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# Stereochemical Analysis of Deuterated Alkyl Chains by MS/MS

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Vicinally deuterated *sec*-alkyl phenyl ethers, $CH_3(CH_2)_mCH(OPh)CHD(CH_2)_nCH_3$, display significant differences in mass spectra between threo and erythro stereoisomers. MS/MS experiments, in which parent ions of a single mass are selected and their fragmentation patterns subsequently measured, show that alkene expulsion represents virtually the only decomposition pathway. Two types of MS/MS experiment are reported: mass-analyzed ion kinetic energy (MIKE) spectroscopy of metastable ions and collisionally activated decomposition (CAD) of stable ions. The expulsion of a deuterated alkene from a monodeuterated precursor yields ionized phenol, $PhOH^{\bullet+}$ (*m*/*z* 94). The expulsion of an undeuterated alkene yields $PhOD^{\bullet+}$ (*m*/*z* 95). Without exception, the ratios ($PhOD^{\bullet+}/PhOH^{\bullet+}$) from precursors in the threo series have values greater than their diastereomers in the erythro series. The ratio of ratios, $r = PhOD^{\bullet+}/PhOH^{\bullet+}$ for the threo divided by $PhOD^{\bullet+}/PhOH^{\bullet+}$ for the erythro, has a value of 1.2 for the 2-phenoxy-3-deuteriobutanes and larger values for all of the higher homologues up through the monodeuterated phenoxyoctanes ($m + n = 4$). The highest degree of stereoselectivity, $r = 5.8$, is measured for 3-phenoxy-4-deuteriohexane. Experiments with multiply deuterated analogues show that alkene elimination is highly regioselective, unlike the corresponding decompositions of ionized *sec*-alcohols or their acetates. The fact that a large fraction of ionized *sec*-alkyl phenyl ethers undergo stereospecific syn-elimination means that mass spectrometry has a useful capacity to distinguish one isotopically labeled diastereomer from another.

Mass spectrometry has been known for more than 30 years to have the capacity to distinguish between acyclic diastereomers, especially (though not exclusively) when there is just one pair of stereogenic centers that are adjacent to one another.[1] As yet, no systematic interpretation has allowed this phenomenon to be employed in the deduction of unknown stereochemistries. This paper examines a homologous series of monodeuterated *sec*-phenoxy-*n*-alkanes, $CH_3(CH_2)_mCH(OPh)CHD(CH_2)_nCH_3$. In these compounds, the abundance of relative fragment ions can be used to tell one diastereomer from another. In 1988, we demonstrated that both *threo*- and *erythro*-2-phenoxy-3-deuteriobutanes (**1t**, **e**) manifest small but reproducible differences in the expulsion of butene from their molecular ions.[2] Recently, we published a study of a half-dozen homologues, showing that alkene expulsion exhibits even greater sensitivity to stereochemistry for homologues with longer chain lengths.[3] While the terms threo and erythro are not, strictly speaking, the correct designations for all of the homologues of **1**, we shall continue to use the symbols **t** and **e** to indicate the series to which a given diastereomer belongs. Here, we report the results for seven additional homologues, completing the chain-length series from $m + n = 0$ to $m + n = 4$ (compounds **1**−**15** in Chart 1).

## Experimental Section

Metastable ion decompositions were studied by mass-analyzed ion kinetic energy (MIKE) spectroscopy on reverse Nier-Johnson (B−E configuration) double-focusing mass spectrometers at UCR and at the Ecole Polytechnique in Palaiseau. The relative ion abundancies from the former instrument were measured by fitting the observed peaks as Gaussians using the multipeak fit function of IGOR Pro 3.03 software, while those from the latter instrument were measured as relative peak areas. Ion ratios differed slightly between the two instruments: for example, $CH_3CHOPhCD_2CH_3$ gave a *m*/*z* 94:*m*/*z* 95 ratio of 2.33 (SD = 0.015) on the former and 2.02 (SD = 0.13) on the latter. GC/MS/MS experiments (70 eV EI) were performed using a quadrupole ion trap (QIT) coupled to a gas chromatograph equipped with a 30 m DB5 fused-silica capillary column (0.25 mm i.d., 0.25 mm film thickness).[3]

Deuterated compounds were prepared by standard methods. Samples of $RCH(OPh)CD_2CH_3$ were synthesized by reacting the carboxylic acids, RCH(OPh)COOH, with excess methyllithium.[4] This was followed by reduction of the ketone product with $LiAlD_4$ to the *vic*-phenoxy alcohol, which was dehydroxylated as described below. $CH_3CH(OPh)CH_2CD_3$ and $CH_3CH_2CH(OPh)CD_2CD_3$ were prepared and purified as previously described.[5] Vicinally perdeuterated compounds were prepared by repetitive exchange of the corresponding ketones with $D_2O$, followed by reduction, conversion to the tosylate, and $S_N2$ displacement with sodium phenoxide in refluxing THF. Single diastereomers (of both pure compounds and mixtures of positional isomers) were synthesized from the corresponding

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[1] (a) Audier, H. E.; Felkin, H.; Fetizon, M.; Vetter, W. *Bull. Soc. Chim. Fr.* **1965**, 3236−3238. For reviews of this subject, see: (b) Green, M. M. *Top. Stereochem.* **1976**, *9*, 35−110. (c) Turecek, F. *Collect. Czech. Chem. Commun.* **1987**, *52*, 1928−1984. (d) Turecek, F.; Splitter, J. S. *Applications of Mass Spectrometry to Organic Stereochemistry*; VCH Publishers: New York, 1994; Chapter 4.

