J. Org. Chem. **2001,** *66,* 7247−7253

The Anionic Oxy-Cope Rearrangement: Using Chemical Reactivity to Reveal the Facile Isomerization of the Parent Substrates in the Gas Phase

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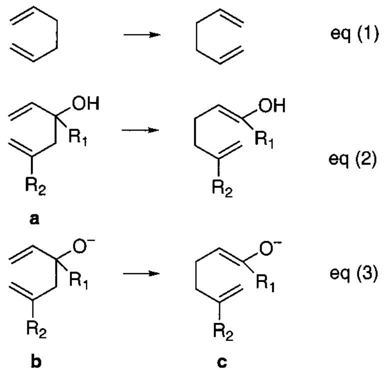
Received August 3, 2000

The rearrangements of 1,5-hexadiene-3-oxide and 3-methyl-1,5-hexadiene-3-oxide have been studied in the gas phase, using both Fourier transform mass spectrometry (FTMS) and the flowing afterglow (FA) technique. Gas-phase studies of ionic rearrangements can be limited by analysis techniques such as collision-induced dissociation, which have the potential of driving the rearrangement prior to fragmentation. In the studies reported here, we have utilized methanol-O-*d*, methyl nitrite, and dimethyl disulfide as chemical reactivity probes to discern whether rearrangement of either of the alkoxides to their corresponding enolates occurs. Of the three structural probe reagents, dimethyl disulfide has been found to be most ideal, since it reacts efficiently with both alkoxides and enolates to produce a unique product from each. On the basis of the reactions observed between dimethyl disulfide and anions generated from 1,5-hexadien-3-ol and 3-methyl-1,5-hexadien-3-ol, we have found that the gas-phase Cope rearrangement of both tertiary and secondary alkoxides occurs under both FTMS and FA conditions. Use of dimethyl disulfide in the FTMS and evaluation of ion residence time in the FA lead to the establishment of an upper limit on the $\Delta H^{\ddagger}$ of the rearrangement of both the parent secondary and tertiary substrates as ~11 kcal mol^{-1} at 298 K. This value is consistent with our B3LYP/6-31+G* prediction. The rearrangement is also faster in the gas phase than in solution, in accord with theoretical predictions.

Introduction

The Cope rearrangement is the well-known [3,3]-sigmatropic reaction of 1,5 hexadienes (eq 1).[1] The oxy-Cope derivative of the rearrangement (eq 2) was first utilized in 1964 by Berson et al. and is a synthetically useful reaction, due to the conversion of an alcohol to an enol/ketone.[2] The Cope, however, that has intrigued mechanistic chemists for the past two decades is the anionic oxy-Cope rearrangement of an alkoxide to an enolate (eq 3).[3−11] Evans et al. found that deprotonation of the alcohol in the oxy-Cope substrate leads to huge rate accelerations on the order of $10^{10}-10^{17}$.[3,12,13] Evans's experimental results as well as model-system calculations by Evans and Goddard indicated that as the negative charge becomes more localized on the oxy substituent, the rearrangement should proceed faster.[12−14] Recent higher-level calculations on the model systems by Houk et al. are in agreement with these early predictions.[6]



1 $R_1 = H, R_2 = CH_3$

2 $R_1 = H, R_2 = H$

3 $R_1 = CH_3, R_2 = H$

The implication of these computational and condensed phase experimental results is that the rearrangement

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10.1021/jo001177e CCC: $20.00

should proceed the most quickly in the gas phase. A "pure" anionic oxy substituent devoid of any counterion or solvent shell would experience the greatest rate acceleration, yet such a species is impossible to generate in the condensed phase. In the gas phase, however, solvent and counterion effects are absent, and the intrinsic, inherent reactivity of molecules is revealed.[11,15]

Early gas-phase studies, using an ion cyclotron resonance (ICR) mass spectrometer, indicated that the tertiary substrate **3b** rearranges but that the secondary substrate **2b** does not.[11] Since the authors also found that the solution phase rate constant (in THF and DMSO, K^+ counterion) for **2b** is smaller than that for **3b** (by a factor of 280 at 298 K), they concluded that the same effect was retarding the rearrangement of the secondary alkoxide in both the solution and gas phase. This effect would therefore have to be intrinsic, as opposed to some solvation effect; the authors postulated a possible stereoelectronic conformational or methyl stabilization effect.[11]

