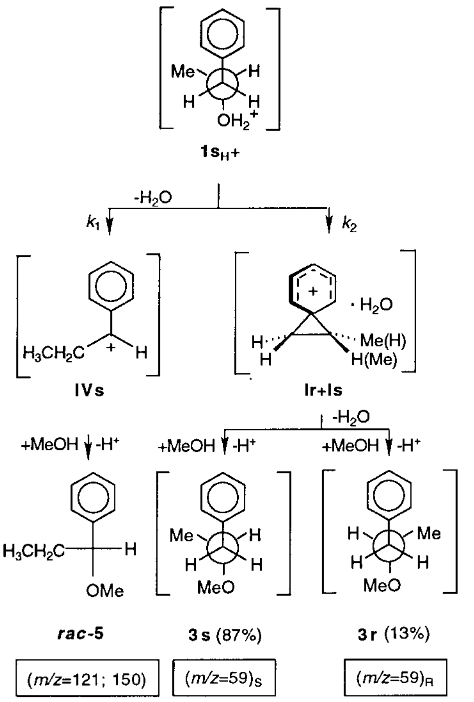
Comparative analysis of the mass spectra of the **3**, **5**, and **6** isotopomeric families of Table 1 exclude any appreciable isotope effect in their fragmentation patterns. However, an imbalance between the *m*/*z* 135 (48.5%) versus *m*/*z* 136

Table 3. Relative abundance of characteristic mass spectrometric fragments of the products from the gas-phase attack of $C_nH_5^+$ ($n = 1, 2$) ions on **2s** and its deuterated isotopomers.

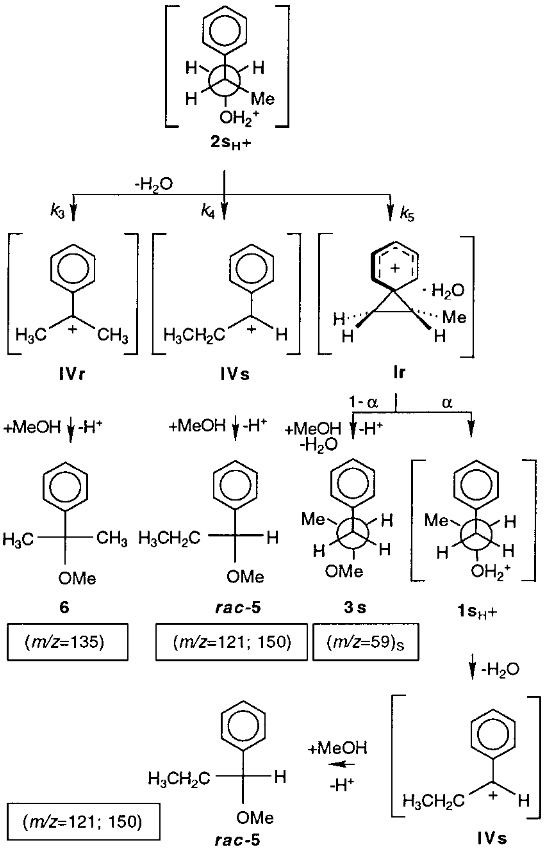
System composition [Torr][a]			Products	Peak intensity ratios[b]
H-substrate	D-substrate	$CH_3{}^{16}OH$		
2s, 0.134	**2*α***, 0.108	0.86	**3**	$\phi = [59]_S/[59]_R = 3.23$
			5	$\gamma = [150]/[151] = 1.25$
			5	$\delta = [121]/[122] = 10.06$
			6	$\varepsilon = [135]/[136] = 3.06$
2s, 0.101	**2*β***, 0.090	0.92	**3**	$\chi = [59]/[60] = 1.31$
			5	$\gamma = [150]/[151] = 1.25$
			5	$\delta = [121]/[122] = 4.01$
			6	$\varepsilon = [135]/[136] = 5.17$

[a] $T = 25\,°C$; CH_4: 750 Torr; O_2: 4 Torr; radiation dose 2×10^4 Gy (dose rate: $1 \times 10^4\ Gy\,h^{-1}$); [b] Standard deviation: ca. 3%.

(51.5%) peak intensities of **6*β*** is observed. An appreciable difference in the fragmentation patterns of unlabeled and labeled ethers is observed only in the case of ***rac*-3** (*m/z* 59: *m/z* 150 = 0.87) and of its trideuterated isotopomer **3*βββ*** (*m/z* 62: *m/z* 153 = 1.08). In this case, the D content in the 1-phenyl-2-methoxypropanes (**3**) arising from the **1s**/**1*βββ*** starting mixtures is determined by considering only the relative abundances of the peaks corresponding to the molecular ions (*m/z* 150, 153). The D content in all the other products has been calculated from the relevant peak intensities after correction for the natural isotopic contributions.



Scheme 2. Reaction pattern from gas-phase O-protonation of (*S*)-1-phenyl-2-propanol in the presence of methanol.

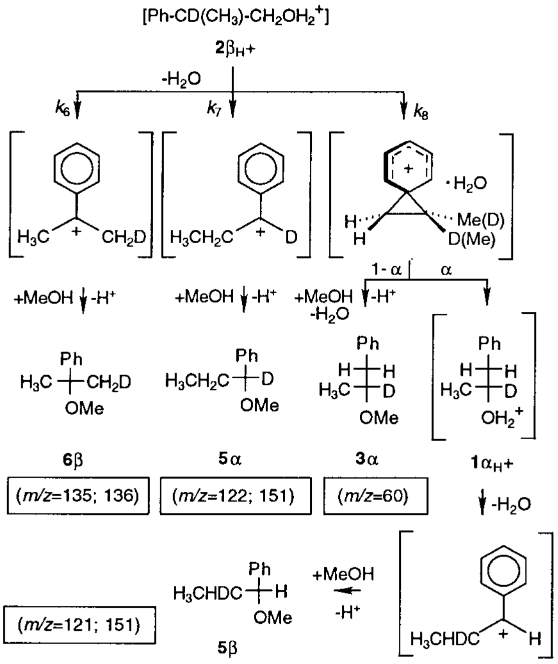


Scheme 3. Reaction pattern from gas-phase O-protonation of (*S*)-2-phenyl-1-propanol in the presence of methanol.