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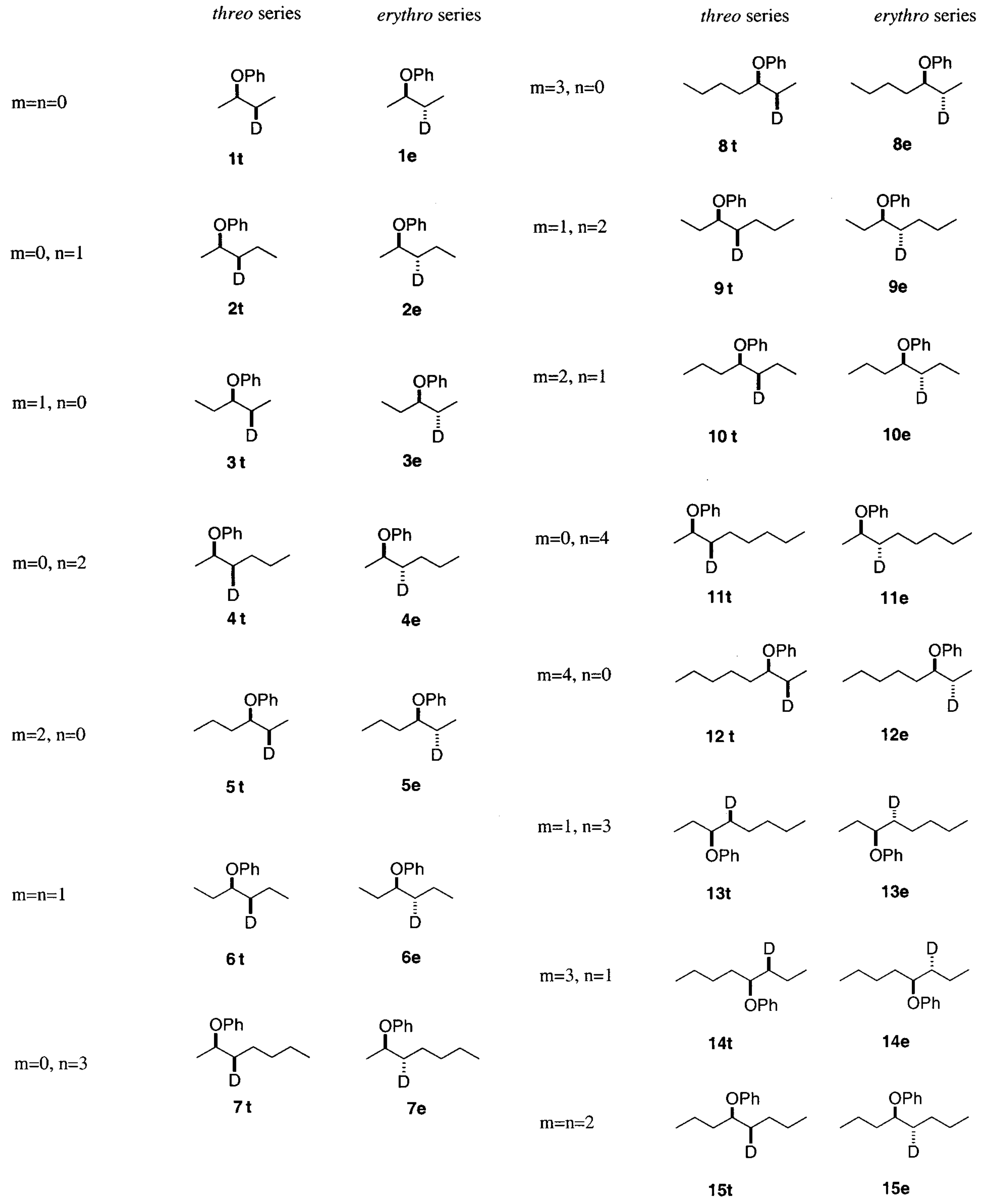
10.1021/jo9912247 CCC: $19.00

**Chart 1. Structures of the Monodeuterated Phenoxy *n*-Alkanes (up through octane) That Possess Two Vicinal Stereogenic Centers**



alkenes by the procedure exemplified below for the stereoisomers of **15** (with the exception of the mixture of *erythro*-**13** and *erythro*-**14**, which was synthesized from *trans*-3-octene via epoxidation, reduction with $LiAlD_4$, conversion to the bromide, and displacement with sodium phenoxide).

