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Anion Structure Determination in the Gas Phase: Chemical Reactivity as a Probe

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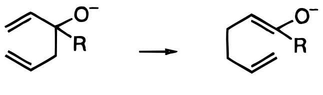
In the gas phase, the discrimination between two isomeric anion structures is a challenge that requires different solutions for different applications. The anionic oxy-Cope rearrangement involves the rearrangement of an alkoxide to an isomeric enolate; the mechanistic study of such a process in the gas phase requires a simple and selective probe process. Using a flowing afterglow mass spectrometer, we have examined the utility and limitations of using chemical reactivity to discriminate between alkoxides and enolates in the gas phase. A series of alkoxides and enolates were allowed to react with three chemical probe reagents: methanol-*O-d*, methyl nitrite, and dimethyl disulfide. Quantitative and qualitative characterization of each probe reagent reveals the especially broad and flexible utility of dimethyl disulfide as a chemical probe. Dimethyl disulfide is a selective reagent with ambident behavior that reacts efficiently with all anions studied and fully capitalizes on the structure/reactivity differences between alkoxides and enolates. Alkoxides behave as classical "hard bases" when allowed to react with dimethyl disulfide, effecting elimination across the C−S bond, whereas enolates, "soft bases", attack at sulfur. Methyl nitrite is also a selective ambident probe reagent but, due to its particularly slow reaction with enolates, is useful only in conjunction with a more reliable probe such as dimethyl disulfide. Methanol-*O-d*, for a variety of reasons detailed in the paper, is unsuitable as a chemical probe reagent for the unequivocal discernment between alkoxides and enolates.

Structure determination is the foundation upon which advances in chemistry are made. Various structural determination methods allow one to declare unambiguously the successful synthesis of a target compound,[1−3] to elucidate aspects of reaction mechanisms via product identification,[4] and to monitor changes in secondary and tertiary protein structure.[5] Many methods of elucidating structure are well-known and used regularly, such as NMR and IR spectroscopy for condensed-phase and solid-phase samples. In the gas phase, methods of structural determination are more limited; examples include various spectroscopic techniques (PES, IR, UV−vis) and methods using mass spectrometry.

An especially challenging aspect of gas-phase structure determination is the structural assignment of reactive intermediates, particularly organic anions. PES can be experimentally difficult to execute,[6] while traditional simple mass spectrometric methods fail since ionized structural isomers themselves possess the same mass-to-charge ratio. One useful solution to such a dilemma for ion structure is collision-induced dissociation (CID) mass spectrometric techniques. CID can be very informative,[7] but is an energetic method which can actually induce an ion to isomerize. Since many methods require instrument modification, a general method of structure determination applicable across the wide range of mass spectrometric approaches used in organic chemistry would ultimately be the most useful to the broadest range of users. Such a general method is the use of chemical reactivity to elucidate structure.[8−11]

Our interest in structure determination stems from our examination of unimolecular rearrangements, and the anionic oxy-Cope in particular.[12,13] In this reaction, an alkoxide undergoes a [3,3]-sigmatropic rearrangement to an enolate (eq 1). In the gas phase, the study of this rearrangement raises a classic problem of structure elucidation: both the starting material (alkoxide) and the product (enolate) have the same mass-to-charge signature. We sought to use chemical reactivity as a general method to discern between these two types of species. Although the use of chemical probe reagents to discern structure is not new, we sought to fully generalize a



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(1) Holton, R. A.; Somoza, C.; Kim, H.-B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597−1598.

(2) Holton, R. A.; Kim, H.-B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599−1600.

(3) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630−634.

(4) Grabowski, J. J.; Zhang, L. *J. Am. Chem. Soc.* **1989**, *111*, 1193−1203.

(5) Raleigh, D. P.; DeGrado, W. F. *J. Am. Chem. Soc.* **1992**, *114*, 10079−10081.

(6) Zittel, P. F.; Ellison, G. B.; ONeil, S. V.; Herbst, E.; Lineberger, W. C.; Reinhardt, W. P. *J. Am. Chem. Soc.* **1976**, *98*, 3731−3732.

(7) Groenewold, G. S.; Gross, M. L. In *Ionic Processes in the Gas Phase*; Almoster Ferreira, M. A., Ed.; D. Reidel Publishing Co.: Boston, 1982; pp 243−266.

(8) Andrist, A. H.; DePuy, C. H.; Squires, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 845−850.

(9) Rozeboom, M. D.; Kiplinger, J. P.; Bartmess, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 1025−1029.

(10) Thomas, D. A.; Bloor, J. E.; Bartmess, J. E. *J. Am. Soc. Mass Spectrom.* **1990**, *1*, 295−300.

(11) Chou, P. K.; Dahlke, G. D.; Kass, S. R. *J. Am. Chem. Soc.* **1993**, *115*, 315−324.

(12) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765−4766.

(13) Lee, J. K.; Grabowski, J. J. Manuscript in preparation.

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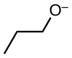
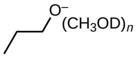
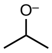
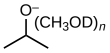
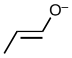
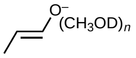
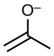
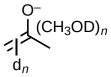
Table 1. Results for the Reactions of Anions with Methanol-*O-d* in the Gas Phase at 298 K[a]

anion (A^-)	$\Delta H°_{acid}$ (AH) (kcal mol^{-1})[a]	number of protons exchanged	other products	$k_{obs} \pm 1\sigma^{b-d}$	Eff[e]
	376.0	0		4.8 ± 0.4	0.24
	375.4	0		4.1 ± 0.4	0.20
	365.3	0		0.30 ± 0.05	0.015
	369.1	5		0.82 ± 0.07	0.041

[a] Products reported can be the result of several sequential anion−methanol collisions (see text and schemes). [b] Gas-phase acidities were obtained from ref 28 unless otherwise noted. [c] The *minimum* number of independent experimental determinations of the rate coefficient (k_{obs}) is 5. [d] Reaction rate in units of 10^{-10} cm^3 $molecule^{-1}$ s^{-1}. [e] This is the *apparent* bimolecular rate coefficient, taken at 0.3 Torr of He; see text. [f] Reaction efficiency, k_{obs}/k_{coll}, where k_{coll} is calculated according to ref 24.