We wish to report here a reliable methodology for examining unimolecular isomerizations in the gas phase and our subsequent study and findings on the anionic oxy-Cope rearrangements of the parent secondary substrate, 1,5-hexadiene-3-oxide (**2b**), and the parent tertiary substrate, 3-methyl-1,5-hexadiene-3-oxide (**3b**). Our new gas-phase measurements indicate that both the secondary and tertiary substrates rearrange. We have studied the gas-phase reaction in both high pressure and low-pressure regimes, using a flowing afterglow (FA) mass spectrometer and a Fourier transform ion cyclotron resonance mass spectrometer (FTMS or FTICR).[16,17] We have put upper limits on the barriers for rearrangement and have conducted quantum mechanical calculations that provide predictions consistent with our gas-phase measurements. The implications of our qualitative and quantitative results are discussed and compared to known condensed phase behavior.

Experimental Section

Flowing Afterglow Experiments. The flowing afterglow experiments were carried out under standard conditions in the flowing afterglow (300 K, 0.30 Torr He), which has been described previously.[18,19] The flow tube is 100 cm long, and the flow velocity of helium is ~10000 cm s^{-1}; therefore, the average residence time of a helium atom as it is transported from the entrance to the exit of the flow tube is about 0.01 s, or 10 ms. Helium comprises 99+% of the total gas present in the reaction region, the remainder being composed of various amounts of either the gases used as neutral reactant or the gases used to form the reagent ion. The concentration of helium is $\sim 10^{16}$ cm^{-3}, the concentration of neutral reactant is $\sim 10^{12}$ cm^{-3}, and the concentration of the ionic reactant is $\sim 10^{8}$ cm^{-3}.[19-21] Precursor ions amide, atomic oxygen radical anion, and methoxide were generated by dissociative electron attachment to ammonia, nitrous oxide, and methanol, respectively, at the upstream end of the flow tube. Hydroxide was formed by allowing the $O^{-\bullet}$ precursor ion to abstract a hydrogen atom from high purity methane.[22] Electron ionization of the nitrous oxide is accomplished by introducing the neutral past an electron gun (typically, emission current 0.05 mA; potential 30 V).[23] The EI method for ion generation has been fully described previously.[23] The other anions discussed in this report were generated by deprotonation of the corresponding neutral by H_2N^-, HO^-, or CH_3O^-.

Methyl nitrite was also prepared following literature procedure.[24,25] All liquid samples were subjected to several freeze−pump−thaw cycles before use to remove any dissolved gases. All other reagents, except 3-methyl-1,5-hexadien-3-ol (vide infra) are commercially available and were used as received.

Fourier Transform Ion Cyclotron Resonance Experiments. The FTICR experiments were conducted on a dual-cell Finnigan 2001 Fourier transform mass spectrometer. Each side of the 2 in. cubic dual cell is evacuated to a baseline pressure of less than 1×10^{-9} Torr. The dual cell is positioned collinearly with the magnetic field produced by a 3.3 T superconducting magnet.

Neutral samples were introduced into the FTMS using a Finnigan heated batch inlet system, a custom-built heated batch inlet system, or via a pulsed valve system. All chemicals, except for 5-methyl- and 3-methyl-1,5 hexadien-3-ol (vide infra), are available commercially and were used as received. Methyl nitrite was produced "in situ" by preparing a solution of methanol:isoamyl nitrite at a ratio of 10:1.[26] The resultant vapor is comprised mostly of methyl nitrite. Anionic oxy-Cope substrate ions were produced by proton transfer to precursor ions. Precursor ions hydroxide, methoxide, and fluoride/trifluoromethide were generated by pulsing water, methyl nitrite, and tetrafluoromethane, respectively, into the cell and sending an electron beam (typically 8 eV, 6 μA, beam time 5 ms) through the center of the cell. Precursor ions were cooled with argon. A trapping potential of −2 V was applied to the cell walls perpendicular to the magnetic field at all times except when ions were transferred from one cell to another. Transfer is accomplished by temporarily grounding (50−150 μs) the conductance limit plate, the trapping plate separating the two cells. The ions then can pass through a 2 mm hole in the center of the conductance limit plate. The typical pulse sequence for the experiment is shown in Table 1. The experiment was generally conducted in the following manner: in one cell, a constant pressure of the anionic oxy-Cope alcohol substrate is added via a batch inlet. The precursor ion, produced from pulsed neutral, deprotonates the alcohol. The $[M - 1]^-$ ion is then isolated and transferred to the next cell, where it is allowed to react with the probe reagent. Rearrangement time is measured from ionization and includes the time in which alkoxide might rearrange to enolate *while* being probed in the second cell.[27,28] The pressure of MeSSMe (P_{MeSSMe}) is $\sim 5 \times 10^{-7}$ Torr in these experiments. It should be noted that this is the value that is read at the ionization gauge; calibration of the ionization gauge on our instrument (using the reaction of $CH_4^+ + CH_4$) indicates that the actual pressure in the cell may be on the order of 1.46 times higher than the gauge reading.[29,30] We have shown that reaction of alkoxides with MeSSMe is unit efficient; that is, every collision between ion and molecule results in reaction.[28] Using the parametrized trajectory theory of Su and Chesnavich,[31,32] and using a dipole

