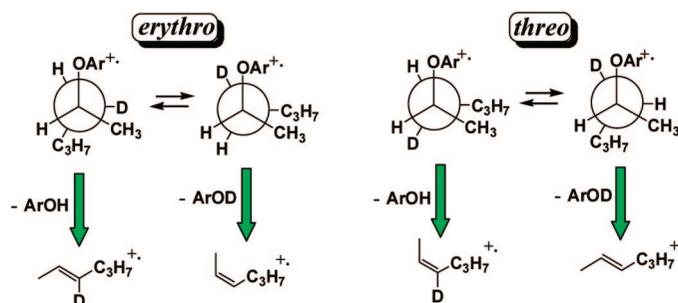# Stereochemical Preferences in 4-Center *Syn*-Eliminations from Gaseous Ions

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Concerted unimolecular eliminations from ionized *sec*-alkyl aryl ethers (ROAr$^{+\bullet}$) display a preference for producing double bonds with *trans* geometry. This preference can be assessed quantitatively, provided that a regioselective variant can be found. Expulsion of neutral alkenes via *syn*-elimination to give ionized ArOH does not exhibit a pronounced preference with regard to the direction of elimination. By contrast, ionized 2-hexyl *p*-trifluoromethylphenyl ether eliminates neutral ArOH regioselectively, giving ionized 2-hexenes rather than ionized 1-hexene. Vicinally monodeuterated 2-hexyl and 3-hexyl ethers were prepared as pure diastereomers. Metastable ion decompositions of their gaseous radical cations are compared over two different time windows. The regioselectivity for the 2-hexyl ether allows the geometric preference for the double bonds to be estimated based on the difference between the *erythro* and *threo* monodeuterated diastereomers (*trans*/*cis* = 2.0 for producing ionized 2-hexene from parent ions with the lowest internal energies). The 3-hexyl ethers and ionized 2- and 3-phenoxyoctanes also undergo stereoselective elimination but give experimental values that reflect their lack of regioselectivity. Examination of *erythro*/*threo* combinations shows that GC/MS/MS has the ability to quantitate stereochemistry in mixtures containing both positional and stereoisomers.

The stereoselectivity of vicinal unimolecular eliminations in the gas phase (*syn*-eliminations, sometimes called *cis*-eliminations) has long intrigued organic chemists.[1,2] Not long ago we reported a 4-center elimination from a vibrationally activated positive ion, which expels water much more quickly than conformational equilibration can take place. Under those conditions, elimination occurs so promptly that the geometry with which the cation initially forms is preserved, leading to >90% *cis* stereochemistry of the recovered alkene.[3]
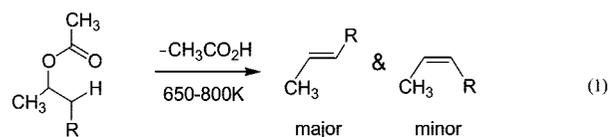

Most eliminations give predominantly *trans*. Thermal 6-center *syn*-eliminations from neutral 2-acetoxy-*n*-alkanes yield *trans*: *cis* ratios on the order of 1.5–1.9:1, as eq 1 illustrates.[1] Gaseous radical cations show very similar selectivity. The isomer distribution inferred from the expulsion of neutral acetic acid from ionized acetate esters has been assessed by means of deuterium labeling, as depicted in eqs 2a and 2b, and gives comparable ratios, in the range 1.4–1.7:1 (depending on ion internal energies) when deuterium isotope effects are taken into consideration.[4]

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(1) (a) DePuy, C. H.; King, R. W. *Chem. Rev.* **1960**, *60*, 431–457. (b) Scheer, J. C.; Kooyman, C. C.; Sixma, F. L. *Recl. Chim. Pays Bas* **1963**, *82*, 1123–1154. (c) Skell, P. S.; Hall, W. L. *J. Am. Chem. Soc.* **1964**, *86*, 1557–1558.

(2) (a) Maccoll, A.; Stone, R. H. *J. Chem. Soc.* **1961**, 2756–2761. (b) Maccoll, A. *Chem. Rev.* **1969**, *69*, 33–60. (c) Chuchani, G.; Martín, I.; Botinov, A.; Domínguez, R. M. *Int. J. Chem. Kinet.* **1990**, *22*, 1249–1253.

(3) Mayer, P. S.; Morton, T. H. *J. Am. Chem. Soc.* **2002**, *124*, 12928–12929.

(2a)

(2b)
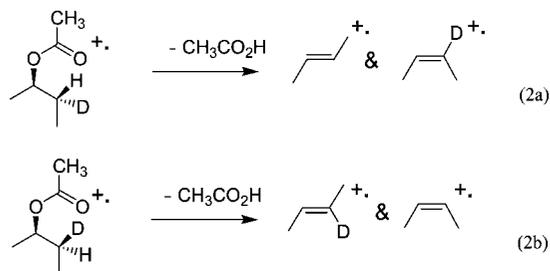
Unfortunately, *trans:cis* ratios have not hitherto been available for eliminations via 4-center transition states. The difficulty arises because published experiments - e.g. the thermal expulsion of HX from neutral *sec*-alkyl halides[2] - have been done under conditions where the geometric isomers of the products equilibrate.

One way to look at 4-center eliminations is to examine unimolecular dissociations of gaseous ions. Assaying stereo-chemical preferences via mass spectrometry can suffer from the complication that elimination may go in two directions - for instance, the unimolecular eliminations in eq 2 give ionized 1-butenes in competition with the products shown, a contribution that needs to be taken into account. For an experiment to provide a more accurate quantitative measure, the elimination needs to be regiospecific. Here we describe such a case.

Compounds such as tartrate or dibromosuccinate esters would appear at first glance to offer promising systems for studies without the necessity of isotopic labeling, but published experiments demonstrate that alternative decomposition pathways dominate. Although the *meso* and racemic compounds exhibit significant differences, ionized tartrate esters exhibit very little water loss, and ionized 2,3-dibromosuccinate esters show virtually no elimination of HBr.[5]

This paper looks at cations that can undergo conformational interconversion prior to vicinal 4-center elimination. Given that these ions are produced at low pressures with a broad internal energy distribution (and do not exchange energy with a thermal bath), the usual suppositions that underlie the Curtin−Hammett principle might not be warranted. Interpreting unimolecular dissociations using first-order kinetics therefore requires justi-fication, for which we provide *a posteriori* tests of consistency.

Background

Secondary *n*-alkyl aryl ethers provide the most promising examples of stereoselective 4-center eliminations to date. Gas phase dissociations of ionized alkoxybenzene derivatives have offered fertile ground for mechanistic investigations over a period of more than four decades. Primary alkyl phenyl ethers dissociate via ion-neutral complexes when ionized, regardless of whether they become positively charged by protonation or by removal of an electron.[6]

(3)
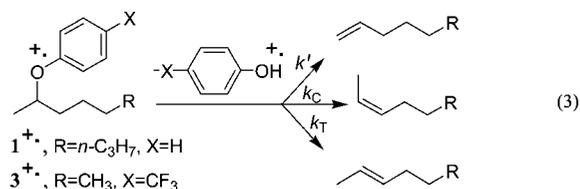
By contrast, ionized *sec-n*-alkyl aryl ethers exhibit stereo-chemical selectivity in their expulsions of neutral alkenes with very little hydrogen scrambling.[7] Many studies have shown that the resulting ions have phenolic structures.[7,8] In these com-pounds, elimination occurs via 4-membered cyclic transition states in preference to passing through ion-neutral complexes. As eq 3 exemplifies, this elimination is not regiospecific. Labeling studies reveal that ionized 2-*n*-alkyl phenyl ethers expel a mixture of 1- and 2-alkenes.[8]

The rate coefficients in eq 3 correspond to the three isomeric, neutral alkenes produced by vicinal elimination: k' for expulsion of the 1-alkene, k_C for expulsion of the *cis*-2-alkene, and k_T for expulsion of the *trans*-2-alkene. A labeling strategy for eq 3, which parallels that of eq 2, permits assessment of the *trans* vs *cis* preference. If the contribution from k' can be determined, placing a deuterium at the methylene vicinal to the aryloxy group, as in Scheme 1, allows k_T/k_C to be measured.