methodology by selectively discriminating between alkoxides and enolates with the use of one ambident reagent.[8−11] The importance of such well-characterized methodology is made clear by identification of gas-phase anionic oxy-Cope rearrangements which were previously believed to not occur.[9,13]

Toward the goal of characterizing probe reagents for general use as a selective reagent for alkoxide/enolate discrimination, we examined a series of prototypical alkoxides and enolates with three promising probe reagents. The reactions of model anions propoxide, isopropoxide, propanal enolate, and acetone enolate were each examined with methanol-*O-d* (MeOD), methyl nitrite (MeONO), and dimethyl disulfide (MeSSMe). MeOD was chosen because of its capability to exchange its deuteron; MeONO and MeSSMe had shown promise in earlier studies for displaying different reactivity with different anions.[4,14−16] Each probe reagent was studied both quantitatively and qualitatively to assess its reliability as a structural determinant, especially with respect to its utility under the thermally-equilibrated conditions as are routinely attained in the flowing afterglow.

Experimental Section

Experiments were conducted at ambient temperature (298 K) and in 0.3 Torr of helium buffer gas in a flowing afterglow[17,18] which has been previously described.[19] Amide was generated by dissociative electron attachment to ammonia (eq 2). Hydroxide was generated by allowing the atomic oxygen radical anion (generated by dissociative electron attachment to N_2O, eq 3) to abstract a hydrogen atom from methane (eq 4). Acetone enolate and propanal enolate were synthesized in the flow tube by exothermic proton transfer from acetone or propanal to amide or hydroxide. Propoxide and isopropoxide were generated by an elimination reaction of either amide or hydroxide with isopropyl ether (eq 5) or propyl ether.[20]

$$NH_3 \xrightarrow{e^-} H_2N^- + H^\bullet \tag{2}$$

$$N_2O \xrightarrow{e^-} O^{\bullet -} + N_2 \tag{3}$$

$$O^{\bullet -} + CH_4 \rightarrow HO^- + CH_3^\bullet \tag{4}$$

$$H_2N^- + (CH_3)_2CHOCH(CH_3)_2 \rightarrow (CH_3)_2CHO^- + CH_3CH{=}CH_2 + NH_3 \tag{5}$$

Methyl nitrite was prepared within 24 h of use by adding a solution of dilute sulfuric acid and methanol to a cooled aqueous solution of sodium nitrite and methanol.[21,22] The gaseous product was collected in a standard glass sample flask which was cooled in an acetone/dry ice bath. The flask was wrapped in aluminum foil to prevent photoinduced decomposition of the methyl nitrite. All other reagents were obtained from standard commercial suppliers and were used as received. Before use, each liquid sample was subjected to several freeze−pump−thaw cycles to remove dissolved gases.

Each reaction of interest was examined rigorously using both qualitative and quantitative methods. Qualitative experiments were run to identify all reaction products and involved examining the products of the reaction at progressive reaction times. Practically, this process involves taking a complete mass scan of the ionic contents of the flow tube at different time points in the reaction. Quantitative examination involved kinetic experiments to measure total reaction rate coefficients and branching ratio experiments to determine the yields of the various product ions. Rate coefficients were obtained by monitoring the disappearance of the reactant ion "A^-" as a function of time (distance) under pseudo-first-order conditions (i.e., a constant concentration, or flow of the neutral reactant "B" was maintained (eqs 6−8)), and all reported results are the average of data collected over several independent experimental days.[23] We estimate the absolute accuracy of our rate coefficients to be ±20% (the precision is as indicated in Tables 1−3); collision rate coefficients (k_{coll}) were calculated according to the variational transition state theory of Su and

$$A^- + B \xrightarrow{k} C^- + D \tag{6}$$

$$\text{rate of reaction} = k[A^-][B] \tag{7}$$

pseudo-first-order conditions ($[B] \gg [A^-]$):

$$\text{rate of reaction} = k'[A^-] \tag{8}$$

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(14) DePuy, C. H.; Bierbaum, V. M.; King, G. K.; Shapiro, R. H. *J. Am. Chem. Soc.* **1978**, *100*, 2921−2922.

(15) King, G. K.; Maricq, M. M.; Bierbaum, V. M.; DePuy, C. H. *J. Am. Chem. Soc.* **1981**, *103*, 7133−7140.

(16) Noest, A. J.; Nibbering, N. M. M. *Adv. Mass. Spectrom.* **1980**, *8A*, 227−237.

(17) Ferguson, E. E.; Fehsenfeld, F. C.; Schmeltekopf, A. L. In *Advances in Atomic and Molecular Physics*; Bates, D. R., Estermann, I., Eds.; Academic Press: New York, 1969; Vol. 5, pp 1−56.

(18) Graul, S. T.; Squires, R. R. *Mass Spectrom. Rev.* **1988**, *7*, 263−358.

(19) Grabowski, J. J.; Melly, S. J. *Int. J. Mass Spectrom. Ion Processes* **1987**, *81*, 147−164.

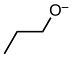
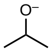
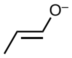
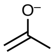
(20) DePuy, C. H.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1981**, *103*, 5034−5038.

(21) Hartung, W. H.; Crossley, F. *Org. Synth.* **1943**, *2*, 108.

(22) Semon, W. L.; Damerell, V. R. *Org. Synth.* **1930**, *10*, 22.

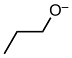
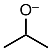
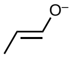
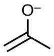
(23) Guo, Y.; Grabowski, J. J. *J. Am. Chem. Soc.* **1991**, *113*, 5923−5931.