Discussion

Kinetic patterns: As outlined in the preceding paper,[1] γ radiolysis of the bulk CH_4 gas generates known yields of the strong $C_nH_5^+$ ($n = 1, 2$) Brønsted acids.[11] Once collisionally thermalized, these ions indiscriminately attack all the nucleophiles present in the mixture, including the alcoholic substrate and its isotopomer, yielding the corresponding O-protonated derivatives in proportions that reflect the molar fraction of their alcoholic precursor. Once formed, the O-protonated derivatives of the starting alcohols undergo, in the gas phase, extensive unimolecular H_2O loss, anchimerically assisted by all the groups adjacent to the leaving moiety. The so-formed $[C_9H_{11}{}^+]$ species (and their isotopomers) are trapped by the external $CH_3{}^{16}OH$ nucleophile well-before further rearrangements. The $[C_9H_{11}–{}^{16}O(H)Me]^+$ adducts are neutralized by fast proton loss to a suitable base and eventually yield the ethereal products listed in Tables 2 and 3.[12]

Therefore, the products in Table 2 are generated by the reaction network in Scheme 2 (the Fischer-type projections reported in Schemes 2–9 do not reflect any specific configuration, but rather represent the racemates of the relevant products), which involves competing neighboring-group assistance in the unimolecular C–O bond cleavage of the $\mathbf{1s}_{H^+}$ precursor. A similar competition network (Scheme 3) accounts for the formation of the products in Table 3. In this respect, the formation at 25 °C of both ethers **5*α*** (60%) and **5*β*** (40%) from 2-phenyl-2-deutero-1-propanol (**2*β***)[1] indicates that these products arise from two different pathways involving H_2O departure from $\mathbf{2s}_{H^+}$; this is anchimerically assisted by the adjacent methyl group ($\mathbf{2s}_{H^+} \rightarrow$ **IVs** $\rightarrow$ ***rac*-5**; k_4 in Scheme 3) or by the vicinal phenyl moiety ($\mathbf{2s}_{H^+} \rightarrow [\mathbf{Ir}+H_2O]$; k_5 in Scheme 3). In this latter case the $[\mathbf{Ir}+H_2O]$ complex undergoes trapping by $CH_3{}^{16}OH$ to yield **3s** (**Ir**+$CH_3{}^{16}OH$→**3s**; $(1-\alpha)k_5$ in Scheme 3), in competition with exothermic back condensation to $\mathbf{1s}_{H^+}$ (Figure 1; [**Ir**+H_2O]→$\mathbf{1s}_{H^+}$; αk_5 in Scheme 3). The so-formed $\mathbf{1s}_{H^+}$ product then follows the reaction pattern given in Scheme 2 to yield the 1-phenyl-1-methoxypropanes ***rac*-5** ($\mathbf{1s}_{H^+}$→**IVs**→***rac*-5**; k_1 in Scheme 2). Of course, if the starting alcohol is **2*β*** instead of **2s**, H_2O loss from the O-protonated substrate ($\mathbf{2\beta}_{H^+}$) may either involve anchimeric assistance by the methyl group to produce **5*α*** or, alternatively, by the phenyl group to yield both **3*α*** and **5*β*** (Scheme 4).

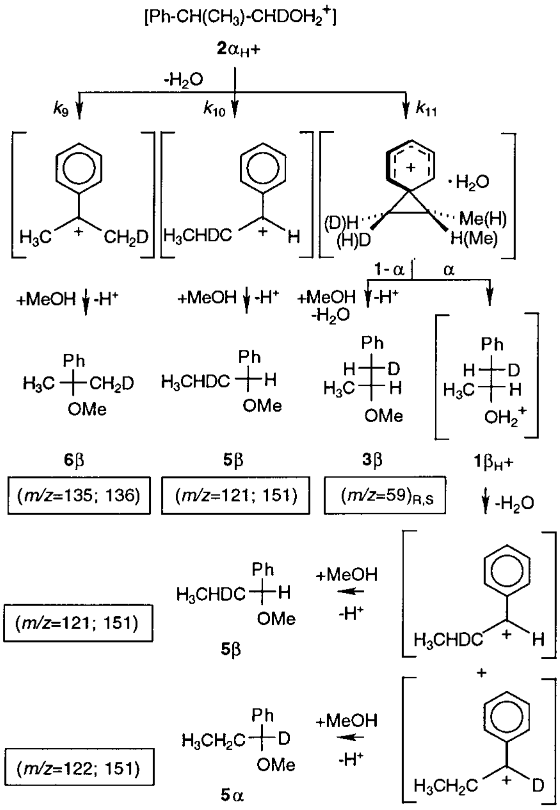


Scheme 4. Reaction pattern from gas-phase O-protonation of the racemate of 2-phenyl-2-deutero-1-propanol in the presence of methanol.

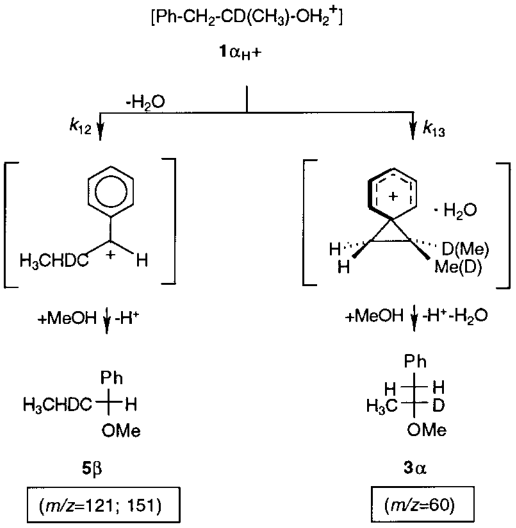
Following the same general pattern, the reaction network promoted by O-protonation of 2-phenyl-1-deutero-1-propanol (**2*α***) is shown in Scheme 5. Schemes 6–9 illustrate the reaction networks induced by O-protonation of 1-phenyl-2-deutero-2-propanol (**1*α***), 1-phenyl-1-deutero-2-propanol (**1*β***), 1-phenyl-1,1-dideutero-2-propanol (**1*ββ***), and 1-phenyl-3,3,3-trideutero-2-propanol (**1*βββ***), respectively.

The deuterium PKIEs and SKIEs on the vicinal-group participation of H_2O loss from O-protonated 1-phenyl-2-propanol can be calculated from the enantiomeric distribution and the fragmentation patterns of the relevant ethereal products reported in Table 2.