Consider eq 3, in which k' is neglected. Scheme 1 portrays two racemic diastereomers (called *erythro* and *threo*) that differ only by configuration at a monodeuterated methylene. The scheme summarizes outcomes expected for the staggered conformations about the C2−C3 carbon−carbon bond. *Syn*-elimination is stereospecific. The preference for one double bond geometry over the other constitutes the stereoselectivity of the reaction.

We report here that tuning the ionization energy (IE) of the aryloxy group gives a regiospecific variant of eq 3, which produces ionized alkene (as does eq 2). This regioselectivity permits relative rate constants to be extracted from the data.

If product analysis were not complicated by the competing expulsion of a 1-alkene (the uppermost pathway in eq 3, corresponding to rate coefficient k'), then observation of different ratios of H to D transfer between the *erythro* and *threo* isomers would provide a direct quantitative measure of stereoselectivity. Ionized **3** displays the requisite regioselectivity when it produces ionized 2-hexenes. In seeking to evaluate stereoselectivity, however, two other issues have to be confronted, as well.

The first issue concerns the validity of algebraic manipulations based on fragment ion abundance ratios. The data analysis depends on how the ratios vary over the time interval of the experiment. Finding solutions to the differential equations is comparatively simple if the reaction has run to completion or if it obeys first-order kinetics (such as when ions are monoen-ergetic[8] or are activated by repeated collisions with a bath gas where the collision rate is much faster than the unimolecular decomposition[9]).

(4) (a) Green, M. M.; Moldowan, J. M.; Hart, D. J. Krakower *J. Am. Chem. Soc.* **1970**, *92*, 3491–3492. (b) Green, M. M.; McCluskey, R. J.; Vogt, J. *J. Am. Chem. Soc.* **1982**, *104*, 2262–2269.

(5) (a) Vairamani, M.; Prabakar, S.; Rama Devi, A.; Madhusudanan, K. P. *Rapid Commun. Mass Spectrom.* **1995**, *9*, 651–654. (b) Vairamani, M.; Prabakar, S.; Rama Devi, A. *Rapid Commun. Mass Spectrom.* **1996**, *10*, 737–741.

(6) (a) MacLeod, J.; Djerassi, C. *J. Am. Chem. Soc.* **1966**, *88*, 1840–1841. (b) Morton, T. H. *J. Am. Chem. Soc.* **1980**, *102*, 1596–1602. (c) McAdoo, D. J.; Morton, T. H. *Acc. Chem. Res.* **1993**, *26*, 295–302. (d) Traeger, J. C.; Morton, T. H. *J. Am. Chem. Soc.* **1996**, *108*, 9661–9668. (e) Jacquet, J. P.; Morton, T. H. *J. Mass Spectrom.* **1997**, *32*, 251–252. (f) Morton, T. H. In *The Encyclopedia of Mass Spectrometry*; Armentrout, P. B., Ed.; Elsevier: London, 2003; Vol. 1, pp 467−469.

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(8) Traeger, J. C.; Luna, A.; Tortajada, J. C.; Morton, T. H. *J. Phys. Chem. A* **1999**, *103*, 2348–2358, references contained therein.

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SCHEME 1. Stereospecific *Syn*-Elimination of a Neutral Alkene from Ionized Monodeuterated Alkyl Aryl Ethers to Produce Phenolic Ions

A *erythro*

B *threo*
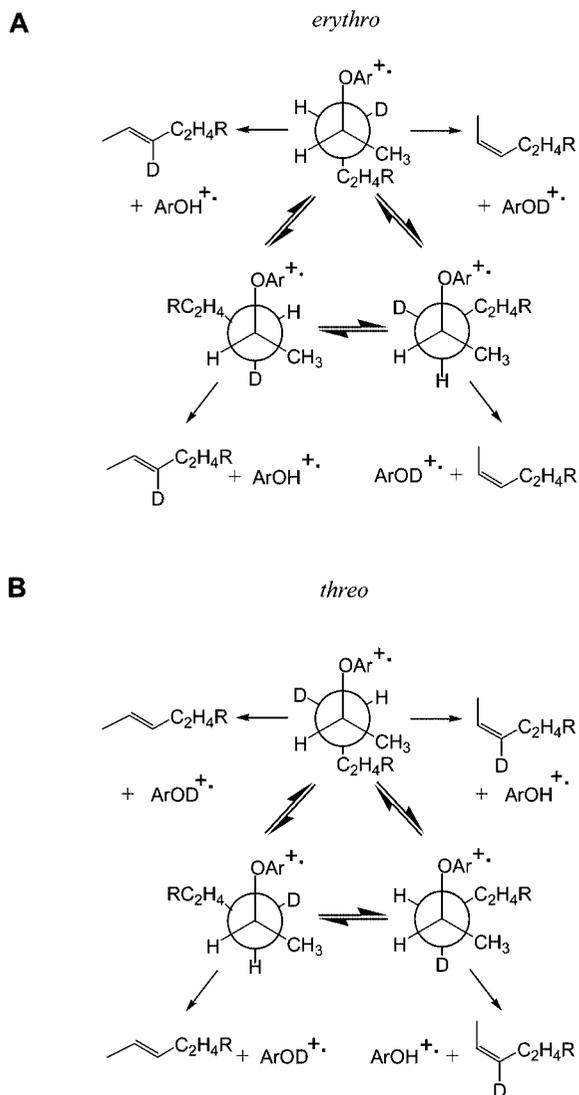
Regimes in which products are viewed through a time window (such as metastable ion dissociations) do not necessarily lend themselves to such a straightforward interpretation. If the fragment ions under consideration do not dissociate further and if their relative abundances vary slowly over the duration of the time window, metastable ion dissociations can still be analyzed as though they obey first-order kinetics.[10] Comparing data taken from two different time windows tests the validity of this analysis.

A double-focusing mass spectrometer has two field-free regions (FFRs). In a reverse Nier-Johnson geometry (B−E), the first FFR intervenes between the ion source (where ions are all accelerated to the same kinetic energy) and mass selection by the magnetic (B) sector. The time window corresponding to the first FFR starts 1−2 μs after ion formation and has a duration of approximately 4 μs for the m/z values under consideration here.

The second FFR intervenes between mass selection and energy selection by the electrostatic (E) analyzer. In the instrument used for the present experiments, this time domain

(10) Kondrat, R.; Morton, T. H. *Org. Mass Spectrom.* **1991**, *26*, 410−415.

begins about 10 μs after ion formation and lasts on the order of 10 μs. Other things being equal, ions that decompose in the first FFR have a greater internal energy than do those that decompose in the second FFR. If pertinent relative dissociation rates (such as *trans/cis* ratios or net isotope effects) do not differ greatly between the two windows, it can be inferred that nonuniform internal energy distributions distort those branching ratios to a negligible extent, and product distributions from metastable ion dissociations can be treated as though they obey first-order kinetics.