Table 2. Results for the Reactions of Anions with Methyl Nitrite in the Gas Phase at 298 K

anion (A^-)	$\Delta H^\circ_{\mathrm{acid}}$(AH) (kcal mol^{-1})[a]	mol formula	product ion (m/z)	observed amounts[b–d]	product yields[e] (%)	$k_{\mathrm{obs}} \pm 1\sigma$[c,f]	Eff[g]
	376.0	NO_2^-	46	major		2.3 ± 0.2	0.11
		$ONCH_2O^-$	60	major			
		$NO^-(C_3H_7OH)$	90	minor			
	375.4	NO_2^-	46	major		6.9 ± 0.1	0.32
		$ONCH_2O^-$	60	major			
		$NO^-(C_3H_7OH)$	90	minor			
	365.3	NO_2^-	46	0.073 ± 0.02	7.1	0.41 ± 0.02	0.019
		$ON\overset{-}{C}HCH_3$	58	0.531 ± 0.01	52.9		
		$CH_3C(NO)CHO^-$	86	0.396 ± 0.01	40.0		
	369.1	$ONCH_2^-$	44	0.262 ± 0.002	25.8	0.26 ± 0.01	0.012
		NO_2^-	46	0.071 ± 0.001	6.9		
		$CH_3C(O^-){=}CHNO$	86	0.667 ± 0.001	67.3		

[a] Gas-phase acidities were obtained from ref 28 unless otherwise noted. [b] The average fractional yield, ± 1 standard deviation, based on observation of only the m/z values listed for that reaction. [c] The *minimum* number of independent experimental determinations of the branching ratio is 2, and of the rate coefficient (k_{obs}), 5. [d] Quantitative branching ratios were not measured for the alkoxides. We suspect (see ref 27) that NO^- is also a product for these reactions; however, NO^- will be collisionally detached before it can be detected in our instrument. [e] The yield of the product ion of given molecular formula actually formed in the reaction cited (i.e., corrected to include all naturally occurring isotopic variants). These values are calculated by taking the "observed amounts" and dividing them by the "isotope factor" and then renormalizing. The isotope factor is the fraction of the product ion with the given molecular formula that will be detected at the m/z value listed (which is the predominant isotopic peak). These values were calculated from values in the Table of the Isotopes in ref 27. The isotope factors for m/z 44, 58, 46, and 86 are 0.9827, 0.9716, 0.9915, and 0.9586, respectively. [f] Reaction rate coefficient in units of 10^{-10} cm^3 molecule^{-1} s^{-1}. [g] Reaction efficiency, $k_{\mathrm{obs}}/k_{\mathrm{coll}}$, where k_{coll} is calculated according to ref 24.

Table 3. Results for the Reactions of Anions with Dimethyl Disulfide in the Gas Phase at 298 K

anion (A^-)	$\Delta H^\circ_{\mathrm{acid}}$(AH) (kcal mol^{-1})[a]	mol formula	product ion (m/z)	observed amounts[b,c]	product yields[d] (%)	$k_{\mathrm{obs}} \pm 1\sigma$[c,f] (cm^3 molecule^{-1} s^{-1})	Eff[f]
	376.0	CH_3S^-	47	0.051 ± 0.01	4.8	23 ± 2	1[g]
		$CH_3SCH_2S^-$	93	0.673 ± 0.03	68.0		
		$CH_3S^-(C_3H_7OH)$	107	0.276 ± 0.02	27.2		
	375.4	CH_3S^-	47	0.016 ± 0.002	1.5	22 ± 1	1[g]
		$CH_3SCH_2S^-$	93	0.735 ± 0.001	74.0		
		$CH_3S^-(C_3H_7OH)$	107	0.249 ± 0.001	24.5		
	365.3	CH_3S^-	47	0.067 ± 0.007	6.5	6.8 ± 0.1	0.33
		$CH_3C(SCH_3)CHO^-$	103	0.933 ± 0.007	93.5		
	369.1	CH_3S^-	47	0.261 ± 0.02	25.4	10 ± 1	0.49
		$CH_3C(O^-)CHSCH_3$	103	0.739 ± 0.02	74.6		

[a] Gas-phase acidities were obtained from ref 28 unless otherwise noted. [b] The average fractional yield, ± 1 standard deviation, based on observation of only the m/z values listed for that reaction. [c] The *minimum* number of independent experimental determinations of the branching ratio is 2, and of the rate coefficient (k_{obs}), 5. [d] The yield of the product ion of given molecular formula actually formed in the reaction cited (i.e., corrected to include all naturally occurring isotopic variants). These values are calculated by taking the "observed amounts" and dividing them by the "isotope factor" and then renormalizing. The isotope factor is the fraction of the product ion with the given molecular formula that will be detected at the m/z value listed (which is the predominant isotopic peak). These values were calculated from values in the Table of the Isotopes in ref 27. The isotope factors for m/z 44, 58, 46, and 86 are 0.9827, 0.9716, 0.9915, and 0.9586, respectively. [e] Reaction rate coefficient in units of 10^{-10} cm^3 molecule^{-1} s^{-1}. [f] Reaction efficiency, $k_{\mathrm{obs}}/k_{\mathrm{coll}}$, where k_{coll} is calculated according to ref 24. [g] The numbers calculated for the efficiency of these two reactions are 1.04 for the propoxide and 1.09 for isopropoxide. That these ratios are calculated to be slightly greater than 1 is a reflection of the imperfections in modeling k_{coll}, the error in the data which is used to calculate k_{coll} (dipole moments and polarizabilities), and the error in k_{obs}.

Chesnavich.[24] Reaction efficiency, the probability of chemical reaction per collision, is determined for a given reaction as the ratio of the observed rate coefficient to the collision rate coefficient (Eff = $k_{\mathrm{obs}}/k_{\mathrm{coll}}$). Branching ratios were obtained by monitoring the reactant and product ion intensities of a given reaction at a fixed concentration of neutral reagent, under pseudo-first-order conditions, as a function of the time (distance).[25] The precision of our branching ratios is as indicated in Tables 2 and 3; we estimate that the absolute accuracy of our branching ratio experiment is ± 2% or less.