**4-Phenoxyoctane-5-$d_1$ (15).** A quantity of 1.12 g (10.0 mmol) of *trans*-4-octene (Sigma) was epoxidized with *m*-CPBA, and the crude, sweet-smelling epoxide was sealed in a Pyrex tube with 1.5 g of a 1:3 mixture of sodium phenoxide/phenol and heated for 18 h at 130 °C in an oven. The reaction mixture was then taken up in water with 30 mL of ether, and the ethereal layer was separated and washed with 6 × 25 mL portions of 20% aqueous NaOH to remove traces of unreacted phenol. After washing with saturated aqueous NaCl and the removal of the solvent, the resulting *vic*-phenoxy alcohol (1.30 g) was converted to the tosylate without any further purification; the tosylate reduced with excess $LiAlD_4$ in refluxing THF to yield 0.23 g of **15t** (bp 143−148°, 20 Torr), after distillation under aspirator pressure. Starting with 0.48 g (4.3 mmol) of *cis*-4-octene (Wiley Organics), the same procedure afforded 0.51 g (2.5 mmol) of **15e** (bp 144−148°, 20 Torr, 57% overall yield), after distillation.

## Results

The approach described here examines the relative intensities of two mass spectrometric fragments that differ by 1 amu. Because the molecular ion decomposition is not 100% stereospecific, $^{13}$C-natural abundance interferes with the measurement of ion abundance ratios. Therefore, the best results are obtained when the dissociation of a single isotopic variant is examined. Many modern mass spectrometers accomplish this by MS/MS, that is, selecting a single *m*/*z* value in the first stage of mass separation and looking at subsequent decompositions in a second stage. Instrumentally, this can be performed by either using two (or more) mass spectrometers in tandem or using a single mass spectrometer that has the ability to store ions of a single *m*/*z* value and then to analyze its fragmentation pattern in the same region of space.

Both methods will be discussed below. MIKE spectroscopy represents a tandem technique, wherein the *m*/*z* value of the parent ion is selected by a magnetic (B) sector and the fragment masses are analyzed later by an electrostatic analyzer (ESA). The quadrupole ion trap (QIT) exemplifies a storage instrument, where parent ions are trapped in an appropriately tailored electric field. Advantages of QIT include the ease with which it can be interfaced with a GC and also the comparative insensitivity of its resolution to the kinetic energy of the fragment ions.

An ion can be given enough energy to dissociate at the time of its creation or subsequently. On one hand, metastable ions are those that form with enough internal energy to decompose, but do so on a time scale longer than that of mass analysis. Such ions pass unchanged through the first stage of selection, and a portion of them fragment prior to the second stage. The dissociations that occur between the two stages of mass selection can be specifically examined by a variety of methods. In the present investigation, MIKE spectroscopy was used to examine metastable ion decompositions.

On the other hand, ions can be activated between the two stages of mass analysis. There are many ways to do this. Here, we have made use of energetic collisions with inert gas atoms. Collisionally activated dissociation (CAD) in the present study was performed in the QIT, with sample introduction via a GC interface. Some of the helium carrier gas leaked into the mass spectrometer, where it served as the collision gas. MIKE spectroscopy can also be used for CAD studies, but we found that the resulting peaks (whose shape was sensitive to the kinetic energy that was released during dissociation) from higher mass parent ions became too poorly resolved to perform useful quantitation.

Metastable ions ordinarily have lower internal energies than those that have been activated after ionization. Consequently, their MIKE spectra often exhibit a smaller variety of decomposition pathways than their corresponding CAD spectra. Therefore, we shall start by presenting data from the metastable ion decompositions. Because some degree of regioselectivity is needed in order to observe stereochemical discrimination to a useful extent, questions of regiochemistry are dealt with first.

**Regioselectivity.** Before dealing with the issue of stereoselectivity, it is important to probe the degree to which an elimination reaction involves the stereogenic center of interest. Figure 1 exhibits a MIKE spectrum of the higher mass ions from vicinally perdeuterated 4-octanol (*m*/*z* ≥ 65, which constitute >95% of the fragment ion intensity). As can be seen, elimination of water takes place, but it is a minor process. The principal dissociation pathways are the formation of pentenyl cations and the loss of alkyl radicals (either propyl or butyl). All of these processes involve isotopic scrambling; hence, there are multiple peaks corresponding to each decomposition of the $d_4$-alcohol. In particular, loss of water shows up as three peaks ($M - H_2O$, $M - HOD$, and $M - D_2O$, in the proportions 0.21:0.61:0.18), and this elimination cannot be considered regioselective to any useful extent. The loss of water from ionized alcohols has long been known to exhibit poor regioselectivity.[6] The present results show that unimolecular hydrogen transposition (possibly by reversible formation of distonic ions) creates an additional complication.

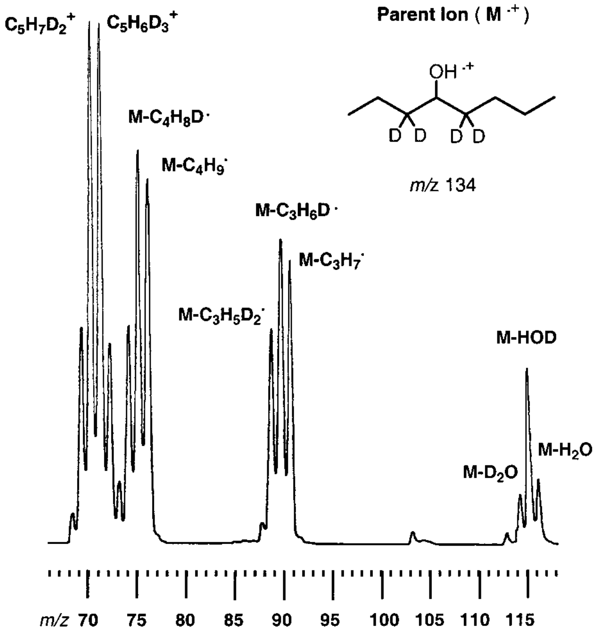


**Figure 1.** Metastable ion decomposition pattern for ionized 4-octanol-*3,3,5,5-d*$_4$ following 70 eV of electron ionization (EI) with 8 kV of accelerating voltage. All fragments ≥*m*/*z* 65 are shown.