The second issue deals with the appropriate model by which to treat isotope effects. In Scheme 1, the *erythro* loses a deuterated phenolic ion (ArOD$^{+\bullet}$) via *syn* elimination to give an undeuterated *cis*-alkene (Scheme 1A). The *threo* loses deuterated phenolic ion to give an undeuterated *trans* alkene (Scheme 1B). If every elimination proceeded from the uppermost *erythro* conformer in Scheme 1A and from the uppermost *threo* conformer in Scheme 1B (where the aryloxy group is staggered between the vicinal H and D), evaluation of the isotope effect could be assumed to be straightforward. For the *erythro*, a primary isotope effect would operate in the elimination of *cis* alkene and a secondary isotope effect in the elimination of *trans* alkene. For the *threo*, the same primary isotope effect would operate for elimination of *trans* alkene and the same secondary isotope effect for elimination of *cis*. The net isotope effects on the two *cis:trans* alkene ratios would therefore correspond to k_D/k_H and k_H/k_D, respectively, and could be canceled out by multiplying the ratios together.

It seems more likely to suppose that the conformations of the reactant ions interconvert rapidly. Scheme 1 illustrates this. It might turn out that the isotope effect for each conformer skews its relative contribution to the overall reaction, such that the net isotope effect for the *erythro* might differ from the reciprocal of the net isotope effect from the *threo*.

Results

To address the aforementioned issues, we consider metastable ion dissociations (i.e., ions that are formed with barely enough energy to decompose, so that fragmentations take place after they leave the ion source). Here the ions are not activated by additional collisions. First we compare first and second FFR decompositions of deuterated analogues of 2-phenoxyoctane, **1**. The sample contained a mixture of positional isomers, which was investigated using GC/MS/MS to separate **1** from its 3-phenoxy isomer.

Molecular ion **1**$^{+\bullet}$ exhibits a single fragment ion in both FFRs, ionized phenol (PhOH$^{+\bullet}$), as eq 3 depicts. The monodeuterated analogues **2** give two fragments, PhOH$^{+\bullet}$ and PhOD$^{+\bullet}$, as Figure 1 indicates. Figure 1 plots the PhOH$^{+\bullet}$/PhOD$^{+\bullet}$ abundance ratio for pure *erythro* and pure *threo* **2** in both the first FFR (measured by means of a B/E linked scan) and the second FFR (measured by means of mass-analyzed ion kinetic energy spectroscopy or MIKES). The ratio of experimental fragment ion abundances is plotted as a function of the mole fraction of *erythro*, X_e.

The precision of these measurements can be seen by noticing that six data points are plotted for each determination. On the one hand, the average PhOH$^{+\bullet}$/PhOD$^{+\bullet}$ ratios for the *erythro* have virtually the same values, 5.64 ± 0.27 and 5.55 ± 0.26 (± values denote 95% confidence limits). While the differences between the ratios for the *threo* in the first and second FFRs are statistically significant, 2.22 ± 0.11 vs 1.97 ± 0.04,
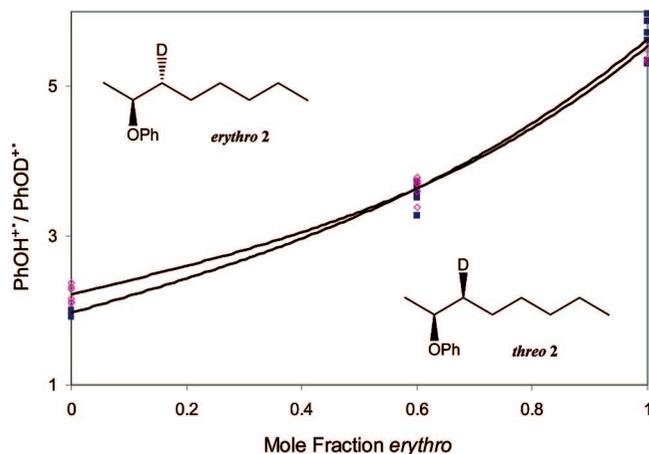
FIGURE 1. $PhOH^{+\bullet}/PhOD^{+\bullet}$ abundance ratios (m/z 94:m/z 95) from metastable ion decompositions (open symbols from B/E scans; closed symbols MIKE spectra) of diastereomers of **2**, as well as of a 60:40 mixture (mole fraction $X_e = 0.6$).

respectively, they do not differ by very much. On the other hand, the differences between *erythro* and *threo* are quite large.

Figure 1 also shows the $PhOH^{+\bullet}/PhOD^{+\bullet}$ ratios for a mixture that contains 60% *erythro* and 40% *threo* ($X_e = 0.6$). It is evident that the mixture exhibits $PhOH^{+\bullet}/PhOD^{+\bullet}$ ratios midway between those of the pure compounds but that the three sets of data points do not lie on a straight line when plotted as a function of mole fraction X_e. That is to say, an isotope effect retards the dissociation of *threo* relative to that of *erythro* when the two are mixed. That result corresponds to what one would anticipate from Scheme 1, bearing in mind that expulsion of the more stable (*trans*) alkene from the *threo* requires transfer of a deuterium.

$$\left(\frac{[PhOH^{+\bullet}]}{[PhOD^{+\bullet}]}\right)_{mixture} =$$

$$\frac{[X_e + W(1 - X_e)]\left(\frac{[PhOH^{+\bullet}]}{[PhOD^{+\bullet}]}\right)_{erythro}\left(\frac{[PhOH^{+\bullet}]}{[PhOD^{+\bullet}]}\right)_{threo}}{W(1 - X_e)\left(\frac{[PhOH^{+\bullet}]}{[PhOD^{+\bullet}]}\right)_{erythro} + X_e\left(\frac{[PhOH^{+\bullet}]}{[PhOD^{+\bullet}]}\right)_{threo}} \quad (4)$$

Prior work has proposed that the observed ratio for a mixture should obey the relationship given in eq 4, where W stands for a weighting factor, which embraces the isotope effect.[5] When there is no isotope effect, $W = 1$ and the plot ought to be linear. In the case of the diastereomers of compound **2**, the experimentally determined weighting factors for metastable ion dissociations (no collisional activation) are found to be $W = 0.80 \pm 0.07$ for the B/E scan and $W = 0.70 \pm 0.06$ for the MIKES experiment. Those values are to be compared with $W = 0.3$ measured using collisionally activated dissociation in a more conventional GC/MS/MS instrument (GC/QIT).[5]

The downward bowing of the curves in Figure 1 is consistent with a preference for *trans* double bonds. Two other features warrant attention. First, as noted in the previous paragraph, the net isotope effect is much closer to unity for the experimental conditions used in the present study, as compared with those previously reported. Second, the experimental values of W do not vary enormously as a function of the time window.