Results

Methanol-*O-d*. The results of the reactions of propoxide, isopropoxide, propanal enolate, and acetone enolate with methanol-*O-d* are summarized in Table 1. In the gas phase, like in the solution phase, certain anions are capable of undergoing proton/deuteron exchange with MeOD.[14] The two alkoxides are found to undergo a facile clustering reaction with MeOD to form varied-size clusters of $RO^-(MeOD)_n$. The lower basicity of the alkoxides (~375 kcal mol^{-1}) relative to the acidity of MeOD (381.7 kcal mol^{-1}) renders proton transfer impossible and the lack of "acidic" protons renders exchange improbable, such that clustering is the only reactivity the alkoxides display with MeOD.[26] Clustering is a process that is not uncommon in the flowing afterglow, where the relatively high pressure of He creates thermally equilibrated conditions which can stabilize ion−molecule clusters. In measuring the k_{obs} of a clustering reaction, the k measured (and listed in Table 1) is only an *apparent* bimolecular rate constant, since clustering is a termolecular

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(24) Su, T.; Chesnavich, W. J. *J. Chem. Phys.* **1982**, *76*, 5183−5185.
(25) Grabowski, J. J.; Lum, R. C. *J. Am. Chem. Soc.* **1990**, *112*, 607−620.
(26) DePuy, C. H.; Bierbaum, V. M. *Acc. Chem. Res.* **1981**, *14*, 146−153.

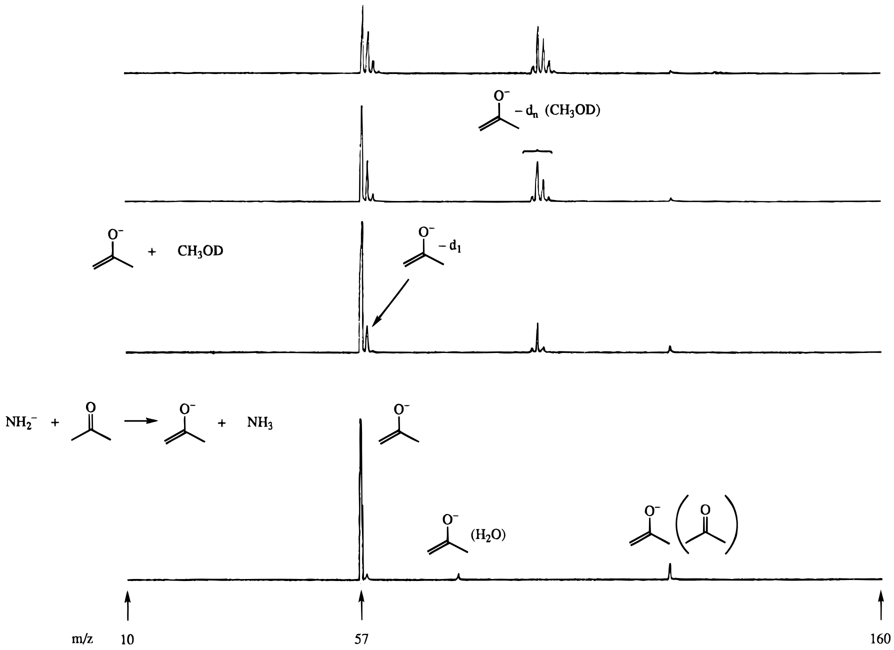
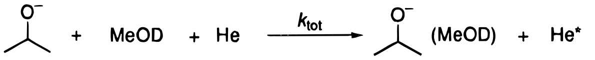


Figure 1. Series of mass spectral scans of the reaction of acetone enolate (m/z 57) with methanol-O-d (molecular weight = 33). Acetone enolate exchanges its protons for deuterons (m/z 57 disappears, m/z 58 and 59 grow in); the cluster of acetone enolate to MeOD (m/z 90) is also observed, as well as deuterated versions of this cluster.

process dependent on the amount of He present (eqs 9−11; He* represents energetic He).



(9)

$$\text{rate} = k_{tot}[(CH_3)_2CHO^-][MeOD][He] \qquad (10)$$

$$k_{obs} = k_{tot}[He] \qquad (11)$$

Acetone enolate, however, behaves in the fashion that makes MeOD's potential as a gas-phase probe reagent clear. Although clustering is a also a facile process for acetone enolate, this ion also exchanges five protons for deuterons (Figure 1). Note that both deuterated as well as undeuterated forms of acetone enolate are observed to cluster with MeOD.

Propanal enolate is about 4 kcal mol^{-1} less basic than acetone enolate and shows, unexpectedly, markedly different patterns of behavior than its sister enolate. Unlike the alkoxides, propanal enolate *does* possess an exchangeable proton; however, unlike acetone enolate, it does not exchange it for a deuteron with MeOD in a 0.3 Torr helium environment. Rather, facile clustering is observed to form $CH_3CHCHO^-(MeOD)_n$. Another cluster formed when propanal enolate is generated is the complex of propanal enolate with neutral propanal, $CH_3CHCHO^-(CH_3CH_2CHO)$. Although acetone enolate clusters to acetone as well, propanal enolate clusters to propanal much more efficiently; experimentalists should beware in that this facile clustering of aldehyde enolates can complicate analysis. An intriguing aside is that when exposed to MeOD, the $CH_3CHCHO^-(CH_3CH_2CHO)$ cluster readily exchanges three protons for deuterons (a simple cluster would contain three exchangeable protons in contrast to none for the covalent adduct).

Methyl Nitrite. The results of the reactions of the model ions with methyl nitrite are collected in Table 2. The product yields (column 6) are calculated from the "observed amounts" and the "isotope factors", as described in footnote *e*.[27] The alkoxides are found to react fairly efficiently with methyl nitrite to produce mostly NO_2^- (m/z 44) and $ONCH_2O^-$ (m/z 60). A minor product is the cluster of $NO^-(C_3H_7OH)$ (m/z 90). Quantitative branching ratios were not measured for these reactions as the major products are the same from the two model alkoxides and are independent of alkoxide; we speculate that NO^- is also a product which is formed, but which undergoes collision-induced detachment under our conditions (EA($NO^\bullet$ = 0.026 eV)).[15,28] In contrast to the alkoxides, the enolates react with low efficiency, 2% or less, and are a factor of 5−30 times slower than the alkoxide reaction. Acetone enolate reacts with methyl nitrite to form the nitrosated enolate ($CH_3C(O^-)CHNO$, m/z 86) as the major product ion (67%). Also formed are $ONCH_2^-$ (m/z 44, 26%) and a minor amount of NO_2^- (m/z 46, 7%). Propanal enolate is also nitrosated by methyl nitrite ($CH_3C(NO)CHO^-$, m/z 86, 40%), but the major product ion formed is $ON\bar{C}HCH_3$ (m/z 58, 53%). A small amount of NO_2^- (7%) is also formed in the propanal enolate reaction.