1) According to the kinetic patterns shown in Schemes 2 and 6, the k_2/k_{13} ratio [Eq. (1)] represents the **s**econdary **k**inetic **i**sotope **e**ffect by **one d**euterium atom located in the *α* position with respect to the leaving moiety in the **ph**enyl-group participation ($[\alpha\text{-D}_1\text{-SKIE}]_{Ph}$) in the loss of H_2O from O-protonated 1-phenyl-2-propanol, and it is simply calculated from the $\chi = [m/z\ 59]:[m/z\ 60]$ ratio from the etheral products **3** recovered from **1s**+**1*α*** systems after correction for the relative concentration of the starting alcohols. Similarly, the k_1/k_{12} ratio [Eq. (2)] represents the $[\alpha\text{-D}_1\text{-SKIE}]_H$ for the same dissociation and is derived from the $\gamma[\mathbf{1\alpha}]/[\mathbf{1s}]$ ratio, with $\gamma = [m/z\ 150]:[m/z\ 151]$ measured from the ionization of the etheral products **5**.



Scheme 5. Reaction pattern from gas-phase O-protonation of the diastereomeric mixture of 2-phenyl-1-deutero-1-propanol in the presence of methanol.

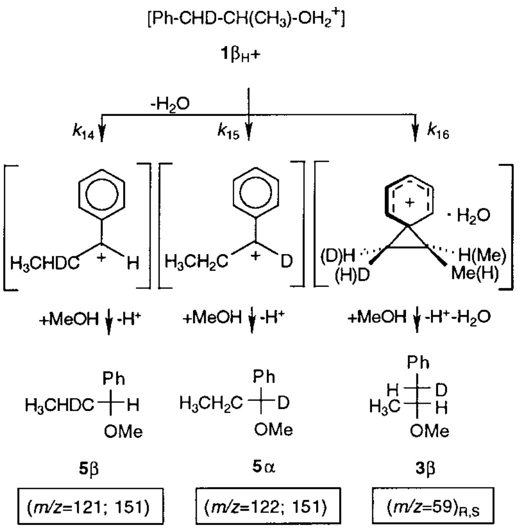


Scheme 6. Reaction pattern from gas-phase O-protonation of the racemate of 1-phenyl-2-deutero-2-propanol in the presence of methanol.

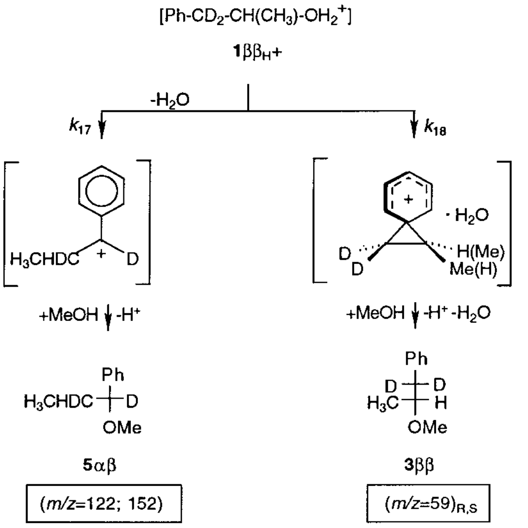
$$k_2/k_{13} = [\alpha\text{-D}_1\text{-SKIE}]_{Ph} = \chi[\mathbf{1\alpha}]/[\mathbf{1s}] \tag{1}$$

$$k_1/k_{12} = [\alpha\text{-D}_1\text{-SKIE}]_{H} = \gamma[\mathbf{1\alpha}]/[\mathbf{1s}] \tag{2}$$

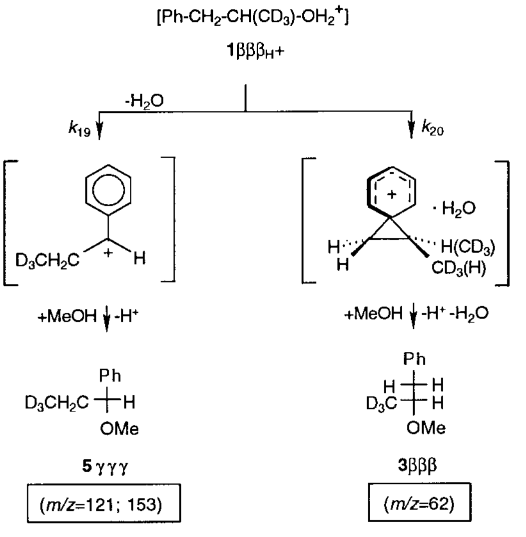
2) The enantiomeric distribution of the ethereal products **3** from irradiation of the **1s**/**1*β**** systems (Schemes 2 and 7)



Scheme 7. Reaction pattern from gas-phase O-protonation of the diastereomeric mixture of 1-phenyl-1-deutero-2-propanol in the presence of methanol.



Scheme 8. Reaction pattern from gas-phase O-protonation of the racemate of 1-phenyl-1,1-dideutero-2-propanol in the presence of methanol.



Scheme 9. Reaction pattern from gas-phase O-protonation of the racemate of 1-phenyl-3,3,3-trideutero-2-propanol in the presence of methanol.

allows us to evaluate the k_2/k_{16} ratio, which represents the $[\beta\text{-D}_1\text{-SKIE}]_{\mathrm{Ph}}$ for the loss of H_2O from O-protonated 1-phenyl-2-propanol. From $[m/z\ 59]_S \sim 0.87\,k_2[\mathbf{1s}] + 0.50\,k_{16}[\mathbf{1}\boldsymbol{\beta}^*]$ and $[m/z\ 59]_R \sim 0.13\,k_2[\mathbf{1s}] + 0.50\,k_{16}[\mathbf{1}\boldsymbol{\beta}^*]$, Equation (3) can be derived in which $\phi = [m/z\ 59]_S/[m/z\ 59]_R$. The $[\beta\text{-D}_1\text{-PKIE}]$ and $[\beta\text{-D}_1\text{-SKIE}]_{\mathrm{H}}$ for the loss of H_2O from O-protonated 1-phenyl-2-propanol cannot be simply evaluated from the analysis of the etheral products **5** from the irradiated **1s**/**1*β****** systems. In fact, the relative rates of formation of these products are affected not only by the kinetic deuterium effects, but also by the relative population of active conformers (Scheme 1) and the activation parameters governing their prototropic rearrangement.[13] To overcome this difficulty, we resorted to the analysis of the etheral products **5** from the irradiated $[\textbf{\textit{rac}-1}]:[\mathbf{1}\boldsymbol{\beta}]:[\mathbf{1}\boldsymbol{\beta\beta}] = 4.8:3.2:1.0$ mixtures (Schemes 2, 7, and 8), as described below.