The mass spectrum of the acetate ester of $CH_3CH_2CD_2$-$CHOHCD_2CH_2CH_2CH_3$ shows fewer peaks. The elimination of acetic acid represents the predominant dissociation of the molecular ion, representing 75–80% of the fragment ion intensity in the metastable ion decompositions that we observe in the MIKE spectrum. This is homologous to the stereoselective elimination that Green and Vogt examined in detail for *sec*-butyl acetate,[7] for which they propose a six-member cyclic transition state analogous to thermal syn-elimination from neutral acetates.[8] In the 4-octyl system, however, the elimination is not regioselective. Losses of $CH_3COOD$ and losses of $CH_3COOH$ (*m*/*z* 115 and 116) have the same abundances, whereas a six-member cyclic transition state involving the carbonyl would demand exclusively the former (unless, of course, the ion rearranges beforehand). The

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**Table 1. $PhOD^{•+}/PhOH^{•+}$ Intensity Ratios from Metastable Ion Decompositions of *Sec*-phenoxy-*n*-alkane Molecular Ions[a]**

| | | | |
|---|---|---|---|
| *vic*-monodeuterated | | dideuterated | |
| **1**[b] | 0.43 | $CH_3CHOPhCD_2H$ | 0.27 |
| **1e**[b] | 0.30 | $CH_3CHOPhCD_2CH_2CH_3$[c] | 0.61 |
| **6t** | 0.26 (0.35[d]) | $CH_3CHOPhCD_2CH_3$ | 2.3 (2.0[d]) |
| **6e** | 0.07 (0.10[d]) | $CH_3CHOPhCH_2CD_2CH_3$[c] | 0.04 |
| **15t** | 0.32 (0.36[d]) | $CH_3CD_2CHOPhCH_2CH_3$ | 0.60 (0.65[d]) |
| **15e** | 0.07 (0.10[d]) | $CH_3CH_2CHOPhCD_2CH_2CH_3$ | 0.54 (0.55[d]) |
| *gem*-monodeuterated | | $CH_3CD_2CHOPhCH_2CH_2CH_3$ | 0.44 (0.52[d]) |
| $CH_3CDOPhCH_2CH_3$[b] | 0.03 | trideuterated | |
| $CH_3CDOPhCH_2CH_2CH_3$[c] | 0.04 | $CD_3CHOPhCH_3$ | 0.58 (0.60[d]) |
| $CH_3CH_2CDOPhCH_2CH_3$ | 0.03 (0.02[d]) | $CD_3CHOPhCH_2CH_3$ | 0.15 (0.16[d]) |
| $CH_3CH_2CDOPhCH_2CH_2CH_3$ | 0.02 (0.025[d]) | $CH_3CHOPhCH_2CD_3$ | 0.03 |
| $CH_3CH_2CDOPhCH_2(CH_2)_2CH_3$ | 0.03 | $CD_3CHOPhCH_2CH_2CH_3$[c] | 0.10 |
| $CH_3(CH_2)_2CDOPhCH_2(CH_2)_2CH_3$ | 0.035 (0.025[d]) | $CD_3CHOPhCH_2(CH_2)_3CH_3$ | 0.15 |
| *vic*-tetradeuterated | | pentadeuterated | |
| $CH_3CD_2CHOPhCD_2CH_3$ | 28 (20[d]) | $CD_3CHOPhCD_2CH_3$ | 20 |
| $CH_3CD_2CHOPhCD_2CH_2CH_3$ | 25 (17[d]) | $CH_3CH_2CHOPhCD_2CD_3$ | 0.65 |
| $CH_3CD_2CHOPhCD_2(CH_2)_3CH_3$ | 8 (10[d]) | hexadeuterated | |
| $CH_3CH_2CD_2CHOPhCD_2(CH_2)_2CH_3$ | 11 (11[d]) | $CD_3CHOPhCD_3$ | >100[d] |
| | | $CD_3CDOPhCD_2CH_3$ | 37 |

[a] Measured by MIKE spectroscopy (70 eV EI, 8 kV accelerating voltage). Except where otherwise noted, reported values are those measured on the 2-sector instrument at UCR. [b] Reference 2. [c] Reference 11. [d] Measured on the 2-sector instrument at Palaiseau.

mechanisms for water elimination from the ionized alcohol and acetic acid elimination from the ionized acetate remain unexplored, but it is apparent that these are not good candidates for the stereoselective mass spectrometry of long-chain compounds.