On the basis of this set of experiments, a comparison of first and second FFR fragment ion intensity ratios (from B/E linked scans and MIKE spectra, respectively) provides a basis for
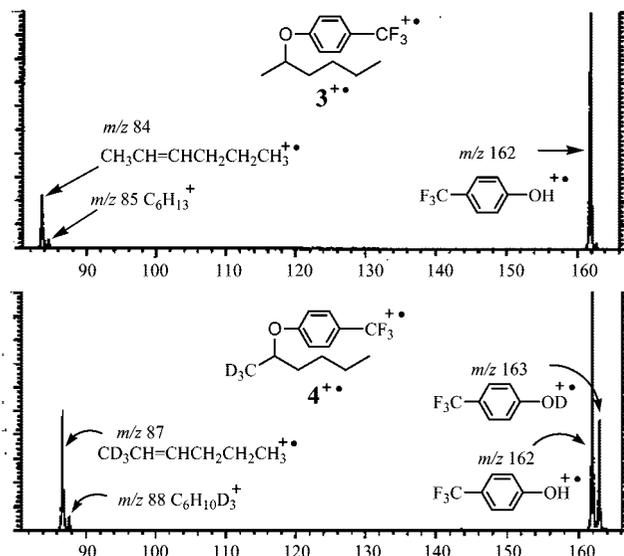

FIGURE 2. B/E scans showing first FFR metastable ion decompositions of the molecular ions of unlabeled 2-hexyl p-trifluoromethylphenyl ether (**3**) and of its d_3-analogue (**4**).

assessing the extent to which relative rate coefficients vary as a function of internal energy. Even when relative abundances differ substantially between the two time windows, one can enquire as to which branching ratios are sensitive to internal energy and which ones are not. As will be described below, net isotope effects and *trans/cis* ratios do not exhibit much sensitivity.

If neutral alkene expulsion were the only elimination taking place, it would be difficult to gauge experimentally the proportions of *cis* and *trans* double bonds produced by eq 3. However, when R = CH_3 and X = CF_3, compound **3**, it turns out that loss of neutral ArOH competes with the loss of neutral alkene. Moreover, the former reaction is regioselective, as the decomposition pathway in eq 5 portrays. The occurrence of a regioselective elimination permits a determination of stereoselectivity based on a comparison of *erythro* and *threo* monodeuterated ethers.

$$(5)$$
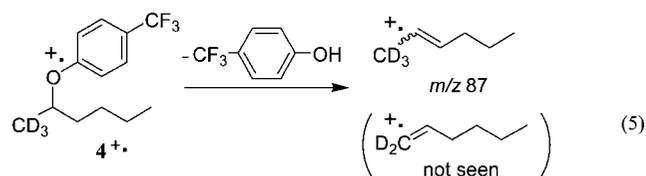
Evidence for regioselectivity comes from MS/MS spectra of the d_3-analogue of racemic 2-n-hexyl p-trifluoromethylphenyl ether, **4**. The molecular ion **4**$^{+\bullet}$ loses trifluoro-p-cresol to form ionized 2-hexenes with a barely detectable yield of ionized 1-hexene, as eq 5 summarizes. The decompositions illustrated in eqs 3 and 5 dominate the metastable ion decompositions, both in the first field-free region of the double-focusing mass spectrometer (B/E linked scan) and in the mass-analyzed ion kinetic energy (MIKE) spectrum of the second field-free region. Expulsion of neutral alkene (eq 3) is not regiospecific, as evidenced by the formation of both ionized trifluoro-p-cresol (X = CF_3, m/z 162) and its monodeuterated analogue (m/z 163) with a fragment ion abundance ratio of $ArOH^{+\bullet}/ArOD^{+\bullet} = 2.70 \pm 0.24$ in the first FFR. By contrast, ionized $C_6H_9D_3$ (m/z 87) forms with virtually no production of ionized $C_6H_{10}D_2$ (m/z 86).
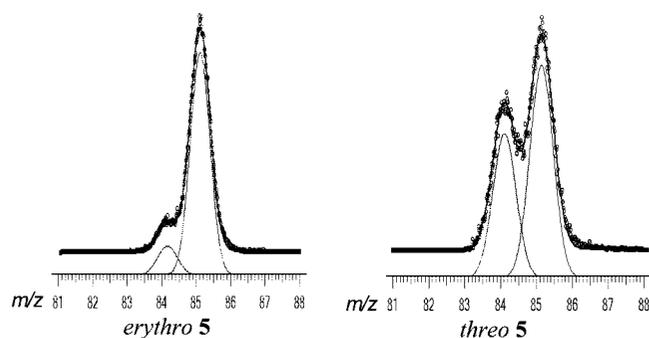
FIGURE 3. Metastable ion decomposition profiles of the ionized hexene region from MIKE spectra of diastereomers of **5** (fitted using Gaussians).

SCHEME 2. Hexene Ions Formed by *Syn*-Elimination from Ionized **5**

TABLE 1. Experimental Ion Abundance Ratios for Neutral Hexene Loss (Giving *m/z* 162) versus Loss of Neutral *p*-Trifluorocresol (ArOH) from Metastable Decompositions of Ionized *sec*-Hexyl *p*-Trifluorophenyl Ethers (±95% Confidence Limits) Based on Gaussian Fits (With Variable Width) of B/E Scans and MIKE Spectra[a]

| | | $[ArOH^{+\bullet}]/[M-ArOH]^{+\bullet}$ | |
neutral precursor	$[M-ArOH]^{+\bullet}$(*m/z*)	B/E	MIKES
3	$C_6H_{12}^{+\bullet}$ (*m/z* 84)	1.68 ± 0.11	4.86 ± 0.33
4	$C_6H_9D_3^{+\bullet}$ (*m/z* 87)	0.80 ± 0.035	3.47 ± 0.50
threo **5**	$C_6H_{11}D^{+\bullet}$ (*m/z* 85)	2.04 ± 0.45	6.71 ± 0.27
erythro **5**	$C_6H_{11}D^{+\bullet}$ (*m/z* 85)	1.52 ± 0.28	4.52 ± 0.35
threo **6**	$C_6H_{11}D^{+\bullet}$ (*m/z* 85)	0.65 ± 0.11	1.82 ± 0.06
erythro **6**	$C_6H_{11}D^{+\bullet}$ (*m/z* 85)	0.55 ± 0.06	1.64 ± 0.03

[a] Fragment ion abundance ratios are averages of at least 6 independent measurements recorded on at least 2 separate days.

TABLE 2. Experimental Ion Abundance Ratios for Metastable Ion Decompositions of Ionized *vic*-Monodeuterated *sec*-Hexyl *p*-Trifluorophenyl Ethers (±95% Confidence Limits) Based on Gaussian Fits (With Variable Width) of MIKE Spectra[a]

| | $[C_6H_{11}D^{+\bullet}]/[C_6H_{12}^{+\bullet}]$ | | $[ArOH^{+\bullet}]/[ArOD^{+\bullet}]$ | |
isomer	B/E	MIKES	B/E	MIKES
threo **5**	1.80 ± 0.05	1.63 ± 0.13	4.82 ± 0.19	5.46 ± 0.77
erythro **5**	5.18 ± 0.17	6.42 ± 0.96	8.55 ± 0.76	12.26 ± 0.64
threo **6**	4.08 ± 0.14	9.69 ± 1.75	3.19 ± 0.09	3.50 ± 0.51
erythro **6**	7.82 ± 0.28	3.77 ± 0.23	4.98 ± 0.32	5.49 ± 0.20

[a] Fragment ion abundance ratios are averages of at least 6 independent measurements recorded on at least 2 separate days.
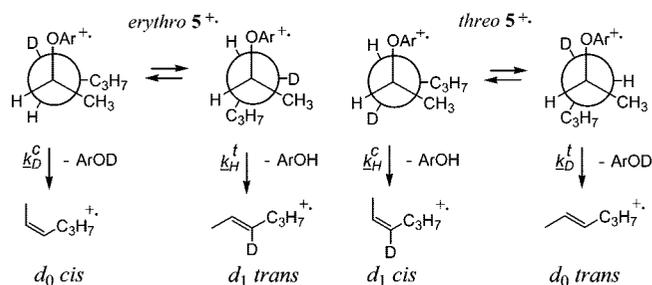
Figure 2 compares B/E scans of 2-*n*-hexyl *p*-trifluorophenyl ether, **3**, and its d_3-analogue **4**. Metastable dissociation of the molecular ions **3**[+•] and **4**[+•] in the first FFR gives a small amount of hexyl cations, $C_6H_{13}^+$ and $C_6H_{10}D_3^+$, respectively, in addition to the aforementioned odd-electron ions. Hexyl cations are absent from the MIKE spectra, indicative of the higher internal energies of the ions dissociating in the first FFR.