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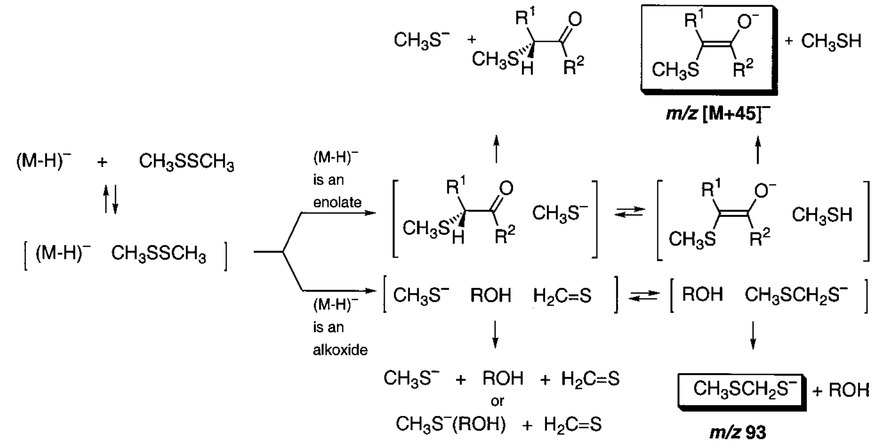
Table 1. Pulse Sequence for Anionic Oxy-Cope Experiment in FTMS

type	time (ms)	comments
delay	5000	start delay allows FTICR cell pressure to recover
APV fill	20	pulsed valve fill, analyzer side, Ar
APV delay	5	pulsed valve delay, analyzer side, Ar
APV open	20	pulsed valve open, analyzer side, Ar
delay	200	delay
SPV fill	50	pulsed valve fill, source side, precursor neutral
SPV delay	10	pulsed valve delay, source side, precursor neutral
SPV open	50	pulsed valve open, source side, precursor neutral
ionize	5	ionize, 8 eV, 6 μA
delay	5	ionization delay
eject		isolation of reactant alkoxide ion
delay	varies	rearrangement time delay
transfer	0.090	transfer of ions from source to analyzer side
delay	2000	delay to allow reaction with probe reagent
excite		excite ions, 4000 Hz/μs, m/z 12−21000
detect		detect, 8 MHz, 64 K data points, attenuation 6 dB
quench	2	quench ions

Scheme 1



moment of 1.99 D and a polarizability of 1.07 × 10^{-23} cm^3, derived from group additivity, we can calculate collisional rate coefficients for the reaction of the secondary and tertiary alkoxides with dimethyl disulfide; the rate constant values are 18.0 × 10^{-10} and 17.5 × 10^{-10} cm^3 molecule^{-1} s^{-1}, respectively.[33,34]

Synthesis. The alcohols 3-methyl and 5-methyl-1,5-hexadien-3-ol were synthesized using the Grignard reaction between allylmagnesium halides and the appropriate aldehyde or ketone.[35]

Calculations. Calculations were conducted at B3LYP/6-31+G* using Gaussian94 and Gaussian98.[36,37]

Results

When 1,5-hexadien-3-ol (**2a**) is deprotonated by hydroxide in the FTICR, an [M − 1]$^-$ ion (m/z 97) is formed that reacts with dimethyl disulfide to form m/z 143, corresponding to the thiomethoxylated enolate. Dimethyl disulfide (MeSSMe) has been shown to be an ambident probe reagent that reacts uniquely with alkoxides and enolates (Scheme 1).[27,28] Alkoxides eliminate across the C−S bond to ultimately form a characteristic ion at m/z 93 ($CH_3SCH_2S^-$), while enolates nucleophilically attack at the sulfur to ultimately produce a [M + 45]$^-$ ion. The presence of the [M + 45]$^-$ ion indicates that the secondary alkoxide **2b** is indeed rearranging in the gas phase.