In contrast to the fragmentation patterns of the alcohol and acetate, the MIKE spectrum of the phenyl ether of $d_4$-4-octanol is dominated by a single peak. Elimination from the ionized phenyl ether gives a neutral hydrocarbon fragment, and the positive charge remains with the functional group, which departs in the form of ionized phenol. This is consistent with the Audier−Stevenson rule,[9] which postulates that the electric charge reposes on the fragment with the lower ionization energy (IE). Since phenol has a lower IE than most disubstituted alkenes (but one that is greater than or equal to the IE of tri- or tetrasubstituted alkenes with ≥8 carbons),[10] the sparseness of the MIKE spectrum of $CH_3CH_2CD_2CHOPhCD_2CH_2CH_2CH_3$ is actually quite informative: the absence of any $C_8$-ions indicates that rearrangement has not taken place to give branched structures that can undergo elimination. $PhOH^{•+}$ and $PhOD^{•+}$ together constitute 95% of the total fragment ion current. All the other phenoxy-*n*-alkanes studied here show even higher proportions of phenol$^{•+}$ in their MIKE spectra. By contrast, the MIKE spectrum of a branched isomer, $(CH_3)_3CCH_2CH(CH_3)CH_2OPh$, exhibits both $PhOH^{•+}$ and $C_8H_{16}^{•+}$, in a ratio of about 5:2, as would be expected on the basis of the Audier−Stevenson rule.

Alkene expulsion exhibits a high degree of regioselectivity: $PhOD^{•+}$ is 11 times more abundant than $PhOH^{•+}$ in the MIKE spectrum of $CH_3CH_2CD_2CHOPhCD_2CH_2CH_2CH_3$. The formation of a small amount of $PhOD^{•+}$ from the geminally monodeuterated analogue, *4-$d_1$*-4-phenoxyoctane (approximately $^1/_{30}$ the intensity of $PhOH^{•+}$), shows that a minor elimination pathway occurs via hydrogen transfer from the carbon to which oxygen is initially attached.

The $PhOD^{•+}/PhOH^{•+}$ intensity ratios for other vicinally perdeuterated homologues that we have looked at ($d_5$-2-phenoxybutane, $d_4$-3-phenoxypentane, $d_4$-3-phenoxyhexane, and $d_4$-3-phenoxyoctane) also show high regioselectivity. Likewise, the ratios for other geminally monodeuterated compounds in the present study (*3-$d_1$*-3-phenoxypentane, *3-$d_1$*-3-phenoxyhexane, and *3-$d_1$*-3-phenoxyheptane) differ only slightly from that for *4-$d_1$*-4-phenoxyoctane. The evidence demonstrates that regioselectivity does not depend greatly upon chain length.

To probe regioselectivity in greater detail, we have examined the effects of perdeuterating one methyl (*1,1,1-$d_3$*-2-phenoxypropane, *1,1,1-$d_3$*-2-phenoxybutane, *4,4,4-$d_3$*-2-phenoxybutane, or *1,1,1-$d_3$*-2-phenoxyheptane) or one methylene group (*2,2-$d_2$*-2-phenoxybutane, *2,2-$d_2$*-3-phenoxypentane, *2,2-$d_2$*-3-phenoxyhexane, or *4,4-$d_2$*-3-phenoxyhexane). Results of MIKE spectra of deuterated analogues (including previously published data) are summarized in Table 1. The degree of regioselectivity that we observe mirrors that which Audier and coworkers demonstrated in their pioneering work a decade ago for 2-phenoxypentanes.[11] A methyl group adjacent to the functionalized methylene makes a small contribution (roughly 15% of the transferred hydrogen, if isotope effects are ignored), while a more distant methyl group contributes far less.

Regioselectivities for the vicinally tetradeuterated compounds are compared in Table 1. We suppose that two decomposition pathways are available:[5] one that involves exclusive transfer of vicinal hydrogen versus a nonselective pathway in which all the nonmethyl hydrogens randomize completely. To a first approximation, we neglect any transfer from methyl groups. Under these assumptions, the $PhOD^{•+}/PhOH^{•+}$ intensity ratio of 28 for $CH_3CD_2CHOPhCD_2CH_3$ represents a lower degree of regioselectivity than the ratio of 25 for $CH_3CD_2CHOPhCD_2CH_2CH_3$. In the former, the nonselective pathway scrambles 4 D's with 1 H, while in the latter, the nonselective pathway randomizes 4 D's with 3 H's. In this simplified model, each observed $PhOD^{•+}/PhOH^{•+}$ intensity ratio should be weighted by the proportion of H's among the randomizing atoms: 1/5 for a $d_4$-pentyl, 3/7 for a $d_4$-hexyl, and 7/11 for a $d_4$-octyl. On the basis of

