Low-Temperature FAB Mass and NMR Spectroscopic Identification of Unstable Episulfoxides

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We report a method (low-temperature fast atom bombardment mass spectrometry, LT-FAB/MS) that greatly aids in characterizing intermediate 2-methyl-2-pentene episulfoxides (**1A** and **1B**, Scheme 1) that are too unstable to isolate. We have had the long-term goal of studying intermediates in the $^1O_2$-ene reaction.[1,2] Compounds **1A** and **1B** have structures analogous to the hypothetical perepoxide (**2**).[3] The stabilities of episulfoxides vary widely;[4] for example, isobutene episulfoxide (**3**) decomposes exothermically at room temperature,[5] while under similar conditions adamantylideneadamantane episulfoxide (**4**) is stable for several days (Scheme 1).[6] This difference probably arises from the position and availability of the "allylic" H's. Since **3** contains β-hydrogens syn to the S–O bond, the ene reaction (intramolecular H-abstraction) is facile. Since the β-hydrogens in **4** are not available for abstraction (Bredt's rule),[7] the ene reaction does not occur; instead, dissociation of SO occurs at elevated temperatures.[8]

In the present work, we focus on the isomeric episulfoxides **1A** and **1B**. Both are unstable above −50 °C but could be characterized using low-temperature (LT) FAB/MS and ^{13}C NMR. LT-FAB/MS has been reported only twice previously for the identification of unstable intermediates in organic chemistry: in 1993, an endoperoxide derived from reaction of a guanosine derivative with $^1O_2$ was detected at −78 °C,[9a] and in 1998, an oxaphosphetane from a Wittig reaction was detected at ca. −40 °C.[9b] Similar low-temperature methods have been used by Kosevich,[10a] Field,[10b] and Falick[11] to study questions related to mass spectrometry but not to detect unstable intermediates in organic chemistry.

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(1) Foote, C. S.; Clennan, E. L. *Active Oxygen in Chemistry*; Foote, C. S., Valentine, J. S., Greenberg, A., Liebman, J. F., Eds.; Chapman and Hall: Glasgow, 1995; pp 105–140 and references therein.
(2) Orfanopoulos, M.; Smonou, I.; Foote, C. S. *J. Am. Chem. Soc.* **1990**, *112*, 3607–3614.
(3) Manring, L. E.; Kanner, R. C.; Foote, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 4707–4710. Manring, L. E.; Foote, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 5, 4710–4717.
(4) Abu-Yousef, I. A.; Harpp, D. N. *Sulfur Rep.* **1997**, *20*, 1.
(5) Kondo, K.; Negishi, A. *Tetrahedron* **1971**, *27*, 4821–4830. Kondo, K.; Negishi, A.; Fukuyama, M. *Tetrahedron Lett.* **1969**, *29*, 2461–2464.
(6) Abu-Yousef, I. A.; Harpp, D. N. *J. Org. Chem.* **1997**, *62*, 8366–8371.
(7) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry,* 3rd ed.; Harper and Row: New York, 1987; p 8.
(8) Abu-Yousef, I. A.; Harpp, D. N. *Tetrahedron Lett.* **1995**, *36*, 201.
(9) (a) Sheu, C.; Foote, C. S. *J. Am. Chem. Soc.* **1993**, *115*, 10446–10447. (b) Wang, C.-H.; Huang, M.-W.; Lee, C.-Y.; Chei, H.-L.; Huang, J.-P.; Shiea, J. *J. Am. Soc. Mass Spectrom.* **1998**, *9*, 1168–1174.
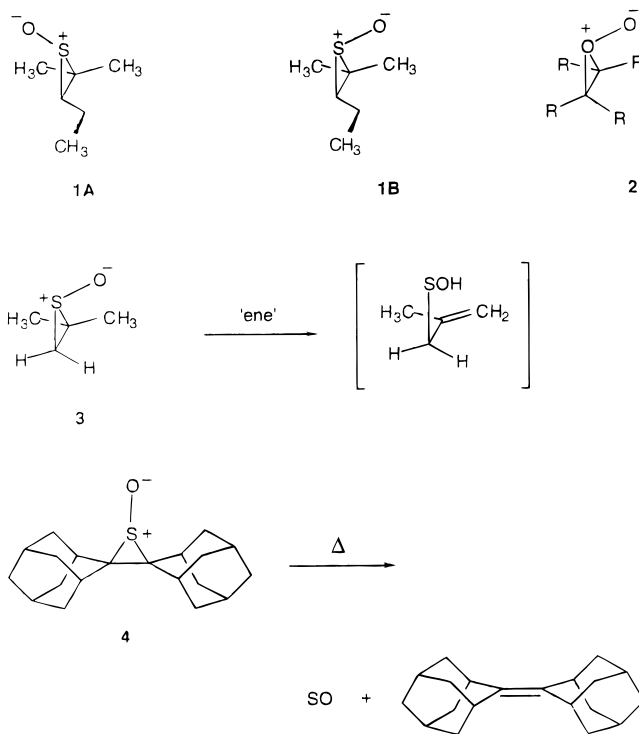(10) (a) Boryak, O. A.; Stepanov, I. O.; Kosevich, M. V.; Shelkovsky, V. S.; Orlov, V. V.; Blagoy, Y. P. *Eur. Mass Spectrom.* **1996**, *2*, 329–339. Boryak, O. A.; Oleg, A.; Kosevich, M. V.; Marina, V.; Shelkovsky, V. S.; Blagoy, Y. P. *Rapid Commun. Mass Spectrom.* **1996**, *10*, 197–199. (b) Katz, R. N. C.; Field, F. H. *J. Am. Chem. Soc.* **1986**, *108*, 3897–3903.
(11) Falick, A. M.; Walls, F. C.; Laine, R. A. *Anal. Biochem.* **1986**, *159*, 132–137.
(12) Takido, T.; Kobayashi, Y.; Itabashi, K. *Synthesis* **1986**, 779–780.
(13) Positive-ion FAB mass spectra were collected on a VG ZAB-SE reverse geometry, extended mass range, magnetic sector mass spectrometer. The xenon and cesium guns were operated at 8 kV (1 mA) and 22 kV (1–2 mA), respectively, accelerating voltage of 8 kV.