To ascertain whether the alkoxide is induced to rearrange by the probe reagent, we also utilized methanol-*O-d* (MeOD) and methyl nitrite (MeONO) to explore this reaction. Using these probes, we find that the rearrangement also appears to proceed.[28,38−40] The m/z 97 ion exchanges its proton in the presence of MeOD, and the m/z 97 slowly reacts with methyl nitrite to produce

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$[M + 28]^-$, characteristic of enolate presence. These data do not preclude the possible role of any probe reagent in inducing the reaction, but the fact that *different* probe reagents show the same qualitative result helps mitigate that possibility.

We next probed the parent tertiary substrate **3b**. As with the secondary substrate, we found that regardless of the probe reagent used, the tertiary alkoxide appears to rearrange as well. Because earlier results showed that the tertiary substrate rearranged while the secondary did not, we also qualitatively examined substrate **1b**. Earlier studies also indicated that **1b** did not rearrange.[11] We find that the $[M - 1]^-$ ion, *m/z* 111, also rearranges in the FTICR.

The FTICR provides relatively high vacuum conditions ($<1 \times 10^{-6}$ Torr) and long trapping times for the ions. To eliminate the influence of pressure in the gas-phase reaction, we also probed the rearrangement in a relatively low vacuum environment (0.3 Torr of helium, in the FA). The high helium pressure ensures that the ions are thermally equilibrated, much as reactants are equilibrated by solvent in the condensed phase. We find, using MeONO and MeSSMe, that the secondary and tertiary alkoxides rearrange in this high-pressure regime as well.[41]

Discussion

We find that the alkoxides **1b**, **2b**, and **3b** all rearrange in the gas phase. Our results are in direct conflict with earlier gas phase results that indicated that only **3b** rearranges.[11] This discrepancy is of import because the earlier results imply that an intrinsic structural effect is responsible for the relative slowness of **2b**, since **2b** is also relatively slower in rearranging in solution. We believe that the key parameter leading to the differences between these two studies is the method used to probe the rearrangement, rather than the occurrence of the rearrangement itself. Dimethyl disulfide is an ideal probe reagent for this reaction because it reacts extremely efficiently with both alkoxides and enolates, producing unique ions for each.[27,28] The previous study utilized methyl nitrite, neopentyl-O-*d*, and MeOD.[11,38−40,42] Methyl nitrite reacts very inefficiently with enolates; in the flowing afterglow, MeONO had to be synthesized in order to add enough neutral to drive the reaction.[28] Deuterated alcohols can also be difficult to use because of both slow exchange and the lack of a unique product for alkoxide reaction.[28] Dimethyl disulfide is an ideal probe reagent, allowing us to unequivocally demonstrate rearrangement of substrates **1b**−**3b**.

A reviewer suggested that another possible reason for the differences between the current FTMS work versus the earlier ICR work could be due to excess energy deposited in the alkoxides. In Bartmess and co-workers' original work, the experiment used a one-section cell with no voltage manipulation ("transfer") of the ions and no high pressure pulses. This experimental difference may be the root of the inconsistencies in reactivity between the FTMS and ICR work. We have also tried to mitigate the experimental differences by probing the rearrangement in one cell; using dimethyl disulfide, we do still see rearrangement. However, because of our instrument configuration, we do transfer our precursor ion (as opposed to the alkoxide), which could still have the potential of ultimately energizing the alkoxide ion through proton transfer.