$$k_2/k_{16} = [\beta\text{-D}_1\text{-SKIE}]_{\mathrm{Ph}} = \{0.50(\phi-1)[\mathbf{1}\boldsymbol{\beta}^*]\}/\{(0.87-0.13\,\phi)[\mathbf{1s}]\} \qquad (3)$$

3) The synthetic procedure for the formation **1*β*** and **1*ββ*** (see Experimental Section) was specifically designed to generate all the possible configurations of 1-phenyl-2-propanol with the deuterium label at C1. In this way, all the objections raised in the point 2,[13] concerning the $0.5\,k_1/k_{14} = [\beta\text{-D}_1\text{-PKIE}]$ and $0.5\,k_1/k_{15} = [\beta\text{-D}_1\text{-SKIE}]_{\mathrm{H}}$ equivalence, are removed (the 0.5 term accounts for the different statistics of hydrogen migration in ***rac*-1** and in **1*β***). Thus, from the analysis of the etheral products **5** obtained from the irradiated $[\textbf{\textit{rac}-1}]:[\mathbf{1}\boldsymbol{\beta}]:[\mathbf{1}\boldsymbol{\beta\beta}] = 4.8:3.2:1.0$ mixtures (Schemes 2, 7, and 8), we get $[m/z\ 121] \sim k_1[\textbf{\textit{rac}-1}] + k_{14}[\mathbf{1}\boldsymbol{\beta}]$; $[m/z\ 122] \sim k_{15}[\mathbf{1}\boldsymbol{\beta}] + k_{17}[\mathbf{1}\boldsymbol{\beta\beta}]$; $[m/z\ 150] \sim k_1[\textbf{\textit{rac}-1}]$; $[m/z\ 151] \sim (k_{14}+k_{15})[\mathbf{1}\boldsymbol{\beta}]$; $[m/z\ 152] \sim k_{17}[\mathbf{1}\boldsymbol{\beta\beta}]$. Thereby, the expressions given in Equations (4)–(7) can be derived in which $\gamma = [m/z\ 150]/[m/z\ 151]$, $\delta = [m/z\ 121]/[m/z\ 122]$, and $\eta = [m/z\ 152]/[m/z\ 151]$.

$$0.5\,k_1/k_{14} = [\beta\text{-D}_1\text{-PKIE}] = \{0.5\,\gamma(\delta+1)[\mathbf{1}\boldsymbol{\beta}]\}/\{[\delta(\eta+1)\text{-}\gamma][\textbf{\textit{rac}-1}]\} \qquad (4)$$

$$0.5\,k_1/k_{15} = [\beta\text{-D}_1\text{-SKIE}]_{\mathrm{H}} = \{0.5\,\gamma(\delta+1)[\mathbf{1}\boldsymbol{\beta}]\}/\{(\gamma+1-\delta\eta)[\textbf{\textit{rac}-1}]\} \qquad (5)$$

$$k_{15}/0.5\,k_{17} = [\beta\text{-D}_2\text{-PKIE}] = \{(\gamma+1-\delta\eta)[\mathbf{1}\boldsymbol{\beta\beta}]\}/\{0.5[\eta(\delta+1)][\mathbf{1}\boldsymbol{\beta}]\} \qquad (6)$$

$$k_{14}/0.5\,k_{17} = [\beta\text{-D}_2\text{-SKIE}]_{\mathrm{H}} = \{(\delta(\eta+1)-\gamma)[\mathbf{1}\boldsymbol{\beta\beta}]\}/\{0.5[\eta(\delta+1)][\mathbf{1}\boldsymbol{\beta}]\} \qquad (7)$$

4) According to the kinetic patterns shown in Schemes 2 and 9, the k_2/k_{20} ratio [Eq. (8)] represents the $[\beta'\text{-D}_3\text{-SKIE}]_{\mathrm{Ph}}$ for the loss of H_2O from O-protonated 1-phenyl-2-propanol and is simply calculated from the $\rho = [m/z\ 59]:[m/z\ 62]$ ratio of the etheral products **3** recovered from **1s**/**1*βββ*** systems after correction for the relative concentration of the starting alcohols, that is, $\rho[\mathbf{1}\boldsymbol{\beta\beta\beta}]/[\mathbf{1s}]$. Similarly, the k_1/k_{19} ratio [Eq. (9)] represents the $[\beta'\text{-D}_3\text{-SKIE}]_{\mathrm{H}}$ for the same dissociation and is derived from the $\sigma[\mathbf{1}\boldsymbol{\beta\beta\beta}]/[\mathbf{1s}]$ ratio, $\sigma = [m/z\ 150]:[m/z\ 153]$, measured from the ionization of the etheral products **5**.

$$k_2/k_{20} = [\beta'\text{-D}_3\text{-SKIE}]_{\mathrm{Ph}} = \rho[\mathbf{1}\boldsymbol{\beta\beta\beta}]/[\mathbf{1s}] \qquad (8)$$

$$k_1/k_{19} = [\beta'\text{-D}_3\text{-SKIE}]_{\mathrm{H}} = \sigma[\mathbf{1}\boldsymbol{\beta\beta\beta}]/[\mathbf{1s}] \qquad (9)$$

In the same way, the deuterium PKIE and SKIEs on the vicinal group participation to H_2O loss from O-protonated

2-phenyl-1-propanol can be calculated from the enantiomeric distribution and the fragmentation patterns of the relevant ethereal products reported in Table 3.

1) According to the kinetic patterns shown in Schemes 3 and 4, and within the reasonable assumption that no appreciable isotope effect operates on the 1-α versus α branching, the k_5/k_8 ratio [Eq. (10)] reflects the $[\beta\text{-D}_1\text{-SKIE}]_{\text{Ph}}$ for H_2O loss from O-protonated 2-phenyl-1-propanol and may be calculated from the $\chi = [m/z\ 59]{:}[m/z\ 60]$ ratio from the etheral products **3** recovered from **2s**/**2*β*** systems after correction for the relative concentration of the starting alcohols, that is, $\chi[\mathbf{2}\boldsymbol{\beta}]/[\mathbf{2s}]$. The k_3/k_6 ratio [Eq. (11)] represents the $[\beta\text{-D}_1\text{-PKIE}]$ for the same dissociation and is derived from the following equations: $[m/z\ 135] \sim k_3[\mathbf{2s}] + 0.485\,k_6[\mathbf{2}\boldsymbol{\beta}]$ and $[m/z\ 136] \sim 0.515\,k_6[\mathbf{2}\boldsymbol{\beta}]$, which were obtained from the fragmentation of the etheral products **6**, with $\varepsilon = [m/z\ 135]/[m/z\ 136]$. The $[\beta\text{-D}_1\text{-SKIE}]_{\text{Me}}$ is represented by the k_4/k_7 ratio [Eq. (12)], which can be expressed by considering the fragments arising from the relevant products **5**. Equation (12) can be derived from the following equations: $[m/z\ 150] \sim (k_4 + \alpha k_5)[\mathbf{2s}]$, $[m/z\ 151] \sim (k_7 + \alpha k_8)[\mathbf{2}\boldsymbol{\beta}]$, $[m/z\ 121] \sim (k_4 + \alpha k_5)[\mathbf{2s}] + \alpha k_8[\mathbf{2}\boldsymbol{\beta}]$, and $[m/z\ 122] \sim k_7[\mathbf{2}\boldsymbol{\beta}]$, with $\gamma = [m/z\ 150]/[m/z\ 151]$, $\delta = [m/z\ 121]/[m/z\ 122]$, and the k_5/k_8 ratio as determined above.