This selectivity of elimination of ArOH can be ascribed to the low adiabatic IE of the 2-hexenes (8.97 eV), as compared with that of 1-hexene (9.48 eV).[11] Trifluoro-*p*-cresol has a calculated IE (8.97 eV)[12] much lower than that of 1-hexene but has virtually the same IE as that of the 2-hexenes. Hence, ionized 2-hexenes result from vicinal elimination, but not ionized 1-hexene. The B/E linked scan spectrum of **4**[+•] in Figure 2 demonstrates that $C_6H_9D_3^{+\bullet}$ prevails over undetected $C_6H_{10}D_2^{+\bullet}$ by a factor of >50:1.

Figure 3 reproduces typical MIKE spectra from ionized diastereomers of the monodeuterated 2-hexyl ethers **5**. Scheme 2 shows an abbreviated variant of Scheme 1 summarizing competing pathways for elimination of neutral *p*-trifluorocresol from ionized *erythro* and *threo* **5**. One can extract the proportions of *trans* vs *cis* 2-hexene ions from the experimental d_1/d_0 fragment ion abundance ratios. These abundance ratios represent composites of *trans/cis* ratios and isotope effects.

The MS/MS experiments on **4**, its d_0 analogue **3**, *erythro* **5**, and *threo* **5** afford 8 experimental ratios from which *cis:trans* ratios can be extracted. Tables 1 and 2 list the experimental data of interest: ionized ArOH relative to ionized CD$_3$CH=CHC$_3$H$_7$ from **4**; ionized ArOH relative to ionized

C$_6$H$_{12}$ from the d_0 ether **3**; ionized ArOH relative to ionized ArOD from *erythro* **5** and from *threo* **5**; ionized ArOH relative to ionized C$_6$H$_{12}$ from *erythro* **5** and from *threo* **5**; and ionized C$_6$H$_{12}$ relative to ionized C$_6$H$_{11}$D from *erythro* **5** and from *threo* **5**.
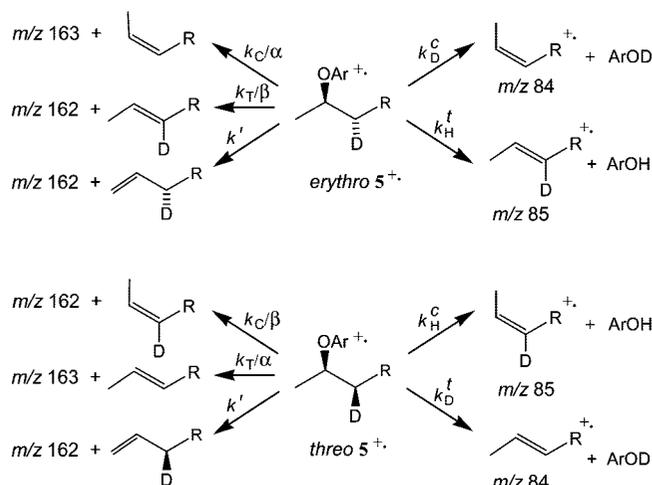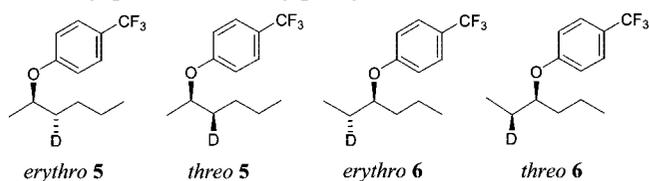
Scheme 2 depicts conformations of the monodeuterated ethers and the corresponding ionized 2-hexenes that come from *syn*-elimination. The scheme uses superscripted rate coefficients (k^c and k^t) to designate eliminations that form ionized 2-hexenes, as differentiated from the subscripts in eq 3. The rate coefficients are underlined in Scheme 2 to indicate that this scheme does not include all of the relevant conformations. The superscripts designate whether a *cis* or *trans* double bond forms, and the subscripts designate whether D or H is transferred. Note that the rate coefficients with subscript H include secondary kinetic isotope effects (2° k.i.e.s), since they correspond to transfer of H from a CHD group. It is important to distinguish between k^c and k^t (which will be used to designate rate coefficients without any isotope effects), on the one hand, vs k^c_H and k^t_H, on the other.

Scheme 3 (R = butyl) shows a more complete picture, which compasses the reactions shown in Schemes 1 and 2, as well as in eq 3. None of the rate coefficients are underlined in Scheme 3, because they are intended to represent the composite of all reacting conformations. As in eq 2, the rate coefficients corresponding to Scheme 1 have subscripts designating whether the corresponding neutral 2-hexenes are formed with *cis* or *trans* double bonds. The isotope effects are represented by the Greek letters α and β, which stand for primary and secondary isotope effects, respectively.

Chart 1 summarizes the stereoisomers investigated. Our synthesis makes them diastereomerically pure, but as a mixture of positional isomers. Hence they were introduced into the MS/MS by means of a GC interface to separate **5** from **6**. MS/MS

(11) Masclet, P.; Grosjean, D.; Mouvier, G. *J. Electron Spectrosc. Relat. Phenom.* **1973**, *2*, 225–237.

(12) Based on CCSD/6−31G** calculations; see Supporting Information. Grotemeyer and coworkers have measured the IE of trifluoro-*m*-cresol to be 8.909 eV (Prof. Dr. J. Grotemeyer, personal communication).

SCHEME 3. Kinetic Scheme for *Syn*-Eliminations from Ionized 5

m/z 163 + ... R ← k_C/α ← OAr$^{+\bullet}$ ... k_D^c → R$^{+\bullet}$ + ArOD   m/z 84

m/z 162 + ... R ← k_T/β ... R ... k_H^t → R$^{+\bullet}$ + ArOH   m/z 85

m/z 162 + ... R ← k' ... *erythro* 5$^{+\bullet}$

m/z 162 + ... R ← k_C/β ← OAr$^{+\bullet}$ ... k_H^c → R$^{+\bullet}$ + ArOH   m/z 85

m/z 163 + ... R ← k_T/α ... R ... k_D^t → R$^{+\bullet}$ + ArOD   m/z 84

m/z 162 + ... R ← k' ... *threo* 5$^{+\bullet}$

CHART 1. Racemic Diastereomers of *vic* Deuterated *sec*-Hexyl *p*-Trifluoromethylphenyl Ethers

erythro 5   *threo* 5   *erythro* 6   *threo* 6

TABLE 3. Relative Rate Constants Extracted from Ion Abundance Ratios of Metastable *Syn*-Eliminations from Ionized 2-*n*-Hexyl *p*-Trifluorophenyl Ethers, Assuming Kinetic Isotope Effects to Be the Same for *Erythro* and *Threo* 5$^{+\bullet}$

relative rates	description	B/E	MIKES
$\sqrt{[(k_H^c k_H^t/k_D^c k_D^t)]}$	Net kie (1°/2°) for $C_6H_{12}^+$	3.05	3.24
$\sqrt{(k_H^t k_H^t/k_D^c k_H^c)}$	Avg *trans/cis* ratio for $C_6H_{12}^+$	1.70	1.98
k'/k_T	1-C_6H_{12}/*trans*-C_6H_{12} from 3^+	1.88	0.64
k_T/k^t	*trans*-C_6H_{12}/*trans*-$C_6H_{12}^{+\cdot}$, 3^+	0.74	3.27
k_T/k_C	Avg *trans/cis* C_6H_{12} from 3^+	1.40	1.68
α/β	Net kie (1°/2°) for C_6H_{12}	4.43	4.55

effect of 3.42 ± 0.06, which is within experimental error of the MIKES value. Despite different internal energy distributions in three different time windows, the invariance of the product of $C_6H_{11}D^{+\bullet}/C_6H_{12}^{+\bullet}$ abundance ratios supports the conclusion that relative fragment ion abundances can be analyzed as though they obey first-order kinetics.