Dimethyl Disulfide. The results of the reactions of propoxide, isopropoxide, propanal enolate, and acetone enolate with dimethyl disulfide are summarized in Table 3. The alkoxides react with unit efficiency with dimethyl disulfide to yield $CH_3SCH_2S^-$ (m/z 93) as the major product. The cluster of methanethiolate to the parent alcohol, $CH_3S^-(C_3H_7OH)$ (m/z 107), is also produced in relatively high yield, as well as a small amount of methanethiolate, CH_3S^- (m/z 47). The enolates ("HA$^-$") react quite efficiently (Eff = 0.33 and 0.49) with dimethyl disulfide, forming the thiomethoxylated enolates CH_3SA^- as the major product ion (for acetone enolate, $CH_3C(O^-)$-$CHSCH_3$; for propanal enolate, $CH_3C(SCH_3)CHO^-$; m/z 103). Some methanethiolate (CH_3S^-) is also formed, in

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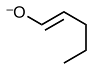
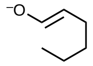
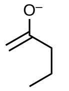
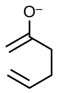
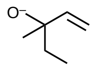
(27) *CRC Handbook of Chemistry and Physics*, 73rd ed.; Lide, D. R., Ed.; CRC: Boca Raton, FL, 1992.

(28) Lias, S. G.; Liebman, J. F.; Levin, R. D.; Kafafi, S. A. Negative Ion Energetics: NIST Standard Reference Database 19B, 1993.

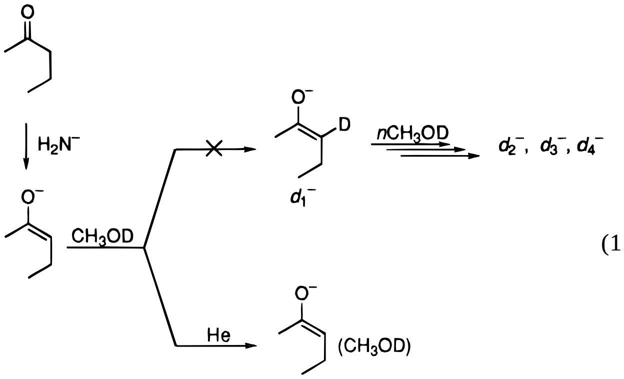
Table 4. Results for the Reactions of a Series of Anions with Dimethyl Disulfide[a]

	observed products			
HA^-	CH_3S^-	CH_3S^- (H_2A)	$CH_3SCH_2S^-$	CH_3SA^-
	✓			✓
				✓
	✓			✓
	✓			✓
	✓	✓	✓	

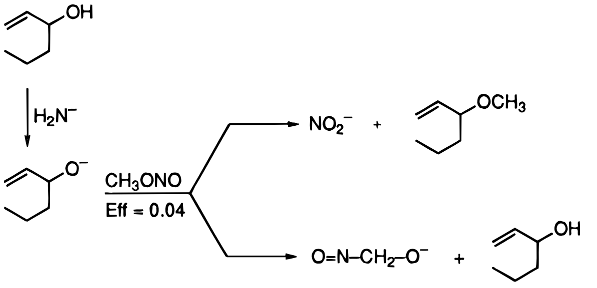
[a] Check mark (✓) indicates the presence of that product.

greater quantities for acetone enolate (25%) than for propanal enolate (7%).

Reactivity of Larger Anions. In order to examine the consistency of reactivity of the probe reagents as the size of alkoxides and enolates increased, we studied each reagent with selected larger ions. For example, the reaction of 2-pentanone enolate ($\Delta H_{\text{acid}} = 368.6$ kcal mol^{-1})[28] with MeOD yielded only cluster as product and did not exhibit the desired exchange (eq 12). Large anion 1-hexene-3-oxide reacts with methyl nitrite in the expected fashion to produce NO_2^- and $ONCH_2O^-$, but the rate of the reaction is a factor of 10 slower than that of its three-carbon counterpart, isopropoxide ($k_{\text{obs}} = (7.7 \pm 0.1) \times 10^{-11}$ cm^3 molecule^{-1} s^{-1}, eq 13).



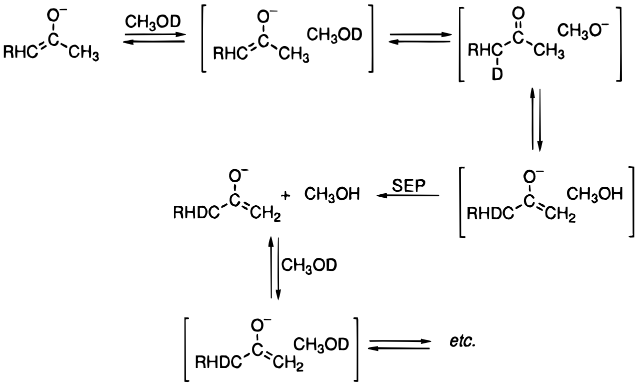
(12)



(13)

The results of various larger anions with dimethyl disulfide are compiled in Table 4. All enolates react efficiently with MeSSMe to generate CH_3SA^- as the major product, and no $CH_3SCH_2S^-$ is formed. The large alkoxide studied generates $CH_3SCH_2S^-$ when allowed to react with MeSSMe, but does not form thiomethoxylated product.

Scheme 1. Reaction Pathways by which Enolates React with Methanol-*O-d*[a]

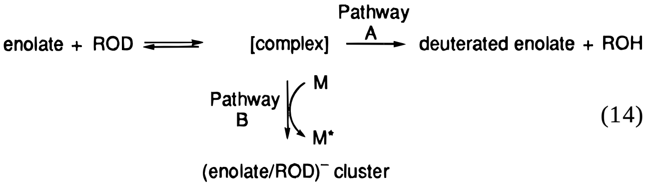


[a] "SEP" refers to separation of an ion−molecule complex. Although not shown, some (enolate/MeOD)$^-$ cluster is formed in these reactions as well (see text).