$$k_5/k_8 = [\beta\text{-D}_1\text{-SKIE}]_{\text{Ph}} = \chi[\mathbf{2}\boldsymbol{\beta}]/[\mathbf{2s}] \tag{10}$$

$$k_3/k_6 = [\beta\text{-D}_1\text{-PKIE}] = \{(0.515\,\varepsilon - 0.485)[\mathbf{2}\boldsymbol{\beta}]\}/[\mathbf{2s}] \tag{11}$$

$$k_4/k_7 = [\beta\text{-D}_1\text{-SKIE}]_{\text{Me}} = \{[\gamma(\delta+1)[\mathbf{2}\boldsymbol{\beta}]]/[(\gamma+1)[\mathbf{2s}]]\} - \{[(\delta-\gamma)k_5]/[(\gamma+1)k_8]\} \tag{12}$$

2) The enantiomeric distribution of the ethereal products **3** from irradiation of the **2s**/**2*α*** systems (Schemes 3 and 5) allows us to evaluate the k_5/k_{11} ratio [Eq. (13)], which represents the $[\alpha\text{-D}_1\text{-SKIE}]_{\text{Ph}}$ for H_2O loss from O-protonated 2-phenyl-1-propanol. Equation (13) can be derived from the following equations: $[\mathbf{3s}] = (1-\alpha)\{k_5[\mathbf{2s}] + 0.50\,k_{11}[\mathbf{2}\boldsymbol{\alpha}]\}$ and $[\mathbf{3r}] = (1-\alpha)0.50\,k_{11}[\mathbf{2}\boldsymbol{\alpha}]$, with $\phi = [\mathbf{3s}]/[\mathbf{3r}] = [m/z\ 59]_S/[m/z\ 59]_R$. The k_3/k_9 ratio [Eq. 14)] represents the $[\alpha\text{-D}_1\text{-SKIE}]_{\text{H}}$ for the same dissociation and is derived from the following equations: $[m/z\ 135] \sim k_3[\mathbf{2s}] + 0.485\,k_9[\mathbf{2}\boldsymbol{\alpha}]$ and $[m/z\ 136] \sim 0.515\,k_9[\mathbf{2}\boldsymbol{\alpha}]$, which were obtained from the fragmentation of the etheral products **6**, with $\varepsilon = [m/z\ 135]/[m/z\ 136]$. The $[\alpha\text{-D}_1\text{-SKIE}]_{\text{Me}}$ is represented by the k_4/k_{10} ratio [Eq. (15)], which can be expressed by considering the fragments arising from the relevant products **5**: $[m/z\ 150] \sim (k_4 + \alpha k_5)[\mathbf{2s}]$, $[m/z\ 151] \sim (k_{10} + \alpha k_{11})[\mathbf{2}\boldsymbol{\alpha}]$, $[m/z\ 121] \sim (k_4 + \alpha k_5)[\mathbf{2s}] + k_{10}[\mathbf{2}\boldsymbol{\alpha}] + \alpha\theta\, k_{11}[\mathbf{2}\boldsymbol{\alpha}]$, and $[m/z\ 122] \sim \alpha(1-\theta)k_{11}[\mathbf{2}\boldsymbol{\alpha}]$, with $\theta = k_{14}/(k_{14} + k_{15})$. The θ factor was calculated to be 0.458 from the $k_{14}/k_{15} = [m/z\ 121]/[m/z\ 122] = 1.183$ value measured by analyzing products **5** from **1*β***. Thus, Equation (15) can be derived from the above equations, with $\gamma = [m/z\ 150]/[m/z\ 151]$ and $\delta = [m/z\ 121]/[m/z\ 122]$.

$$k_5/k_{11} = [\alpha\text{-D}_1\text{-SKIE}]_{\text{Ph}} = \{0.50\,(\phi - 1)[\mathbf{2}\boldsymbol{\alpha}]\}/[\mathbf{2s}] \tag{13}$$

$$k_3/k_9 = [\alpha\text{-D}_1\text{-SKIE}]_{\text{H}} = \{(0.515\,\varepsilon - 0.485)[\mathbf{2}\boldsymbol{\alpha}]\}/[\mathbf{2s}] \tag{14}$$

$$k_4/k_{10} = [\alpha\text{-D}_1\text{-SKIE}]_{\text{Me}} = \{[\gamma(\delta+1)(1-\theta) - 0.5(\theta-1)(\gamma+1)][\mathbf{2}\boldsymbol{\alpha}]\}/\{[\delta(1-\theta) - (\gamma+\theta)][\mathbf{2s}]\} \tag{15}$$

Kinetic isotope effects: An additional piece of evidence in favor of the intervention of competing anchimeric assistance in the H_2O loss from $\mathbf{1s}_{\text{H}^+}$ and $\mathbf{2s}_{\text{H}^+}$ arises from the evaluation of the relevant kinetic isotope effects, calculated by inserting the ion intensity ratios of Tables 2 and 3 into the corresponding equations derived in the previous section. The calculated deuterium PKIEs and SKIEs are given in Tables 4 and 5.

Table 4. Deuterium isotope effects in the acid-induced intramolecular isomerization of 1-phenyl-2-propanol **1** in CH_4 at 750 Torr and 25 °C.