If the primary and secondary isotope effects for *erythro* are assumed to be the same as those for *threo*, then the ArOH$^{+\bullet}$/ArOD$^{+\bullet}$ abundance ratios and the experimental intensity ratios listed in Table 1 can be combined with the foregoing relative rate constants to obtain additional relative rates.[9] The data analysis is detailed in the Supporting Information. For example, the calculated primary isotope effects in the MIKES have the values $k^c/k_D^c = k^t/k_D^t = 2.64$ and $\alpha = 4.31$, while the corresponding secondary isotope effects are inverse: $k^c/k_H^c = k^t/k_H^t = 0.91$ and $\beta = 0.95$. As Table 3 summarizes, the net isotope effect for elimination of neutral 2-hexenes, α/β, has nearly the same value for the first and second FFRs. Likewise, the ratio of neutral *trans* to neutral *cis*-2-hexene expulsion varies by <20%.

Two branching ratios do exhibit pronounced differences between the FFRs. These correspond to the third and fourth entries in Table 3: the proportion of 1-hexene from $3^{+\bullet}$ in eq 3 (represented by k'/k_T, which diminishes in going from the first to the second FFR) and the proportion of ArOH$^{+\bullet}$ relative to ionized 2-hexenes (represented by k_T/k^t, which increases in going from the first to the second FFR). The small changes in net isotope effects and *trans/cis* ratios as a function of internal energy are striking in comparison to the large changes in these latter relative rates. This outcome lends further credence to the supposition that relative fragment abundances can be analyzed using schemes based on first-order kinetics.

As indicated above, ions observed in B/E scans have greater average energy content than those in the MIKES. The relative rate k'/k_T increases with internal energy, while k_T/k^t decreases with internal energy. The first of these represents the branching between expulsions of 1-alkene and 2-alkenes in eq 3. The same trend with increasing internal energy (an increase in hydrogen transfer from methyl versus from a methylene) was reported in Threshold Photoelectron Photoion Coincidence (TPEPICO) studies of reaction 2 and therefore has precedent.[4b]

The other relative rate that changes markedly between B/E and MIKES corresponds to the partition of electric charge between expelled 2-hexene and trifluorocresol. As previously noted, the 2-hexenes and trifluorocresol have nearly the same ionization energy in their lowest vibrational states. The Audier-Stevenson rule posits that charge resides on the fragment with the lower IE.[13] Relative IEs vary with vibrational state; hence, it should not be surprising to find that competition between the

spectra of ionized **6**, whose decompositions are not regioselective, provide a control for comparison with those of ionized **5**.

Taking the quotient of the two experimental $C_6H_{11}D^{+\bullet}/C_6H_{12}^{+\bullet}$ intensity ratios from *erythro* and *threo* **5** gives the product of the *trans/cis* branching ratios $(k_D^t/k_D^c)(k_H^t/k_H^c)$. The square root of that quotient gives the geometric mean of the two branching ratios, which provides an estimate of the rate coefficient k^t relative to k^c for dissociation of unlabeled ion $3^{+\bullet}$ to give *trans* vs *cis* $C_6H_{12}^{+\bullet}$.

This estimate gives *trans/cis* ratios of 1.70 ± 0.05 for the first FFR (B/E scan) and 1.98 ± 0.24 for the second FFR (MIKES). More elaborate algebra can extract a number of other relative rate coefficients from the experimental data, but the accuracy of such a data analysis hinges on the validity of treating Scheme 3 as though the rate coefficients behave like first-order rate constants. One way to test that notion is to examine how the ratios vary with the choice of time window. The aforementioned *trans/cis* ratios from the first and second FFRs lie within 95% confidence limits of one another.

One might expect isotope effects to show sensitivity to time window, if the rate coefficients deviate substantially from first-order behavior. A net isotope effect for ArOH versus ArOD expulsion can be estimated by supposing that the primary isotope effects k^c/k_D^c and k^t/k_D^t are the same and that the secondary isotope effects k^c/k_H^c and k^t/k_H^t also equal one another. If so, then the net isotope effect (primary kie divided by the secondary k.i.e.) corresponds to the square root of the product of the two $C_6H_{11}D^{+\bullet}/C_6H_{12}^{+\bullet}$ intensity ratios. As Table 3 summarizes, the net isotope effects estimated in this way have values that are the same within experimental error, 1°/2° = 3.05 ± 0.10 for the first FFR versus 3.24 ± 0.39 for the second FFR.

It is worth noting that the relative peak heights in the 70 eV source mass spectra, 4.05 for the *erythro* and 2.88 for the *threo* (after correction for ^{13}C natural abundance) lead to a net isotope

(13) Gross, M. L.; Giblin, D. In *The Encyclopedia of Mass Spectrometry*; Nibbering, N. M. M., Ed.; Elsevier: London, 2004; Vol. 4, pp 59−64.
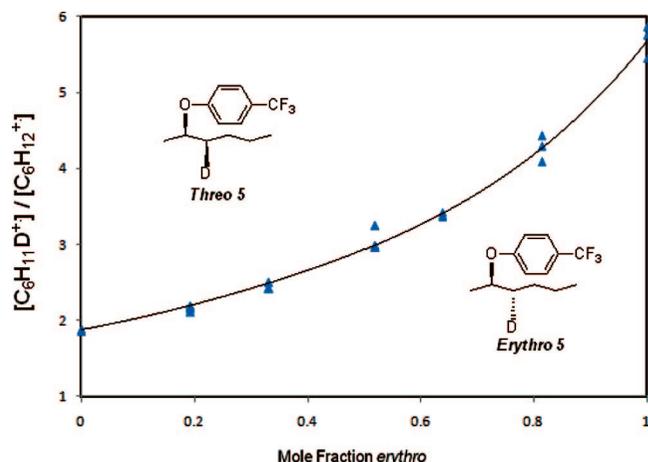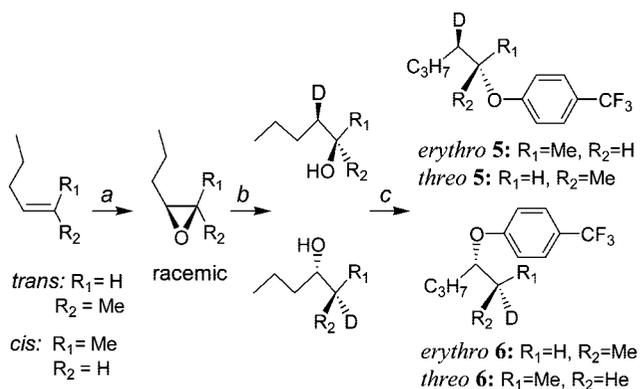
FIGURE 4. Ratio of *m/z* 85:*m/z* 84 abundances for B/E scans of diastereomeric mixtures of *erythro* and *threo* **5** (three independent measurements at each mole fraction X_e shown as blue triangles) analyzed using a GC interface to separate **5** from **6**.