Discussion

When establishing a general methodology, certain criteria must be met in order to ensure a standard for reliability. For these chemical probes, we sought the following qualities. First, the probe should yield a unique product when allowed to react with an alkoxide or an enolate; that is, its reaction with all alkoxides should yield a product indicative of reaction with an alkoxide as opposed to an enolate, and its reaction with all enolates should yield a product indicative of reaction with an enolate. Second, its reactions with both alkoxides and enolates should be fast and efficient; if reactions are too slow, then a "negative" result wherein one does not see an expected product could mean either that the ion of unknown structure is not of the correct form for the probe reaction or that its reaction with the probe is too slow to yield any observable products. Third, on a practical level, the probe should be readily available, easy to use, and generally applicable to other systems in addition to those described herein.

Methanol-*O-d*. The ability of enolates to exchange their protons for deuterons when allowed to react with an appropriate deuterated substrate is well-known (Scheme 1).[14] The general utility of MeOD as a probe to discern between enolates and alkoxides, however, is limited. First, alkoxides and enolates are *both* observed to cluster; therefore, presence of an (anion/MeOD)$^-$ cluster is inconclusive of either alkoxide or enolate presence. Since clustering is the *only* behavior alkoxides exhibit, the unequivocal assignment of structure as an alkoxide is not possible. Second, the efficiency for the overall enolate reactions are low. The main complication of this type of slow reaction is that the *lack of observed exchange* is inconclusive; no exchange could mean either that the unknown structure is *not* an enolate or else that the probe reaction is simply too inefficient to yield the expected exchange product. An extension of this is the problem displayed by propanal enolate: clustering and exchange are probably in kinetic competition, and the clustering is far more efficient (eq 14, pathway B). This issue is also evidenced by the interesting observation that $CH_3CHCHO^-(CH_3CH_2CHO)$ *cluster* exchanges three pro-



(14)

tons for deuterons, although no exchange is observed for CH_3CHCHO^-. Third, and perhaps most important, the exchange reaction is not general for all enolates: although acetone enolate exchanges five protons (complicated by an equally efficient clustering reaction in 0.3 Torr of helium), propanal enolate and 2-pentanone enolate do not. Therefore, MeOD is an unreliable structural probe reagent, useful in a small number of cases, all of which would require extensive controls in order to ensure a high degree of confidence in any results obtained.

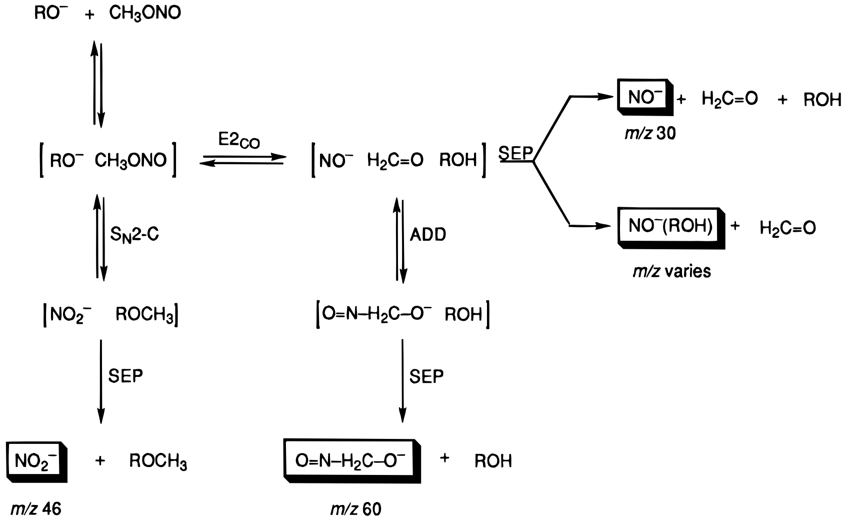
Methyl Nitrite. The reactivity of enolates and alkoxides with methyl nitrite has been described by King[15] and Nibbering[16] and their co-workers and is generalized in reaction Schemes 2 and 3. Methyl nitrite is an ambident reagent with several potential reaction sites, including at carbon, at hydrogen, and at nitrogen. Its potential as a probe reagent can be explained using classical hard−soft acid−base (HSAB) theory: one would expect a hard base to favor the H site (deprotonation) while a soft base would favor an alternative site.[29] Reaction at the two different sites would yield two discrete products, indicative of soft or hard base reaction. The main issue, then, is whether alkoxides and enolates will behave in classic HSAB fashion. Such behavior is indeed observed when alkoxides and enolates are allowed to react with MeONO. Alkoxides (Scheme 2) behave as hard, localized bases which eliminate across the C−O bond of methyl nitrite.[16] The resultant NO^- can undergo nucleophilic addition with the newly formed $H_2C{=}O$ within the complex, to ultimately yield $O{=}NCH_2O^-$ (m/z 60).[10] Alternatively, the NO^- can cluster to the newly formed neutral alcohol to yield $NO^-(ROH)$. NO^- itself is not observed in our flowing afterglow, and if any is formed, it undergoes collision-induced electron detachment under the existing swarm conditions ($P = 0.3$ Torr, $T = 300$ K). In addition to the three ion channels from the initial elimination reaction, alkoxides also display a substantial amount of S_N2 at carbon (S_N2-C) to yield NO_2^-.

The enolates behave as nucleophiles (soft bases) and react, at least in part, by attack at the nitrogen of methyl nitrite, followed by extrusion of CH_3O^- in a Claisen-type condensation (Scheme 3). Subsequent deprotonation of the nitrosated carbonyl compound by methoxide within the ion−molecule complex ultimately yields the nitrosated enolate anion (m/z 86 for propanal and acetone). Alternatively, if after the Claisen-like reaction the methoxide adds to the carbonyl carbon, a retro-Claisen condensation occurs and $ONCH_2^-$ (m/z 44) and $ON\bar{C}HCH_3$ (m/z 58) are produced for acetone and propanal enolate, respectively. Like alkoxides, enolates exhibit S_N2-C as well, but in minor amounts (7% for acetone and propanal enolates).