$C_\beta \rightarrow C_\alpha$ Migrating group	Rate constant ratios	Isotope effects
Ph	$k_2/k_{13} = 1.11 \pm 0.03$	$(\alpha\text{-D}_1\text{-SKIE})_{\text{Ph}}$
	$k_2/k_{16} = 1.23 \pm 0.03$	$(\beta\text{-D}_1\text{-SKIE})_{\text{Ph}}$
	$k_2/k_{20} = 1.06 \pm 0.04$	$(\beta'\text{-D}_3\text{-SKIE})_{\text{Ph}}$
β-H	$0.5\,k_1/k_{14} = 1.22 \pm 0.04$[a]	$(\beta\text{-D}_1\text{-PKIE})$
	$k_1/k_{12} = 1.09 \pm 0.03$	$(\alpha\text{-D}_1\text{- SKIE})_{\text{H}}$
	$0.5\,k_1/k_{15} = 1.04 \pm 0.04$[a]	$(\beta\text{-D}_1\text{-SKIE})_{\text{H}}$
	$k_1/k_{19} = 1.08 \pm 0.04$	$(\beta'\text{-D}_3\text{-SKIE})_{\text{H}}$
β-H	$k_{15}/0.5\,k_{17} = 1.19 \pm 0.06$[b]	$(\beta\text{-D}_2\text{-PKIE})$
	$k_{14}/0.5\,k_{17} = 1.01 \pm 0.06$[b]	$(\beta\text{-D}_2\text{-SKIE})_{\text{H}}$

[a] β-H, as the spectator atom; [b] β-D, as the spectator atom.

Table 5. Deuterium isotope effects in the acid-induced intramolecular isomerization of 2-phenyl-1-propanol **2** in CH_4 at 750 Torr and 25 °C.

$C_\beta \rightarrow C_\alpha$ Migrating group	Rate constant ratios	Isotope effects
Ph	$k_5/k_{11} = 1.12 \pm 0.02$	$(\alpha\text{-D}_1\text{-SKIE})_{\text{Ph}}$
	$k_5/k_8 = 1.17 \pm 0.02$	$(\beta\text{-D}_1\text{-SKIE})_{\text{Ph}}$
Me	$k_4/k_{10} = 1.33 \pm 0.08$	$(\alpha\text{-D}_1\text{-SKIE})_{\text{Me}}$
	$k_4/k_7 = 1.05 \pm 0.03$	$(\beta\text{-D}_1\text{-SKIE})_{\text{Me}}$
β-H	$k_3/k_6 = 1.94 \pm 0.05$	$(\beta\text{-D}_1\text{-PKIE})$
	$k_3/k_9 = 1.09 \pm 0.03$	$(\alpha\text{-D}_1\text{-SKIE})_{\text{H}}$

Kinetic isotope effects are determined primarily by changes in vibrational frequencies along the reaction coordinate. It has been generally accepted that, besides proton tunneling, PKIE is primarily determined by the loss of zero-point energy (ZPE) owing to conversion of one stretching vibration in the reactant into the reaction coordinate. The absolute value of PKIE is expected to be dependent on the hydrogen-transfer symmetry and the looseness of the relevant TS structure.[14]

Hybridization and crowding effects determine α-SKIE, primarily through changes in the C_α–H(D) out-of-plane bending vibrations. The absolute value of α-SKIE increases by increasing the TS looseness, that is, by increasing the C_α-leaving-group bond length and by decreasing the size of the leaving moiety. The contribution of C_α–H(D) stretching vibrations to the α-SKIE value are also important. The variation of α-SKIE from the stretching vibrations with TS looseness is opposite to that of the bending contribution, causing a level-off in the α-SKIE for tight TS structures.[15]

Hyperconjugation and relief of nonbonding interactions determine β-SKIE, whose value depends upon the magnitude of positive charge at C_α and the dihedral angle between the C_β–H(D) bond and the incipient empty p-orbital on C_α.[16] The β–D_1 isotope effect on the H_2O loss from $\mathbf{2s}_{\text{H}^+}$ with $C_\beta \rightarrow C_\alpha$ hydrogen migration is as large as 1.94 ± 0.05 (Table 5). This value exceeds ordinary β-D_1-SKIE[17] and falls in the classical range of primary isotope effects for intramolecular 1,2 hydrogen shifts (β-D_1-PKIE = 1.5 – 3.0).[18] This conclusion was corroborated by the accompanying modest $[\alpha\text{-D}_1\text{-SKIE}]_{\text{H}} = 1.09 \pm 0.03$ value, which points to a rather tight TS structure characterized by an intense H(D)$-$C$_\alpha$ interaction coupled with limited C$_\alpha$$-OH_2^+$ bond cleavage.

The β-D$_1$ isotope effects on the H$_2$O loss from $\mathbf{1s}_{\text{H}^+}$ with $\text{C}_\beta \rightarrow \text{C}_\alpha$ hydrogen migration amount to 1.22 ± 0.04 and 1.19 ± 0.06 (Table 4), that is, in a range which may reflect either a small β-D$_1$-PKIE[18] or a large β-D$_1$-SKIE.[17] However, the limited magnitude of the accompanying $[\beta\text{-D}_1\text{-SKIE}]_{\text{H}} = 1.04 \pm 0.04$, 1.01 ± 0.06, $[\beta'\text{-D}_3\text{-SKIE}]_{\text{H}} = 1.08 \pm 0.04$, and $[\alpha\text{-D}_1\text{-SKIE}]_{\text{H}} = 1.09 \pm 0.03$, the latter coinciding with that measured in the H$_2$O loss from $\mathbf{2s}_{\text{H}^+}$ (Table 5), speaks in favor of the first hypothesis involving anchimeric assistance by the β hydrogen via a TS structure, characterized by significant H(D)$-$C$_\alpha$ bonding and limited C$_\alpha$$-OH_2^+$ bond cleavage. The low $[\beta\text{-D}_1\text{-PKIE}] = 1.22 \pm 0.04$ and $[\beta\text{-D}_2\text{-PKIE}] = 1.19 \pm 0.06$ values, compared with that measured for the H$_2$O loss from $\mathbf{2s}_{\text{H}^+}$ (1.94 ± 0.05; Table 5), are indicative of the operation of both C$_\beta$$-$H(D) stretching and bending vibrations in the TS structure of the intramolecular nonlinear $\text{C}_\beta \cdots \text{H(D)} \cdots \text{C}_\alpha$ transfer.[14b, 19] Since the C$_\beta$$-$H stretching frequency should be reduced more by deuteration than a bending mode,[20] the comparatively small [β-D$_1$-PKIE] on the H$_2$O loss from $\mathbf{1s}_{\text{H}^+}$ (Table 4) suggests a greater weight of C$_\beta$$-$H(D) bendings in its TS structure than in that of the corresponding process in $\mathbf{2s}_{\text{H}^+}$ (Table 5).[21]