Scheme 1

2-Methyl-2-pentene episulfide (**5**), synthesized in 60% yield by the Takido method,[12] reacted with equimolar concentrations of dimethyldioxirane (DMD, 0.05 M) in acetone/CD_2Cl_2 at −78 °C to give a mixture of **1A** and **1B**. This mixture was characterized by LT-FAB/MS and ^{13}C NMR spectroscopy. Approximately 4 μL of glycerol matrix was placed on the tip of the stainless steel FAB probe. The probe tip was immersed in dry ice/acetone (−78 °C) for 2–3 min, and then 3 μL of the cold DMD-**5** reaction mixture was placed on the frozen matrix/probe and the unit was immediately loaded into the source chamber and bombarded with xenon atoms or cesium ions.[13] The low-resolution mass spectrum ($R = 500$, mass error = +0.11 amu) revealed peaks corresponding to the matrix (glycerol$_n$H$^+$, m/z observed 93.16 ($n = 1$), calcd 93.055; m/z obsd 185.21 ($n = 2$), calcd185.1025) and **1A**,**B** (m/z observed 133.00 [M + H]$^+$, calcd 133.0687) (Figure 1A). The high-resolution measurement ($R = 3000$, mass error = 3.7 ppm) was conducted with m-nitrobenzyl alcohol as the matrix, cesium as the bombarding ion, and leucine and glutamine as calibrants, with experimental conditions otherwise identical to those above. The spectrum revealed well-separated peaks corresponding to leucine (calcd [M + H]$^+$ 132.1025), cesium (m/z obsd 132.9039, calcd 132.9054), **1A**,**B** (m/z obsd 133.0692 [M + H]$^+$, calcd 133.0687), and glutamine (calcd [M + H]$^+$ 147.0770) (Figure 1B). This technique provides mass identification for **1A**,**B** but gives no information about structure or stereochemistry.
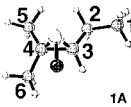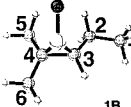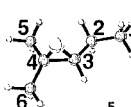
The following NMR experiments establish the structure and stereochemical assignments for **1A**,**B** and verify the FAB/MS results. In previous studies, ^1H NMR spectroscopy has been used to make stereochemical assignments for episulfoxides.[14] For example, for the oxidation of *trans*-butene episulfide to episulfoxide, methyl H's are assigned

(14) Kondo, K.; Negishi, A.; Ojima, I. *Tetrahedron Lett.* **1969**, *29*, 3173–3174.
(15) Glass, R. S.; Jung, W. *Sulfur Lett.* **1995**, *36*, 201.
(16) Rohling, C. M.; Allen, L. C.; Ditchfield, R. *Chem. Phys.* **1984**, *87*, 9.