SCHEME 4. Preparation of Diastereomers of Ethers 5 and 6 as Mixtures of Racemic Positional Isomers

(*a*) mCpBA, Et$_2$O; (*b*) LiAlD$_4$, Et$_2$O; (*c*) p-CF$_3$C$_6$H$_4$OH, DIAD, PPh$_3$

right and left-hand sides of Scheme 3 exhibit a pronounced dependence on internal energy.

The values in Table 3 stand in contrast to those obtained from the 3-hexyl ethers **6**, summarized in Tables 1 and 2. Elimination from the 3-hexyl ethers is not regioselective, because ionized 2-hexene and 3-hexene (which have nearly the same IE[11]) both form. Multiplying the two experimental C$_6$H$_{11}$D$^{+•}$/C$_6$H$_{12}$$^{+•}$ ion abundances gives a function of relative rates that includes competition of three hydrogens vs one deuterium and therefore has values much larger than does **5**. Taking the square roots gives results <5, larger than the isotope effects in Table 3, a consequence expected from the participation of additional hydrogens.

The experimental C$_6$H$_{11}$D$^{+•}$/C$_6$H$_{12}$$^{+•}$ ratios from **6** includes the formation of ionized *cis*- and *trans*-3-hexenes (both of which are monodeuterated) as well as of *cis*- and *trans*-2-hexenes. The quotient of these ratios should thus be less than the actual *trans/cis* ratio. As would be anticipated, the square roots of the quotients of the ratios from **6** are less than the *trans/cis* ionized 2-hexene ratios in Table 3. This comparison between positional isomers provides a control that substantiates our interpretation of the data.

The final test of the foregoing kinetic analysis comes from analyzing stereoisomer mixtures, by analogy to the curve in

Figure 1. As Figure 4 shows, a plot of isotopomer ratios (*m/z* 85 intensity divided by *m/z* 84 intensity) versus mole fraction of *erythro* **5** (X_e) gives a curve that is well fit by an expression analogous to eq 4, where [C$_6$H$_{11}$D$^{+•}$] and [C$_6$H$_{12}$$^{+•}$] replace [PhOD$^{+•}$] and [PhOD$^{+•}$], respectively. Figure 4 gives an empirical value of $W = 0.85 \pm 0.07$, while the value predicted on the basis of the ratio $(k^c_H + k^t_D)/(k^c_D + k^t_H)$ is 0.77 ± 0.03, using the B/E values from Table 3. The predicted W assumes that $k^c_H/k^c_D = k^t_H/k^t_D = 3.05$ and that $k^t_D/k^c_D = 1.70$. The quality of agreement between experimental and predicted values of W serves to justify the assumptions used to analyze the data.

Discussion

A widely used model of stereoselectivity correlates the conformational analysis of cyclic transition states with the *trans* vs *cis* preference in the analogous cycloalkanes. Kinetic control reflects a steric preference in the competition between accessible transition states. For instance, *trans*-1,2-dimethylcyclohexane has a heat of formation 1.9 kcal mol^{-1} lower than that of the *cis* isomer[14] which accounts for the preference for the *trans* over *cis* alkene product in eqs 1 and 2.

Assuming this model to be qualitatively accurate, the selectivity of 4-center eliminations still remains difficult to predict. Published values for the energy difference between *trans* and *cis*-1,2-dimethylcyclobutane range from 1.0[15] to 2.6 kcal mol^{-1}.[16] If the former value is correct, then 4-center eliminations ought to display lower stereoselectivity than do 6-center eliminations. The data reported here, however, demonstrate a 4-center elimination that favors *trans* product at least as much as do eqs 1 and 2.

Published evidence that eq 3 represents concerted *syn*-eliminations includes the following measurements. First, the appearance energies for alkene expulsion from *sec*-alkyl phenyl ethers corresponds to the concomitant formation of ionized phenol,[8] rather than the much higher onset that would be expected if ionized cyclohexadienone were the fragment ion. This result requires that the reaction pass through a 4-center transition state.

Large stereochemical effects have been reported for stepwise eliminations from gaseous radical cations (such as the McLafferty rearrangement[4,17]). Such eliminations take place via distonic intermediates, where the radical and the cationic sites reside on different atoms.[18] In the present case, however, the data closely resemble a case where a stepwise mechanism seems implausible.

(6)
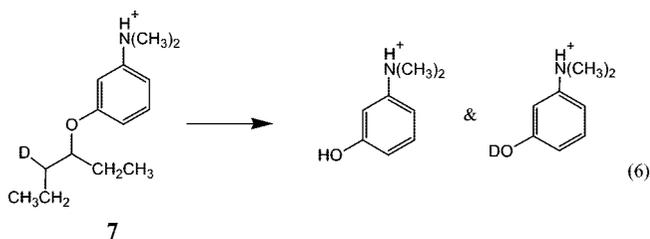
Equation 6 summarizes a charge-remote elimination, with which 4-center eliminations from radical cations can be compared. Our results parallel the stereochemical effects for

(14) Eliel, E.; Wilen, S. H. *Stereochemistry of Carbon Compounds*; Wiley-Interscience: New York, 1994; p 702.
(15) Benson, S. W.; O'Neal, H. E. *Kinetic Data on Gas Phase Unimolecular Reactions*; National Bureau of Standards: Washington, 1970; p 271.

the even-electron ions **7**, where alkene expulsion must be concerted rather than stepwise.[7c] *Erythro* and *threo* **7** display different proportions of H vs D transfer, with curves for mixtures that (*mutatis mutandis*) look much like those in Figures 1 and 4. Nearly the same *erythro/threo* H/D preferences are observed for the corresponding diastereomeric monodeuterated 3-phenoxyhexane radical cations,[5] as well as for *erythro* and *threo* **6** (which give a curve much like that of Figure 4 with $W = 0.77 \pm 0.13$, but with greater scatter of the data points).

Ion **7** cannot form distonic ions. Indeed, it is difficult to conceive any other type of intermediate that might intervene in order for eq 6 to be stepwise. If eq 6 is not stepwise, then the proportions of H vs D transfer reflect the preference for elimination to make *trans* vs *cis* double bonds via concerted elimination. Since radical cations and **7** show differences of comparable magnitude between diastereomers, the simplest conclusion is that both operate via the same type of pathway.

For a regioselective concerted elimination such as Scheme 2, H vs D ratios therefore directly measure the relative yields of *cis* and *trans* double bonds. Algebra based in Scheme 3 gives a *trans:cis* preference on the order of 2:1 for metastable ion decompositions corresponding to Eq 5. The legitimacy of the data analysis hinges on a pair of suppositions: (1) treatment of fragment ion abundance ratios as though they correspond to a first-order kinetic scheme, and (2) using the same kinetic isotope effects (such as the primary and secondary k.i.e.s α and β) for both *erythro* and *threo* isomers. Validation of the first of these suppositions comes from analysis of two time windows (the first and second FFRs of the mass spectrometer), which gives nearly the same values for net isotope effects and *trans:cis* preferences. At the same time, the proportion of 1-hexene expulsion (k' in eq 3) and the $[M - ArOH]^{+\bullet}/[ArOH^{+\bullet}]$ fragment ion abundance ratio decrease markedly in going from the first to the second FFR.