In the gas phase, the α-D$_1$ isotope effect on H$_2$O loss from $\mathbf{1s}_{\text{H}^+}$ with $\text{C}_\beta \rightarrow \text{C}_\alpha$ phenyl-group migration amounts to 1.11 ± 0.03 (Table 4), a value which is in agreement with those measured in the aryl-group-assisted solvolysis of 1-aryl-2-alkyl tosylates in the condensed phase.[8a] However, this gas-phase isotope effect is accompanied by a sizable β-D$_1$($= 1.13 \pm 0.03$) and a limited β'-D$_3$ ($= 1.06 \pm 0.04$) isotope effect (Table 4). This pair of values is inconsistent with the corresponding pairs measured in both the aryl-group-assisted solvolysis of 1-(p-anisyl)-2-propyl tosylate ($[\beta\text{-D}_1\text{-SKIE}] = 0.998$; $[\beta'\text{-D}_3\text{-SKIE}] = 1.123$) and the unassisted solvolysis of 1-phenyl-2-propyl tosylate ($[\beta\text{-D}_1\text{-SKIE}] = 1.295$; $[\beta'\text{-D}_3\text{-SKIE}] = 1.242$).[8a] This apparent contradiction can be solved by considering the stereochemistry of the aryl-group participation in the corresponding systems. In the condensed phase, solvation and ion-pairing factors induce a backside interaction between the aryl group and the C$_\alpha$$-$OTs. In contrast, in the gas phase the H$_2$O loss from $\mathbf{1s}_{\text{H}^+}$ involves both a backside (major) and a frontside (minor) phenyl-group participation.[1] Therefore, the gas-phase $\beta\text{-D}_1 = 1.23 \pm 0.03$ and $\beta'\text{-D}_3 = 1.06 \pm 0.04$ values reflect a convolution of β-D effects for both the backside ($[\beta\text{-D}_1\text{-SKIE}]_{\text{Ph}}^{\text{back}} \leq 1$) and the frontside phenyl-group participation ($[\beta\text{-D}_1\text{-SKIE}]_{\text{Ph}}^{\text{front}} \cong 1.4$),[17] whose TS structures involve different charge location at C$_\alpha$ and different dihedral angles between the C$_\beta$$-$H(D) bond and the incipient empty p-orbital on C$_\alpha$ (Scheme 1).[16, 17] Therefore, despite its large value for the solution chemistry standards, the gas-phase $[\beta\text{-D}_1\text{-SKIE}]_{\text{Ph}} = 1.23 \pm 0.03$ is interpreted in terms of backside and frontside phenyl-group-assisted H$_2$O losses from different conformers of $\mathbf{1s}_{\text{H}^+}$, via early TS structures with a weak Ph$-$C$_\alpha$ interaction coupled with a partial C$_\alpha$$-OH_2^+$ bond cleavage ($[\alpha\text{-D}_1\text{-SKIE}] = 1.11 \pm 0.03$). This conclusion is in agreement with the small gas-phase $\beta'\text{-D}_3 = 1.06 \pm 0.04$ value, which corresponds to a limited development of the p-orbital vacancy at C$_\alpha$ caused by the phenyl-group participation in the only partial C$_\alpha$$-OH_2^+$ bond cleavage. In this respect, the observed $[\beta'\text{-D}_3\text{-SKIE}]_{\text{Ph}} < [\beta\text{-D}_1\text{-SKIE}]_{\text{Ph}}$ order is suggestive of a more pronounced hyperconjugation and relief of nonbonding interaction for the benzylic C$_\beta$$-$H(D) bonds of unsolvated $\mathbf{1s}_{\text{H}^+}$ than for its C$_\beta'$$-$H(D) bonds. Of course, given the strict similarity of the $[\alpha\text{-D}_1\text{-SKIE}]_{\text{Ph}}$ and $[\beta\text{-D}_1\text{-SKIE}]_{\text{Ph}}$ values of Tables 4 and 5, the same conclusion applies to H$_2$O loss from $\mathbf{2s}_{\text{H}^+}$ with $\text{C}_\beta \rightarrow \text{C}_\alpha$ Ph migration.

The α-D$_1$ isotope effect on H$_2$O loss from $\mathbf{2s}_{\text{H}^+}$ with $\text{C}_\beta \rightarrow \text{C}_\alpha$ Me migration is large (1.33 ± 0.08; Table 5), relative to the α-D$_1$ effect when the participating groups are hydrogen (1.09 ± 0.03) or phenyl (1.12 ± 0.02). This observation, coupled with the reduced $\beta\text{-D}_1 = 1.05 \pm 0.03$ (Table 5), points to methyl-group-assisted H$_2$O loss from $\mathbf{2s}_{\text{H}^+}$ proceeding through a TS structure characterized by an advanced Me$-$C$_\alpha$ bonding coupled with extensive C$_\alpha$$-OH_2^+$ bond cleavage.[22] The above conclusions about the nature of the TS structures involved in the competing anchimeric assistance of H$_2$O loss from $\mathbf{1s}_{\text{H}^+}$ and $\mathbf{2s}_{\text{H}^+}$ find further support from the comparative analysis of the relevant activation parameters, reported in Figure 1.[1]

Early TS structures, characterized by a partial C$_\alpha$$-OH_2^+$ bond cleavage coupled with a weak Ph$-$C$_\alpha$ interaction, are fully consistent with the relatively large A_{Ph} and E^*_{Ph} values measured for H$_2$O loss from $\mathbf{1s}_{\text{H}^+}$ and $\mathbf{2s}_{\text{H}^+}$. In these flexible TS structures, the charge is essentially distributed over the C$_\alpha$$-$O atoms and the Ph$-C_\beta$ rotor is only partially restrained. In contrast, the small A_{H} and E^*_{H} values, governing the competing β-hydrogen participation, conform to a rigid TS structure, characterized by significant H(D)$-$C$_\alpha$ bonding and limited C$_\alpha$$-OH_2^+$ bond cleavage. Here, the positive charge is transferred essentially to the benzylic moiety, with consequent quenching of the Ph$-$C$_\beta$ rotor. The intermediate A_{Me} and E^*_{Me} values, associated to β-methyl participation in the H$_2$O loss from $\mathbf{2s}_{\text{H}^+}$, can be well-accounted for by a borderline TS structure, in which intense Me$-$C$_\alpha$ bonding is now coupled with more extensive C$_\alpha$$-OH_2^+$ bond cleavage.