An important consideration in probing the rearrangement is the possibility that the probe reagents are responsible for inducing the rearrangement. However, the fact that three different probes result in qualitatively the same conclusion—the occurrence of rearrangement—indicates that the probes' roles in inducing the rearrangement is probably minimal. In addition, other examples from the literature indicate the inability of probes to induce rearrangement. Chou et al. have shown that regardless of the probe reagent used, the rearrangement of various cyclopropyl anions is clearly temperature dependent and is observed to begin to occur, or "turn on" as a function of temperature, not as a function of probe used.[43] In another example, Grabowski and Cheng showed that the enolate monoanion of acetic acid did not undergo intramolecular proton transfer to generate the carboxylate; nor did the probing of the monoenolate cause that four-center rearrangement to occur.[44]

Of particular interest with the anionic oxy-Cope reaction is the barrier to rearrangement. If we can estimate the rate constant for rearrangement, *k*, we can derive an upper limit for the $\Delta G^{\ddagger}$ of the rearrangement by using the Eyring equation. In the flowing afterglow, the residence time of an ion traveling the entire length of the flow tube is 10 ms (see Experimental Section). Deprotonation of the parent Cope alcohol yields the alkoxide, which then rearranges to enolate. We detect rearrangement because reaction with dimethyl disulfide produces thiomethoxylated enolate. The unimolecular rearrangement of the alkoxide ion, before reaction with the probe reagent, therefore, occurs within the 10 ms time scale. This time scale corresponds to a lower limit for the rate constant *k* of 100 s^{-1}. From this value, we can derive an upper limit for the $\Delta G^{\ddagger}$ of the rearrangement of 15 kcal mol^{-1}.

In the FTMS, we utilized the probe reagent dimethyl disulfide to help in quantitating the rearrangement. The fast reaction of alkoxides with dimethyl disulfide allowed us to use the $CH_3SCH_2S^-$ (*m/z* 93) ion as a marker; the lack of appearance of that ion signaled the absence of alkoxide, and therefore the completion of the rearrangement. The isolated $[M - 1]^-$ ion of the secondary substrate (*m/z* 97) was given different rearrangement times before probing with MeSSMe in our ICR. We find that at short times—less than 0.04 s—both *m/z* 93 ($CH_3SCH_2S^-$) and *m/z* 143 (thiomethoxylated enolate) are observed. At greater than 0.04 s rearrangement time, only *m/z* 143 is observed. This places a lower limit on the rate constant of the rearrangement of the bare alkoxide at 25 s^{-1}.[45] Furthermore, to eliminate the possibility that HO^-, which is a very strong base (proton affinity, or PA = 390.7 kcal mol^{-1}), induces any unexpected isomerizations, we used a mixture of F^-/CF_3^- (PA (F^-) = 371.6 kcal mol^{-1}; PA (CF_3^-= 376.9 kcal mol^{-1}) as the precursor ion. Under these conditions, we still obtain

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[41] MeOD is an unsuitable reagent in this high-pressure regime, because it tends to cluster with the alkoxides and enolates. Therefore, exchange is often not observed, as clustering is too rapid.