Alkoxides, (hard bases) react with MeONO to produce the unique ion $O{=}NCH_2O^-$ whereas enolates, soft bases, produce nitrosated products.[29] MeONO, however, possesses drawbacks which hinder it from being an ideal probe. First, as in the case of MeOD, even small, simple enolates react with MeONO with a low reaction efficiency whereas an ideal probe would be near unit efficient in its reactions. Even more limiting is the fact that the efficiency decreases with increasing anion size; 1-hexene-3-oxide reacts with an efficiency of 0.040 whereas the propoxides react at efficiencies of 0.11 and 0.32. Second, on a more practical level, methyl nitrite is inconvenient. It is not readily available in pure form; it is a gas and must be synthesized and isolated, preferably on the day of experimentation as the compound is photoactive (BDE [$CH_3O{-}NO$] = 41.8 kcal mol^{-1}).[27] Although methyl nitrite can be generated in situ (the bulk of the evaporate from a 10:1 mixture of methanol:isoamyl nitrite is CH_3-ONO),[30] we have found that this method does not provide the concentration of MeONO necessary to drive a diagnostic reaction to any degree of completion in a flowing afterglow and should not be used when utilizing MeONO as a chemical probe.[9,13] Thus, while methyl nitrite neatly capitalizes on the differences in activity between an alkoxide and an enolate, its low efficiency and its changing reactivity properties with increasing anion size urge caution when used for careful structural determination.

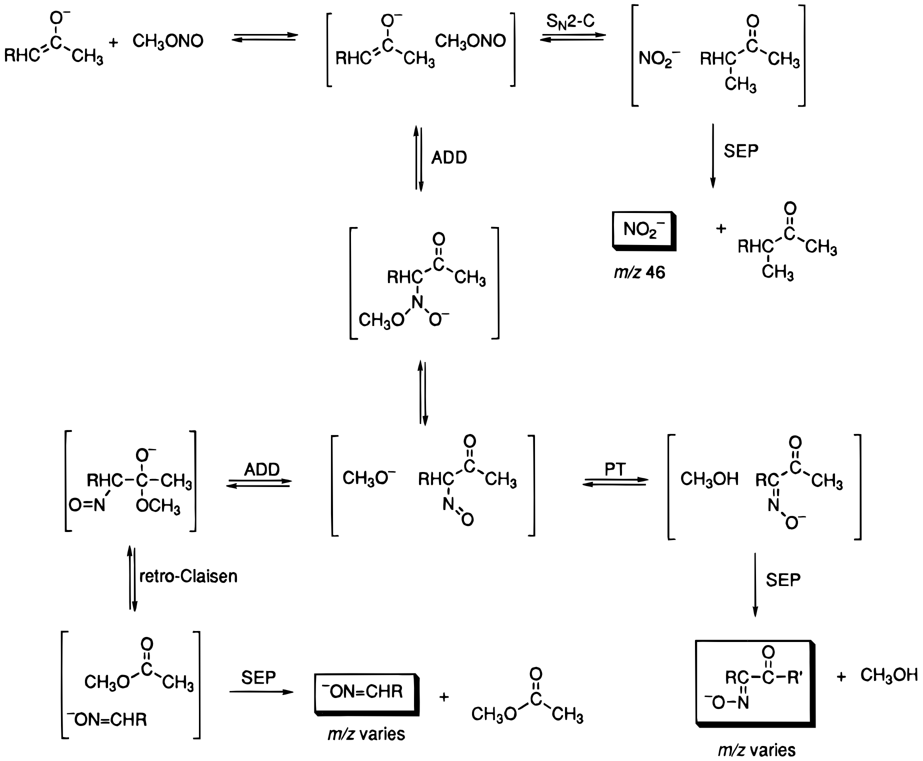
Dimethyl Disulfide. The reactions of anions with dimethyl disulfide are described in Schemes 4 and 5.[4] Dimethyl disulfide, like methyl nitrite, possesses at least

Scheme 2. Reaction Pathways by which Alkoxides React with Methyl Nitrite[a]



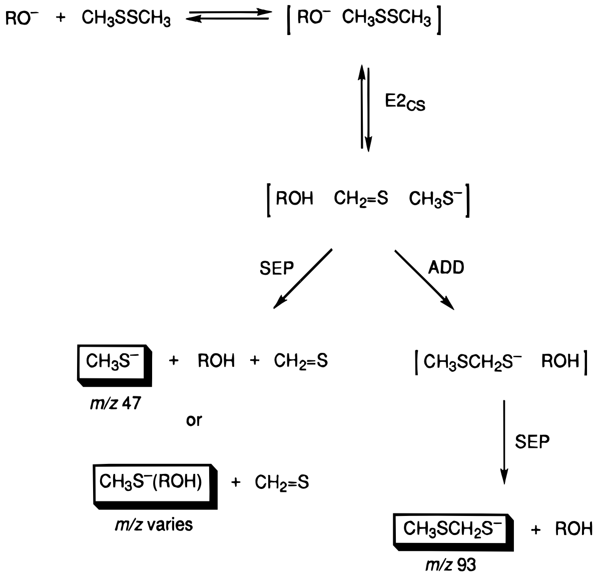
[a] The ultimate ionic products of the various competing channels are shown in heavy boxes for clarity. "SEP" refers to separation; "ADD", addition; "E2$_{CX}$", elimination across a C−X bond, "S_N2-X", substitution at atom X.

Scheme 3. Reaction Pathways by which Enolates React with Methyl Nitrite[a]



[a] The ultimate ionic products of the various competing channels are shown in heavy boxes for clarity. "SEP" refers to separation; "ADD", addition; "PT", proton transfer; "S_N2-X" substitution at atom X.

Scheme 4. Reaction Pathways by which Alkoxides React with Dimethyl Disulfide[a]



[a] The ultimate ionic products of the various competing channels are shown in heavy boxes for clarity. "SEP" refers to separation; "ADD", addition; "$E2_{CX}$", elimination across a C−X bond.

two potential reaction sites, at hydrogen and at sulfur. Again, HSAB theory would predict that a hard base would prefer deprotonation while a soft base would prefer an alternative site. This potential ambident behavior of MeSSMe, as with MeONO, renders it ideal as a choice for further exploration as a chemical probe reagent.