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**Table 2. Regio- and Stereochemical Dependence in the QIT/CAD Spectra in Terms of Observed $PhOD^{\bullet+}/PhOH^{\bullet+}$ Intensity Ratios from GC/MS/MS Experiments[a]**

| | | | |
|---|---|---|---|
| $CD_3CHOPhCH_2CH_3$ | 0.13[b] | $CH_3CDOPhCH_2CH_3$ | 0.07 |
| $CH_3CHOPhCD_2CH_3$ | 2.0 | $CH_3CHOPhCH_2CD_3$ | 0.01 |
| $CD_3CHOPhCD_2CH_3$ | 13 | $CD_3CDOPhCD_2CH_3$ | 18 |
| **1t** | 0.44[b] | **1e** | 0.36[b] |
| **2t** | 0.61 | **2e** | 0.17 |
| **3t** | 0.34 | **3e** | 0.08 |
| **4t** | 0.59 | **4e** | 0.26 |
| **5t** | 0.29 | **5e** | 0.12 |
| **6t** | 0.41 | **6e** | 0.07 |
| **7t** | 0.55[b] | **7e** | 0.21[b] |
| **8t** | 0.37[b] | **8e** | 0.21[b] |
| **9t** | 0.36[b] | **9e** | 0.14[b] |
| **10t** | 0.39[b] | **10e** | 0.14[b] |
| **11t** | 1.34[b] | **11e** | 0.47[b] |
| **12t** | 0.66[b] | **12e** | 0.39[b] |
| **13t** | 0.63 | **13e** | 0.29 |
| **14t** | 0.63 | **14e** | 0.25 |
| **15t** | 0.28 | **15e** | 0.15 |

[a] Experiments in which all other ions were ejected except the molecular ion, followed by collisionally activated decomposition (CAD) by collisions with neutral helium. [b] Reference 2.

this rationale, the weighted regioselectivities become 5.6 for 3-pentyl, 10.7 for 3-hexyl, 5.1 for 3-octyl, and 7.0 for 4-octyl. Consequently, 3-hexyl gives the greatest degree of regioselectivity. This is borne out by the observation that the *3-$d_1$*-3-hexyl analogue gives the lowest $PhOD^{\bullet+}/PhOH^{\bullet+}$ intensity ratio of all of the geminally monodeuterated compounds examined.

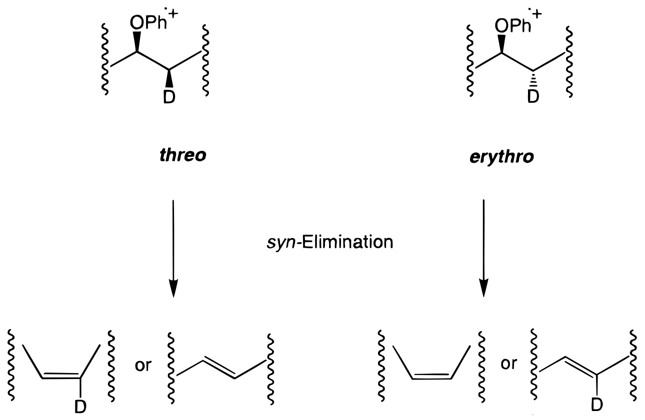
**Stereoselectivity.** In every example studied here, the isomer corresponding to the threo series exhibits a larger $PhOD^{\bullet+}/PhOH^{\bullet+}$ intensity ratio than does its diastereomer from the erythro series. This may be seen by comparison of the CAD spectra listed in Table 2.

Regioselectivity in the CAD experiments (as exemplified by the tabulated results for 2-phenoxybutanes) does not vary greatly from what is observed in the MIKE spectra.

It is tempting to try to correlate regioselectivity and stereoselectivity in these elimination reactions, but the data do not support such an inference. Consider the ratio of ratios, ***r*** equals the $PhOD^{\bullet+}/PhOH^{\bullet+}$ ratio from the threo divided by the $PhOD^{\bullet+}/PhOH^{\bullet+}$ ratio from the erythro, as a measure of the degree of stereoselectivity. 3-Phenoxyhexane shows the highest degree of regioselectivity in Table 1, and its *4-$d_1$*-analogues, **6,** show the highest values of $r$ (3.7 in the MIKES, 5.8 in the CAD). 3-Phenoxypentane also displays a high degree of regioselectivity, and it turns out that the $PhOD^{\bullet+}/PhOH^{\bullet+}$ ratios from CAD on the ionized *2-$d_1$*-3-phenoxypentanes, **3**, are not significantly different from those for **6**. Yet the $PhOD^{\bullet+}/PhOH^{\bullet+}$ ratios in both cases do differ from those for the respective 2-phenoxy-3-deuterated analogues **2** and **4**. In other words, it is not possible to establish a clear-cut correlation between regioselectivity and stereoselectivity, because the *2-$d_1$*-3-phenoxyhexanes (**4**) display some of the lowest values of $r$.

We cannot discern a systematic variation with chain-length. The 2-phenoxybutanes (**1**) display the lowest degree of stereoselectivity ($r = 1.2$). Beyond that, however, the degree of stereoselectivity shows no regular increase with the number of carbons in the chain. The only trend appears to be that, among the 3-phenoxyalkanes, compounds with $d_1$-ethyls display lower degrees of stereoselectivity ($r = 2.4$ for **5**, 1.8 for **8**, 1.7 for **12**) than their isomers in which the deuterium resides in a longer alkyl group ($r = 5.8$ for **6**, 2.6 for **9**, 2.1 for **13**).