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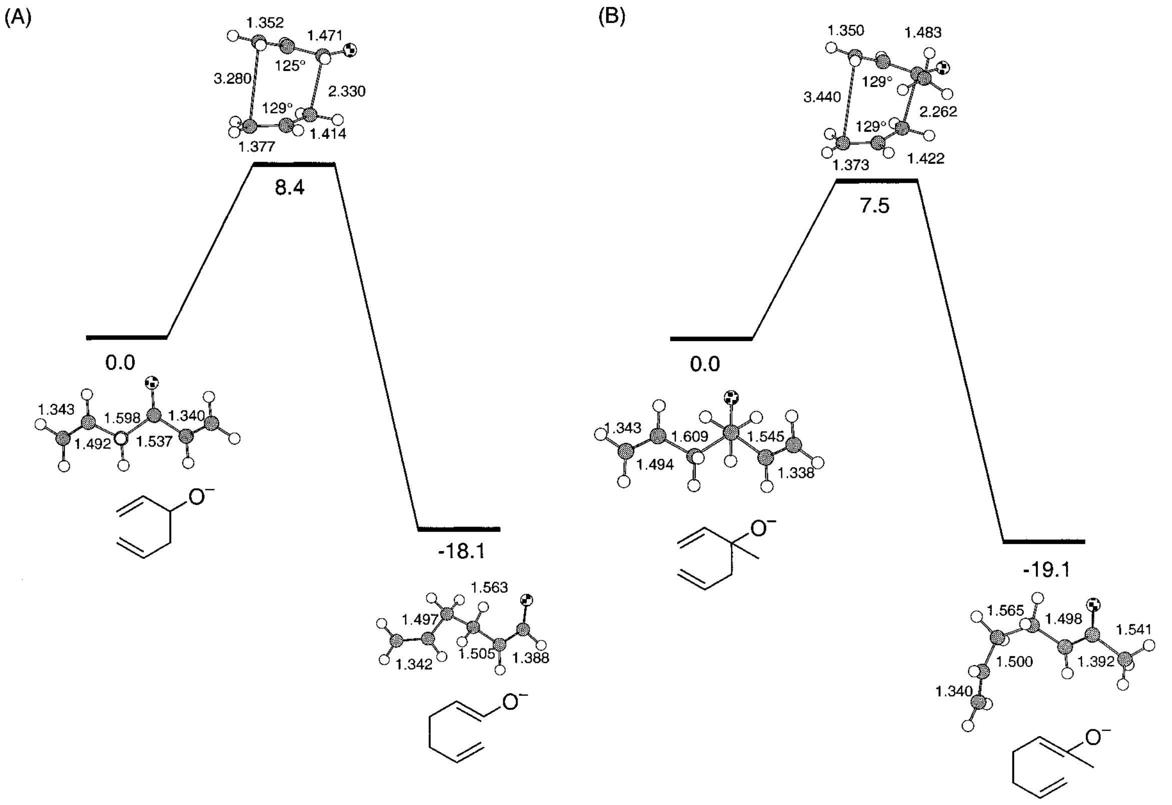
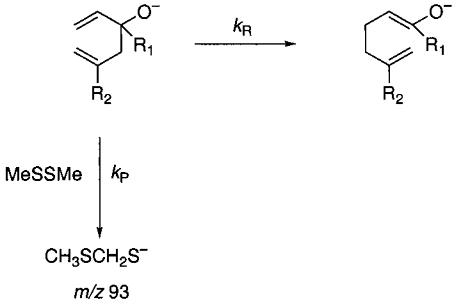


Figure 1. Energies and structures of stationary points for the reaction of (A) 1,5-hexadiene-3-oxide (**2b**) and of (B) 3-methyl-1,5-hexadiene-3-oxide (**3b**) at the B3LYP/6-31+G* level. Energies are in kcal mol^{-1} and bond lengths are in angstroms.

a rearrangement rate constant of >25 s^{-1}. With the tertiary substrate, we also explored different rearrangement times and found that at greater than 0.04 s, no *m*/*z* 93 was detected any longer, indicating the absence of alkoxide and allowing an estimate of the rate constant *k* of the rearrangement to be placed at 25 s^{-1}, as with the secondary substrate.[45] This value corresponds to a $\Delta G^{\ddagger}$ of 15 kcal mol^{-1} at 298 K, comparable to the value obtained from the flowing afterglow. The circumstances under which this barrier is applicable to the reaction studied is for the thermalized ion, free of solvation, undergoing rearrangement.[45]

The estimation of the lower limit on the rate constant for rearrangement can also be confirmed by using the pseudo-first-order rate constant for the reaction of the Cope alkoxide with dimethyl disulfide. Using the values for P_{MeSSMe} and the collisional rate coefficients described in the Experimental Section, we can calculate the pseudo-first-order rate constant for the reaction of alkoxide with MeSSMe as being 28−29 s^{-1} for the secondary and tertiary alkoxides (k_{P}, Scheme 2). If k_R is 25 s^{-1}, at 0.04 s, only 63% of Cope alkoxide should react before probing; then the remaining 37% will partition fairly equally between the k_{R} and k_{P} pathways. Since *no* alkoxide is detected, k_{R} >25 s^{-1} is a reasonable, conservative lower limit. Furthermore, Bartmess and co-workers also used

Scheme 2



reaction with MeOD to estimate a lower limit on the rate constant for rearrangement for the *tertiary* substrate at >10 s^{-1}. This corresponds to a $\Delta G^{\ddagger}$ of 16 kcal mol^{-1}, in agreement with our FA and FTICR values for all anionic oxy-Cope substrates.[11]