The prototypical alkoxides and enolates were found to behave as classic hard and soft bases, respectively, when allowed to react with dimethyl disulfide. Alkoxides eliminate across the C−S bond of dimethyl disulfide (Scheme 4); elimination followed by separation yields methanethiolate (CH_3S^-, *m/z* 47) and/or the cluster of methanethiolate with the newly formed alcohol (CH_3S^-(ROH), *m/z* 107 for model three-carbon alcohols). Elimination can also be followed by readdition of the methanethiolate into the resultant thioformaldehyde, to ultimately yield the unique product $CH_3SCH_2S^-$ (*m/z* 93).[4] Enolates, in analogy to their reactions with MeONO, behave solely as nucleophiles, attacking a sulfur center of dimethyl disulfide to form a complex containing the thiomethoxylated carbonyl compound and methanethiolate (CH_3S^-). Deprotonation of the thiomethoxylated neutral by methanethiolate within the complex, followed by separation, yields the unique thiomethoxylated enolate ion ($(CH_3S)RC{=}C(O^-)CH_3$), *m/z* 103 for model three-carbon enolates).

In summary, the prototypical alkoxides react with dimethyl disulfide to form mostly $CH_3SCH_2S^-$ and no thiomethoxylated product; in contrast, the propanal and acetone enolates form mostly thiomethoxylated product and do not produce $CH_3SCH_2S^-$. Interestingly, no S_N2-C to generate CH_3SS^- is observed for any of the anions ($\Delta H_{acid}(CH_3SSH) = 343.1$ kcal mol^{-1}).[31] In addition to the formation of unique products for the different types of reactant ions, the reactions of both types of anions proceed at high efficiency (unit efficiency for the alkoxides, and 0.3−0.5 efficiency for the enolates). Dimethyl disulfide therefore fulfills the criteria required for a reliable, general structural probe. First, alkoxides yield the unique product $CH_3SCH_2S^-$, and enolates, thiomethox-

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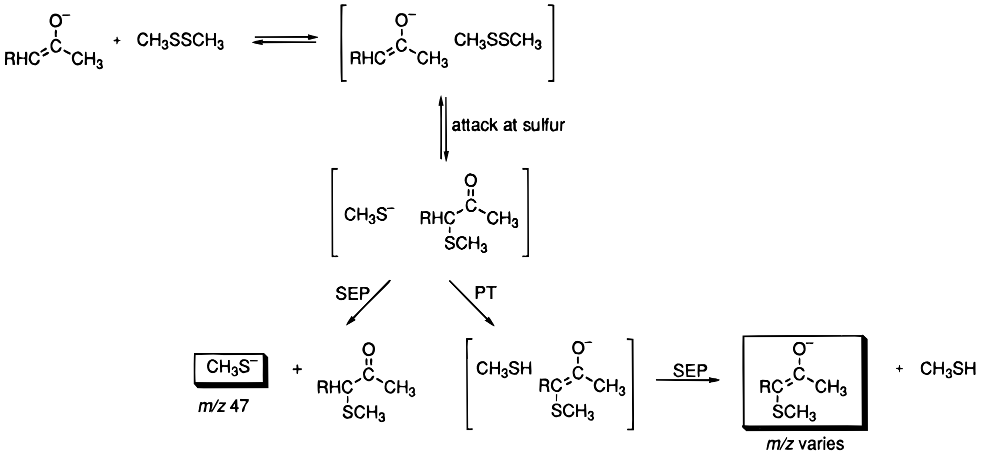
(29) Pearson, R. G. *Surv. Prog. Chem.* **1969**, *5*, 1−52.

(30) Caldwell, G.; Bartmess, J. E. *Org. Mass Spectrom.* **1982**, *17*, 456.

(31) Moran, S.; Ellison, G. B. *J. Phys. Chem.* **1988**, *92*, 1794−1803.

Scheme 5. Reaction Pathways by which Enolates React with Dimethyl Disulfide[a]



[a] The ultimate ionic products of the various competing channels are shown in heavy boxes for clarity. “SEP” refers to separation; “PT”, proton transfer.

ylated product. This uniqueness of reactivity for alkoxides versus enolates is also consistent over a range of larger alkoxides and enolates (Table 4). Second, the reactions of both alkoxides and enolates with dimethyl disulfide are efficient; furthermore, the efficiency stays quite high for larger anions (Eff (hexanal enolate) = 0.22)). Third, dimethyl disulfide is practical: commercially available in high purity, it can be used without further purification and is easily handled since it is a volatile liquid. The importance of the establishment of dimethyl disulfide as the chemical reagent of choice for alkoxide/enolate isomer discrimination is borne out by our use of it to successfully probe anionic oxy-Cope rearrangements which were heretofore believed to not proceed in the gas phase.[9,13]

Conclusions

Gas-phase mechanism elucidation is of particular importance in revealing intrinsic reactivity, free of solvent and counterion effects. Mechanistic studies by nature must rely on structure determination. Our initial interest in the elucidation of the gas-phase anionic oxy-Cope rearrangement led to the need for a general, selective process to discriminate between alkoxides and enolates. Toward this end, we examined chemical probes which would capitalize on the differences in structure and reactivity between alkoxides and enolates. The chemical probes characterized in our search for a general methodology were methanol-*O-d*, methyl nitrite, and dimethyl disulfide. In the course of our studies, we have found dimethyl disulfide to be the most reliable chemical probe reagent: not only is it easily obtained in a pure and readily handled form, but it reacts efficiently with both alkoxides and enolates, and its ambident nature leads to a mode of reactivity that generates a unique, distinctive product for alkoxides versus enolates. Such a general, reliable probe can be used not only for the model compounds described herein but for any alkoxide and for any enolate, whenever such differentiation is needed, whether for rearrangement studies or any other structural studies.[13] Methyl nitrite in concentrated form, as opposed to in situ generation, is useful when used in conjunction with a more reliable probe such as dimethyl disulfide.[13] Methanol-*O-d*, however, is not suitable for use as a structural probe reagent, and cannot be dependably used for alkoxide−enolate discrimination.[9]

Acknowledgment. We gratefully acknowledge support of this research through a grant farm the National Science Foundation. J.K.L. thanks the Department of Defense (National Defense Science and Engineering Graduate Fellowship in Chemistry P-28231-CH-NDF) for support and the Dow Chemical Co. for a fellowship administered by the Organic Division of the American Chemical Society.

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