**Scheme 1**



**Scheme 2**

$$\begin{tikzcd}
\mathrm{iPrOPh}^{\cdot+} + \mathrm{H}^{\cdot} \arrow[r, "\mathrm{HA} = -\Delta H"] \arrow[d, "\Delta H = 313.5\ \mathrm{kcal\ mol^{-1}}"] & \overset{\mathrm{H}^+}{\mathrm{iPrOPh}} \\
\mathrm{iPrOPh}^{\cdot+} + \mathrm{H}^+ + e^- \arrow[r, "\Delta H = -183.5\ \mathrm{kcal\ mol^{-1}}"'] & \mathrm{iPrOPh} + \mathrm{H}^+ \arrow[u, "\Delta H = -196.5\ \mathrm{kcal\ mol^{-1}}"']
\end{tikzcd}$$

## Discussion

The method described here is based on reactivity differences between diastereomers. A mechanistic interpretation complements the empirical correlation. The general trend can be rationalized in terms of syn-elimination, in which expulsion of a neutral *trans*-alkene is favored over the *cis*-alkene, as Scheme 1 represents. Density functional calculations on the simplest *sec*-alkyl phenyl ether (2-phenoxypropane, $^i$PrOPh) indicate that alkene expulsion passes through a four-member cyclic transition state,[5] a view that is corroborated by the following experimental data: (1) the calculations predict an energy barrier for the decomposition of $^iPrOPh^{\bullet+}$ that agrees with the observed lower bound;[12] (2) the fragment ion has the structure of a phenol radical cation rather than a cyclohexadienone;[3,12] and (3) the high degree of regioselectivity is described here.

The contrast with alkene expulsions from neutral acetates (which pass through six-member cyclic transition states)[8] and with ionized alcohols or acetates (which do not display high regioselectivity, as exemplified by Figure 1) suggests that ionized alkyl phenyl ethers constitute a special category. The peculiarity of this category derives, in part, from the low hydrogen atom affinities (HA) of their radical cations. The thermodynamic cycle in Scheme 2 summarizes how to calculate the HA of $^i$PrOPh from its proton affinity (PA, which is $-\Delta H$ for putting $H^+$ onto a gaseous molecule) and its ionization energy (IE), as well as the ionization energy of a hydrogen atom (IE = 313.5 kcal $mol^{-1}$).[10] The ionization energy for $^i$PrOPh[13] is 183.5 ± 1 kcal $mol^{-1}$

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[12] Weddle, G. H.; Dunbar, R. C.; Song, K.; Morton, T. H. *J. Am. Chem. Soc.* **1995**, *117*, 2573−2580.

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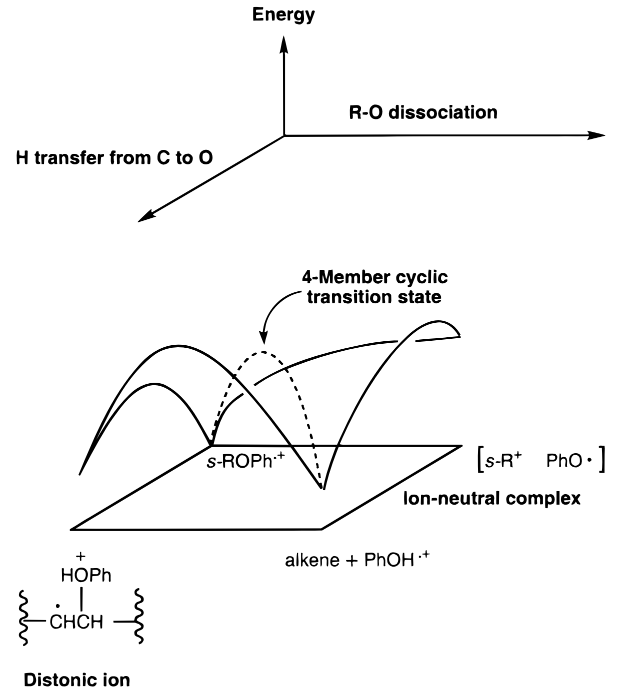


**Figure 2.** Three-dimensional reaction coordinate diagram illustrating plausible mechanisms for expulsion of alkene from an ionized *sec*-alkyl phenyl ether ($s$-ROPh$^{\bullet+}$) in the gas phase.

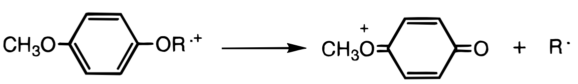
(the same as for longer homologues up to 2-phenoxyoctane[5]). The PA of $^{i}$PrOPh is calculated to be $\sim$2 kcal mol$^{-1}$ greater than that of coumaran (measured experimentally as 204 kcal mol$^{-1}$),[14] with the para-carbon as the most basic site. It is not easy to measure the PA of the oxygen of $^{i}$PrOPh experimentally, but it is calculated to be $\sim$7.5 kcal mol$^{-1}$ less basic than coumaran. On that basis, the HA of the oxygen of ionized $^{i}$PrOPh is 66.5 kcal mol$^{-1}$, while the HA of the para-carbon is 76 kcal mol$^{-1}$. The oxygen HA is at least 25 kcal mol$^{-1}$ lower than the weakest C$-$H bond dissociation energy in an unbranched, neutral alkyl ether.[15]

By contrast, the same calculation on ionized ethyl acetate (IE = 230.5 kcal mol$^{-1}$, PA = 200.5 kcal mol$^{-1}$)[10] gives an HA for the carbonyl oxygen of 117.5 kcal mol$^{-1}$. This is comparable to the bond dissociation energy of water and is much higher than the bond dissociation energy of any sp$^3$ C$-$H bond. Hence, an ionized acetate ester can easily abstract a hydrogen atom from an alkyl chain to form a distonic ion. Following the reactivity/selectivity principle, one should not be surprised that long-chain *sec*-alkyl acetates do not appear to discriminate among methylene hydrogens in their mass spectrometric decompositions.