How do our gas-phase experimental values compare to the calculated values? The computational results at B3LYP/6-31+G* are summarized in Table 2 and are shown pictorially in Figure 1.[6,36,37] The predicted barrier to rearrangement for the secondary substrate, initially calculated at 0 K by Houk and co-workers, is 8.4 kcal mol^{-1} at 298 K.[6] Our calculations for the tertiary substrate indicate a $\Delta H^{\ddagger}$ of 7.5 kcal mol^{-1}. These values compare favorably with our $\Delta G^{\ddagger}$ of 14−15 kcal mol^{-1}. Cope rearrangements typically have $T\Delta S^{\ddagger}$'s on the order of −4 kcal mol^{-1} (at 298 K), which places the upper limit for the $\Delta H^{\ddagger}$ for **2b** and **3b** at ~11 kcal mol^{-1}, consistent with our calculations.[11,46−48]

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[45] This barrier holds for a situation where the bare alkoxide is rearranging. For hydroxide to deprotonate the alcohol, an ion molecule complex must form; after proton transfer, this leaves an ion−molecule complex of [H_2O·Cope alkoxide]. If this ion molecule complex rearranges, the barrier is not measurable. If, however, the alkoxide desolvates then rearranges, the barrier is measurable. Given that we see *m*/*z* 93, which could only result from desolvated alkoxide, we do believe that some, if not all, of the detected enolate results from bare alkoxide.

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Table 2. Theoretical Results: B3LYP/6-31+G* Activation Enthalpies (kcal mol^{-1}) for the Anionic Oxy Cope Rearrangements of 2b and 3b at 298 K

substrate	$\Delta H^{\ddagger}$, kcal mol^{-1}
2b	8.4
3b	7.5

How do our gas-phase experimental values compare to solution values? In an absolute sense, the prediction that the reaction should proceed the fastest in the gas phase has been validated—computational predictions and our experimental results agree. The rapid rearrangements of the original Evans compounds have solution phase $\Delta H^{\ddagger}$ values of 17−18 kcal mol^{-1}.[3,11,48]

Our experimental results also validate the Evans−Goddard (EG) model and the Yoo−Lee−Houk (YLH) paradigm for the rapidity of the anionic oxy-Cope rearrangement.[3,6,12,13] The well-accepted EG model for the rapidity of the anionic oxy-Cope rearrangement is that the substantial acceleration is related to the bond-weakening effect of the anionic alkoxy group on the adjacent C3−C4 bond.[12−14] Yoo, Lee, and Houk developed a corollary to this model that established a new paradigm, wherein bond homolysis and bond heterolysis both must be compared; this paradigm confirms the EG model for concerted reactions such as the anionic oxy-Cope.[6] Houk et al. used density functional theory to calculate the C−H bond strengths in methanol and methoxide and found a 22.9 kcal mol^{-1} bond weakening of the C−H bond in methoxide, relative to methanol. The $\Delta H^{\ddagger}$ for the oxy-Cope rearrangement is on the order of 36 kcal mol^{-1}.[3,6,49] The difference between these two values, or the effect of bond weakening, is 13 kcal mol^{-1}, which is remarkably close to our experimental $\Delta H^{\ddagger}$ and validates the bond-weakening model as a predictor of reactivity.

A referee brought up the possibility that the relative acidity of alcohols and ketones in the gas phase versus in solution is responsible for the lowering of the transition state, reflecting the increased exothermicity of the reaction in the gas phase. In essence, how much of the reaction barrier is attributable to a “thermodynamic” component, and how much to an “intrinsic” component, as described by Marcus Theory?[50−52] Previous work by Houk et al. on the Claisen rearrangement indicate that a generous estimate of the relative thermodynamic contribution to the barrier in pericyclic reactions is one-half of the exothermicity.[53−56] In the gas phase, *tert*-butyl alcohol has an acidity of 374.3 kcal mol^{-1}, while acetone has an acidity of 369.1 kcal mol^{-1}—only a 5 kcal mol^{-1} difference.[57] *tert*-Butyl alcohol has a pK_a of 19 while acetone has a pK_a of 19.1 (in water).[58−62] Therefore, the increased exothermicity due to acidity differences is about 5 kcal mol^{-1}. The thermodynamic contribution of this exothermicity to the barrier would be ~2.5 kcal mol^{-1}, not enough to explain the observed acceleration. Furthermore, model compounds with even more similarity to the actual Cope substrates have an even smaller gas-phase acidity difference: while 1-hexen-3-ol has a gas-phase acidity of 369.4 kcal mol^{-1}, butanal has a gas-phase acidity of 366.1 kcal mol^{-1}.[57,63,64] In addition, the solution phase rearrangement is most commonly explored in DMSO or in THF;[3,11,47] in DMSO, the pK_a of *tert*-butyl alcohol is 32.2, while that of acetone is 26.5; that is, alcohols are actually less acidic than ketones in DMSO, just as in the gas phase.[65,66] However, any result is subject to interpretation, and the relative acidity could in fact be responsible for the gas-phase acceleration.