Conclusions

a) This paper presents a combined pattern of β-D$_1$-PKIE, α-D$_1$-SKIE, β-D$_1$-SKIE, and β'-D$_3$-SKIE as the only unequivocal mechanistic criterion for the TS structures of the gas-phase H$_2$O loss from O-protonated (S)-1-phenyl-2-propanol ($\mathbf{1s}_{\text{H}^+}$) and O-protonated (S)-2-phenyl-1-propanols ($\mathbf{2s}_{\text{H}^+}$).

b) While the measured gas-phase β-D$_1$-PKIE, α-D$_1$-SKIE, and β'-D$_3$-SKIE values fall in the classical range of deuterium effects for analogous solvolytic processes, the relatively large $[\beta\text{-D}_1\text{-SKIE}]_{\text{Ph}}$'s are accounted for by partitioning between backside and frontside phenyl-group participation to the process. This fact warns against thoughtless correlations of the observed isotope effects to a single TS structure.

c) Discussion of the measured deuterium PKIEs and SKIEs in the light of the relevant activation parameters provides conclusive insights into the TS structures governing gas-phase anchimeric assistance to H$_2$O loss from $\mathbf{1s}_{\text{H}^+}$ and $\mathbf{2s}_{\text{H}^+}$ by all the groups adjacent to the reaction center. Thus, an early TS structure is involved in the phenyl-group assistance, characterized by partial C_α–OH_2^+ bond cleavage coupled with a weak Ph–C_α interaction. In contrast, β-hydrogen participation involves a much tighter TS structure, characterized by significant H(D)–C_α bonding and limited C_α–OH_2^+ bond cleavage. Finally, β-methyl group participation in $\mathbf{2s}_{H^+}$ involves a borderline TS structure, in which intense Me–C_α bonding is coupled with a pronounced C_α–OH_2^+ bond elongation.

d) It is a generally accepted view[5, 16a] that neighboring-group participation in ionic processes is enhanced as the nucleophilicity and the dielectricity of the reaction medium decrease. Accordingly, the results of the present and the preceding[1] papers demonstrate that gas-phase solvolysis of $\mathbf{1s}_{H^+}$ and $\mathbf{2s}_{H^+}$ involves unsubstituted phenyl-group anchimeric assistance (a k_Δ process), whereas the analogous acetolysis of 1-phenyl-2-ethyl tosylate proceeds through competing solvent- (a k_S process) and anchimeric-assisted (k_Δ) mechanisms,[8b] and that of 1-phenyl-2-propyl tosylate by predominant anchimeric- and solvent-unassisted unimolecular dissociation (a k_C process).[8a]

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[12] Neutralization of the O-protonated ethers, arising from addition of isomeric $[C_9H_{11}^+]$ to methanol, may proceed through several pathways, including proton transfer to the substrate itself, to the walls of the reaction vessel, or to adventitious bases that are either initially added to the gaseous mixture or formed by its radiolysis.

[13] According to Schemes 2 and 7, $[m/z\ 150] \sim k_1[\mathbf{1s}]$, $[m/z\ 151] \sim (k_{14} + k_{15})[\mathbf{1}\boldsymbol{\beta}]$, $[m/z\ 121] \sim k_1[\mathbf{1s}] + k_{14}[\mathbf{1}\boldsymbol{\beta}]$, and $[m/z\ 122] \sim k_{15}[\mathbf{1}\boldsymbol{\beta}]$. From these relations, $0.5\,k_1/k_{14} = \{0.5\gamma(1+\delta)[\mathbf{1}\boldsymbol{\beta}]\}/\{(\delta-\gamma)[\mathbf{1s}]\}$ and $0.5\,k_1/k_{15} = \{0.5\gamma(1+\delta)[\mathbf{1}\boldsymbol{\beta}]\}/\{(1+\gamma)[\mathbf{1s}]\}$, with $\gamma = [m/z\ 150]/[m/z\ 151]$ and $\delta = [m/z\ 121]/[m/z\ 122]$. Using the $\gamma = 1.46$ and $\delta = 2.96$ values of Table 2, measured for products **5** from the $\mathbf{1s}/\mathbf{1}\boldsymbol{\beta}^*$ systems, $0.5\,k_1/k_{14} = 2.01$ and $0.5k_1/k_{15} = 1.23$. These phenomenological values reflect three different factors, namely: i) the relative population of active conformers of O-protonated 1-phenyl-2-propanol (Scheme 1) involved in the H/D anchimeric assistance to H_2O loss; ii) the activation parameters governing hydrogen-atom anchimeric assistance in each conformer; iii) the isotope effect on these activation parameters. Indeed, the above values significantly diverge from those derived from the ***rac*-1/1*β*** systems, that is $0.5\,k_1/k_{14} = 1.22$ and $0.5\,k_1/k_{15} = 1.04$, where no differences in factors i) and ii) are present and, therefore, the only rate difference is due to factor iii).

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[17] For an S_N1 reaction on tertiary chlorides in solution, β-D_1-SKIE varies from 1.31 to 0.99 as the dihedral angle between the C_β–H(D) bond and the incipient p-orbital at C_α is varied from 180(0) to 90° (V. J. Shiner, Jr., J. S. Humphrey, Jr., *J. Am. Chem. Soc.* **1963**, *85*, 2416). The β-D_1-SKIE on the ethanolysis of *cis*-4-*tert*-butylcyclohexyl brosylate amounts to 1.436, when the β-D is axial, and to 1.096, when the β-D is equatorial (V. J. Shiner, Jr., J. G. Jewett, Jr., *J. Am. Chem. Soc.* **1965**, *87*, 1382).

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[21] An alternative rationale can be found in some minor contribution of tunneling in the more strained TS structure of the β-hydrogen participation in H_2O loss from O-protonated 2-phenyl-1-propanol relative to the that of the same process in O-protonated 1-phenyl-2-propanol (see ref. [14b]). Strain is expected to be higher in the first TS structure than in the latter one on account of the more intense H(D)–C_α interaction required for the same C_α–OH_2^+ bond elongation.

[22] The low $[\beta\text{-}D_1\text{-SKIE}]_{Me}$ and $[\beta\text{-}D_1\text{-SKIE}]_H$, relative to the corresponding $[\beta\text{-}D_1\text{-SKIE}]_{Ph}$, may not only reflect later TS structures, but also a less extensive frontside participation.

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