The invariance of net isotope effects and of stereoselectivities with the choice of time window validates the fashion in which the data are treated, but it does not deal with the question of whether the same net isotope effects ought to be used for *erythro* and *threo* isomers. The number of available data does not permit a separate evaluation of all isotope effects. How much does the measured stereoselectivity depend upon the assumptions that $k^t_H/k^t_D = k^c_H/k^c_D$ and that the same values of the k.i.e.s α and β apply to both *erythro* and *threo* isomers?

This question also concerns the justification for inferring that the stereoselectivities derived from Scheme 3 have the same value, $k^t_D/k^c_D = k^t_H/k^c_H$ as for the unlabeled ion **3**$^{+\bullet}$, k^t/k^c. Sensitivity analysis shows that these *trans:cis* preferences do not exhibit a strong dependence on the supposition that the same isotope effects operate for *erythro* and *threo*. If we assume that the net isotope effects on expulsion of ArOH vs ArOD and on alkene expulsion for the *erythro* differ from the corresponding values for the *threo* by the same factor, then numerical simulations become tractable. The outcome is that the *trans:cis* preference k^t/k^c varies by no more than the square root of that factor. For example, if the net isotope effects for the *threo* differ from those for the *erythro* by 20%, then the value of k^t/k^c varies by ≤10% from the value of $\sqrt{(k^t_D k^t_H/k^c_D k^c_H)}$ in Table 3. Whether k^t/k^c increases or decreases depends on the relative changes in primary and secondary isotope effects. The quality of fit between observed and predicted values of W for Figure 4 rule out the likelihood of *threo* and *erythro* isotope effects differing by more than 20%.

Conclusions

These experiments demonstrate that 4-center *syn*-eliminations exhibit the same or greater stereoselectivity than synclinal 6-center eliminations. Samples were introduced via a GC interface so as to separate positional isomers. Relative ion abundances from metastable ion decompositions were used to measure stereoselectivity. Two possible sources of systematic error have been examined: (1) from analyzing the data in terms of competing reactions that obey first-order kinetics, and (2) from assuming that kinetic isotope effects (k.i.e.s) are the same for pairs of diastereomers.

The first source of systematic error was probed by looking at two different time windows, corresponding to the two field-free regions (FFRs) of a double-focusing mass spectrometer. The experimental values of particular interest (net isotope effects and *trans/cis* preferences) do not change substantially as a function of time window. That result affirms the appropriateness of the method by which branching ratios are extracted from the experimental data.

The second source of systematic error has been probed by sensitivity analysis. If net k.i.e.s for stereoisomers are taken to differ by a given factor, derived values for *trans/cis* preferences do not change by more than the square root of that factor.

The graph of ion intensity ratios plotted in Figure 4 places upper limits on the consequences of systematic error. The level of agreement between two ways of assessing the weighting factor W—one from direct measurement and the other derived from the values summarized in Table 3—demonstrates a level of consistency that validates our data analysis.

We have previously described the use of MS/MS to analyze proportions of acyclic diastereomers in a mixture.[7,19] The magnitude of the stereochemical effects reported in the present work show that GC/MS/MS has the capacity to quantitate acyclic stereochemistry in mixtures that contain positional isomers (**5** and **6**) as well as stereoisomers. The curvature of the graph in Figure 4 indicates that an admixture of *threo* in a mixture with *erythro* can be measured, in favorable cases, with a precision of better than ±5%.

Experimental Section

Racemic mixtures containing 2-phenoxyoctane-3-*d* (**2**) and 3-phenoxyoctane-2-*d* were prepared from *trans*- and *cis*-2-octene, respectively, as previously described.[5] Racemic 2-(*p*-trifluorom-ethyl)phenoxyhexane (**3**) was prepared via a Mitsunobu reaction: a solution of 2-hexanol (0.71 g, 7.0 mmol), *p*-trifluorocresol (1.14 g, 7.06 mmol) and PPh3 (1.85 g, 7.06 mmol) in 5 mL THF was cooled to 0 °C under N_2 and a solution of diisopropyl azodicar-boxylate (1.43 g, 7.06 mmol) in 5 mL THF added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 5 days. Solvent was removed under reduced pressure and the product purified by column chromatography with pure hexane, followed by 4:1 hexane/CH_2Cl_2 to give 1.31 g (76%) **3**: bp 94−5° (1.5 Torr); ^{1}H NMR (300 MHz, CDCl3) δ 7.52 (d 2H, *J*=8.1 Hz), 6.93 (d 2H, *J* = 8.1 Hz), 4.41 (tq 1H, *J* = 6.0 and 6.3

(16) Scacchi, G.; Back, M. H. *Int. J. Chem. Kinet.* **1977**, *9*, 525–534. DFT and ab initio calculations do not give conclusive results; see Supporting Information.

(17) Loos, J.; Schröder, D.; Schwarz, H. *J. Org. Chem.* **2005**, *70*, 1073–1076.

(18) Hammerum, S. *Mass Spectrom. Rev.* **1988**, *7*, 123–202.

(19) (a) Serafin, S. V.; Zhang, K.; Aurelio, L.; Hughes, A. B.; Morton, T. H. *Org. Lett.* **2004**, *6*, 1561–1564. (b) Morton, T. H. in *The Encyclopedia of Mass Spectrometry*; Nibbering, N. M. M., Ed.; Elsevier: London, 2003; Vol. 4, pp 433–443.

Hz)), 1.8−1.33 (m 6H), 1.31 (d 3H, J = 6.3 Hz), 0.91 (t 3H, J = 7.2 Hz); Mass spectrum (70 eV) m/z (relative intensity): 55(31), 56(36), 57(17), 69(18), 84(43), 85(7), 143(19), 145(12), 162(100), 163(7), 189(6), 246(5). Hexanol-1,1,1-d_3 was prepared by addition of methyl-d_3 magnesium iodide (Aldrich, 99 atom % D) to pentanal and converted to the *p*-trifluoromethylphenyl ether **4** in the same fashion as described above.

Racemic *threo* and *erythro* isomers of monodeuterated *sec-n*-hexyl *p*-trifluoromethylphenyl ethers were synthesized from the corresponding *trans-* and *cis*-2-hexenes, as portrayed in Scheme 4. The alkenes were epoxidized, reduced with LiAlD$_4$ to mixtures of monodeuterated 2- and 3-hexanols, and converted (with inversion of stereochemistry) to their *p*-trifluoromethylphenyl ethers using the foregoing Mitsunobu conditions. Details are given in Supporting Information. As shown, the synthesis yields mixtures of positional isomers, **5** and **6**, but having high diastereomeric purity. Isomers **5** and **6** were introduced into the mass spectrometer using a gas chromatographic interface.

The positional isomers were resolved on a DBWax capillary column and introduced directly into the source of a double-focusing reverse Nier-Johnson (B-E) mass spectrometer. Electron ionization (70 eV) gave the molecular ions, which were either mass selected and dissociated in the second field-free region by spontaneous metastable ion decomposition (MIKE spectroscopy) or else analyzed by means of a fixed-ratio B/E scan. MIKES profiles were deconvolved as Gaussian profiles with variable width using IGOR Pro software (Wavemetrics Inc., Lake Oswego, OR). Experimental errors (±values) represent 95% confidence limits.

Supporting Information Available: DFT and ab initio calculations, preparative details, kinetic schemes, and NMR and MIKES peak profile spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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