Also intriguing is the difference, or lack thereof, in the rate constants of the secondary and tertiary rate constants in the gas phase. In solution, the secondary proceeds 280 times more slowly than the tertiary. In the gas phase, however, we find that, contrary to previous results, both rearrangements are comparably fast; although our calculations predict a 0.9 kcal mol^{-1} difference in barriers, we find that the m/z 93 consistently disappears between 0.03 and 0.04 s for both substrates. Therefore, the difference in solution versus the gas phase is ascribable to solvent effects—that is, intrinsically, both substrates should rearrange quickly.

So why is the secondary slower in solution? An acid−base argument can be made to rationalize this discrepancy. It is known that while *tert*-butoxide is less basic than isopropoxide in the gas phase (ΔH_{acid} (tBuOH) = 374.3 kcal mol^{-1}; ΔH_{acid} (^{i}PrOH) = 375.9 kcal mol^{-1}), the opposite is true in solution.[57,59−62,65,66] Alkyl groups destabilize anions through an inductive effect, but stabilize anions through a polarizability effect; in the gas phase, the polarizability effect dominates.[60,67−72] In solution, however, where charge is spread out among solvent molecules, the polarizability effect, which has larger charge and distance dependencies than does the inductive effect, is mitigated. Thus, the inductive effect dominates,

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and alkyl-substituted anions appear less stable. The transition states are presumably fairly immune to solvent effects due to charge delocalization; calculations show concerted, dissociative transition states (Figure 1). The expected result in solution is a less stable tertiary alkoxide, which would more easily rearrange than a secondary alkoxide. In the gas phase, in the absence of solvent, rearrangement of all three parent Cope substrates **1b**, **2b**, and **3b** can proceed with intrinsic facility.

Conclusion

In summary, we have found that the anionic oxy-Cope rearrangement of the parent substrates 3-methyl, 5-methyl, and unsubstituted 1,5-hexadiene-3-oxide *all* proceed in the gas phase under our flowing afterglow and FTMS conditions. Rearrangement occurs regardless of probe reagent used or pressure regime. Dimethyl disulfide has proven most convenient and reliable to use: no synthesis or purification is necessary, diagnostic reactions are all efficient, and distinct reaction products are found for each isomeric ion (alkoxides and enolates). For the rearrangement of the parent secondary and tertiary substrates (**2b** and **3b**), the upper limit for the $\Delta H^{\ddagger}$ is $\sim$11 kcal mol^{-1}, consistent with calculations at B3LYP/6-31+G*. Absolutely speaking, the prediction first made by Evans and Goddard more than 20 years ago has been borne out to be true: rearrangement is indeed faster in the gas phase than in solution, where the alkoxide is "most anionic". Furthermore, we have shown that differences in the gas phase and the condensed phase reactivity could be attributable to differential solvation of the alkoxide ion reactants. We plan to continue studies of anionic heteroatom Cope rearrangements in the gas phase, focusing next on the anionic amino-Cope. The EG/YLH paradigm predicts the amino substrates should follow a stepwise heterolytic cleavage pathway in the gas phase, which may or may not result in rearrangement.[6]

Acknowledgment. We are extremely grateful to Professor John E. Bartmess for helpful discussions. We thank the ACS-PRF (Grant #32732-G4), the NSF (CHE-0092215) and the Rutgers Busch Grant Program for support, and the National Center for Supercomputing Applications and the Boston University Scientific Computing Facilities for computational resources.

Supporting Information Available: Energies (in hartrees) and Cartesian coordinates for the optimized structures of **2b**, **3b**, and the transition states and products associated with the rearrangement of those substrates. This material is available free of charge via the Internet at http://pubs.acs.org.

JO001177E