Table 1. Experimental and GIAO-B3LYP Theoretical Isotropic ^{13}C Chemical Shifts

Compd	Carbon	Expt[c]	GIAO-DFT/dz[a,b]		
			in-conformer	*out*-conformer	weighted value[e]
1A	1	12.6	13.4	12.1	12.4
	2	18.8	21.9	20.7	21.0
	3	64.9	66.5	68.2	67.8
	4	*d*	57.6	57.0	57.1
	5	16.6	15.9	16.1	16.6
	6	18.1	16.5	16.8	16.7
1B	1	12.2	11.9	12.4	12.3
	2	13.1	17.1	13.6	14.1
	3	57.5	58.9	60.9	60.6
	4	*d*	54.5	54.7	54.7
	5	11.1	9.9	9.9	9.9
	6	22.9	23.3	22.6	22.7
5	1	13.5	12.9	12.8	12.8
	2	25.2	27.8	25.9	26.4
	3	52.5	53.2	55.8	55.2
	4	47.4	50.6	49.9	50.1
	5	22.8	21.2	22.2	22.0
	6	30.6	29.4	28.9	29.0

[a] Structures optimized at the B3LYP/6-31G* level. [b] δ^{13}C shifts calculated at the GIAO-B3LYP/6-31+G* level; referenced to TMS (absolute chemical shift, δ^{13}C=188.03). [c] Experimental values of 5 in CDCl$_3$ (25°C) and **1A,B** in acetone/CD$_2$Cl$_2$ (-78°C). [d] Obscured by the solvent. [e] Calculated for the weighted averages of the "in" and "out" conformers.
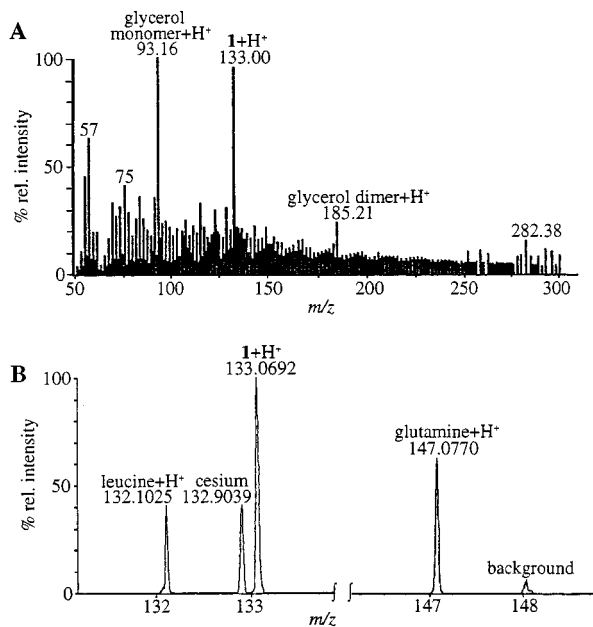

Figure 1. (A) Positive-ion LT-FAB (low-resolution) mass spectrum. (B) Positive-ion LT-FAB (high-resolution) mass spectrum.

as anti and syn to the S–O shift upfield (0.17 ppm) and downfield (0.20 ppm), respectively, relative to the episulfide.[14,15] A better way to establish the stereochemical assignments compares experimental (−78 °C) and computed ^{13}C NMR values. The experimental ^{13}C spectrum shows that the peak sizes of the isomers are different; thus, the anti- and syn-stereochemical assignments for **1A** and **1B** (7:3) are readily made by correlation with the computed gas phase ^{13}C NMR values using density function methods. Calculations performed at the GIAO-B3LYP/6-31+G* level[16] on B3LYP/6-31G*[17,18] optimized geometries of **1A,B** give relative δ^{13}C values in excellent agreement with the experimental values (Table 1).[19] The root mean square error between

experiment and theory is less than 2.6 ppm. Minima were located for "in" and "out" rotamers of **1A** and **1B** representing

rotational conformers around the C–C bond of −CH$_2$CH$_3$; however, calculated relative energies indicate that the out rotamers are more stable (by 0.4 kcal/mol for **1A** and 0.9 kcal/mol for **1B**).[20] Separate resonances for the rotamers are not observed in the −78 °C ^{13}C spectra, and the δ^{13}C$_{calc}$ values are weighted averages of the theoretical contributions of the two conformations.

The experimental and theoretical ^{13}C shift data are fully consistent with the structures of **1A,B** and confirm the LT-FAB/MS results. In summary, LT-FAB mass spectrometry is practical for the detection of **1A,B** despite their instability above −50 °C. We believe that the LT-FAB technique has promise as a general method for determining masses of unstable intermediates.

(17) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. Ziegler, T. *Chem. Rev.* **1991**, *91*, 651. Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989.

(18) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian-94*; Gaussian, Inc., Pittsburgh, PA, 1994.

(19) For comparison, the geometry of the B3LYP/6-31G*-optimized structure of ethylene episulfoxide is in fair agreement with the (experimental) values: S–O = 1.489 Å (1.483 Å); C–S = 1.862 Å (1.822 Å); >OSC = 112.6° (111.1°); >CSC = 47.1° (48.5°). Saito, S. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 663.

(20) "In" denotes syn geometry relative to the CC of the ring; "out" denotes anti geometry relative to the ring.