Alkene expulsion from ionized *sec*-alkyl phenyl ethers ($s$-ROPh$^{\bullet+}$) can take place via three pathways, as the 3-dimensional reaction coordinate diagram (sometimes called a More O'Ferrall Jencks plot[16]) in Figure 2 portrays. This diagram depicts two limiting cases by means of solid curves, depending upon whether C$-$O dissociation occurs prior to or after the transfer of a hydrogen from carbon to oxygen. Because an ionized phenoxy group has such a low HA, formation of a distonic ion, as represented on the left of Figure 2, should be endothermic (unlike the formation of distonic ions from ionized aliphatic ethers[17]). The other limiting case, represented by the solid curve to the right, corresponds to dissociation of the C$-$O bond to form an ion-neutral complex. Photoionization studies of deuterated *sec*-alkyl phenyl ethers[5] have been interpreted as showing that 20$-$50% of the molecular ions decompose via this mechanism, depending on internal energy. However, a complex-mediated pathway that proceeds via a classical *sec*-alkyl carbocation cannot display stereochemical discrimination, because (by definition) the cation must be able to rotate freely within the complex.[18,19]

The [$s$-R$^+$ PhO$^\bullet$] ion$-$neutral complex does not correspond to a local minimum on the potential energy surface, because there is no energetic barrier to its collapse back to $s$-ROPh$^{\bullet+}$. Nevertheless, such ion$-$neutral complexes behave as bona fide intermediates with nonzero lifetimes, because the degrees of freedom liberated by breaking a covalent bond stabilize them entropically. As noted above, the majority of ions do not decompose via ion$-$neutral complexes. Published density functional calculations[5] predict that the favored pathway does not correspond to either of the solid curves in Figure 2 but instead passes through a four-member cyclic transition state (the dashed curve, which represents a concerted pathway in Figure 2). This accounts for the observed diastereoselectivity of vicinal alkene expulsion, although the experimental data do not rule out a distonic intermediate unequivocally.

The reaction coordinate diagram in Figure 2 prompts the question as to how energetic perturbations affect the reaction coordinate. What happens when the HA of the aryloxy group is further decreased (such as by putting on a *p*-methoxy group, which ought to lower the IE by about 10 kcal mol$^{-1}$)[8] or is increased (such as by replacing the phenoxy with a pyridyloxy)? Thus far, the variations that have been studied have exerted too drastic of an effect, and it has not proven possible to explore their consequences for diastereoselection. We observe that, on one hand, a *p*-methoxy substituent leads predominantly to the homolytic fragmentation shown in eq 1.[19] On the other hand, ionized *sec*-alkyl pyridyl ethers undergo double-hydrogen transfer,[20] as exemplified by ionized 4-*iso*-propoxypyridine in eq 2.[21] In the former instance, no hydrogen transfer takes place, while in the latter instance, two hydrogens move from the side chain to the aryloxy. Neither case is suitable for exploring stereoselectivity.



(1)

There may well exist patterns of substituting the phenoxy group that will enhance discrimination between

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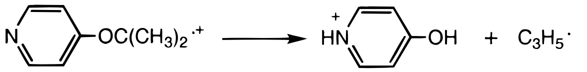

(2)

threo and erythro, but they have yet to be discovered. The effect of the position of deuteration on the degree of stereoselectivity also remains to be understood. The correlation between regiochemistry and stereoselectivity is by no means obvious. The pair of dideuterated 3-phenoxyhexanes in Table 1 exhibit PhOD$^{\bullet+}$/PhOH$^{\bullet+}$ intensity ratios that are nearly the same. While there is little regioselective discrimination between methylenes at positions 2 and 4, the stereoselectivity between monodeuterated **t** and **e** isomers in position 2 (compounds **5**), $r = 2.4$, is dramatically less than that observed between ***t*** and ***e*** isomers in position 4 (compounds **6**), $\boldsymbol{r} = 5.8$. Conformational equilibria may play an important role, but that issue has only begun to be addressed in simpler alkyl phenyl ethers.[22]

## Conclusions

All unbranched *sec*-alkyl phenyl ethers with a single deuterium vicinal to the phenoxy group exhibit more expulsion of undeuterated alkene (to form PhOD$^{\bullet+}$) in the mass spectra of the threo series than their respective stereoisomers from the erythro series. Vicinal syn-elimination expels *trans*-alkenes preferentially. The consistency of this difference in fragment ion intensity ratios provides a general method for discriminating between diastereomers.

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**Supporting Information Available:** Source GC mass spectra (70 eV) and infrared C–D stretching frequencies of compounds **2**–**15**.This material is available free of charge via the Internet at http://pubs.acs.org.

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