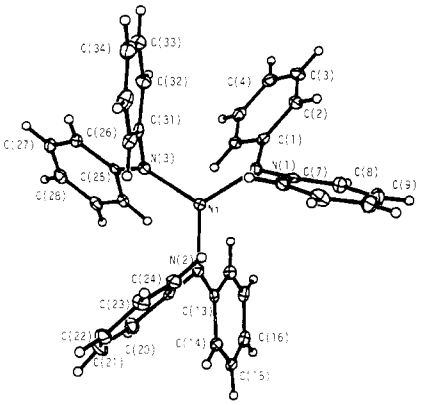

Figure 1. Computer-generated drawing of the anion $[Ni(NPh_2)_3]^-$. Important bond distances and angles: Ni-N(1), (2), (3) 1.889 (3), 1.895 (3), 1.877 (3) Å; N(1)NiN(2) 122.9 (1)°, N(1)NiN(3) 115.0 (1)°, N(2)NiN(3) 121.7 (1)°.

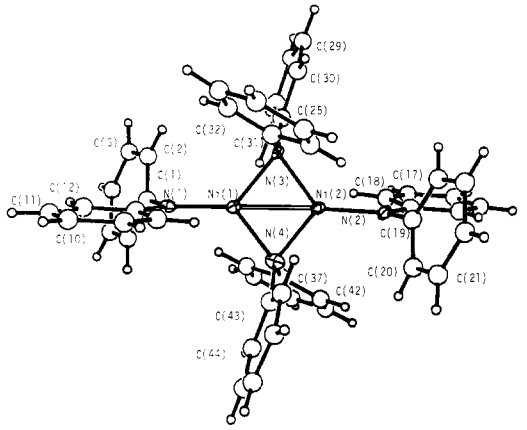

Figure 2. Computer-generated drawing of **2**; **4** has a similar structure but possesses an inversion center. Important bond distances and angles for $[\{M(NPh_2)_2\}_2]$: M = Ni{Co}; M···M 2.327 (2) {2.566 (3)} Å, M-N (terminal) 1.837 (9), 1.819 (8) {1.889 (8)} Å, M-N (bridging) 1.916 (9), 1.924 (8), 1.907 (9), 1.898 (9) {2.004 (7), 1.993 (8)} Å; NMN 104.3 (4)°, 105.7 (4)° {100.1 (3)°}; MNM 75.0 (3)°, 75.0 (3)° {79.9 (3)°}.

structure of **2** consists of dimers of the $Ni(NPh_2)_2$ unit with the diphenylamides behaving as both a bridging and a terminal ligand. The Ni-N (terminal) distances average 1.83 Å and are somewhat shorter than those in **1** possibly due to the lower negative charge density in **2**. The bridging Ni-N distances have the somewhat longer value of 1.91 (av) Å. The Ni-Ni distance of 2.327 (2) Å is extremely short and implies a significant Ni-Ni interaction. Short Ni-Ni distances have also been seen in a small number of other nickel complexes.[15-18] So far as we are aware **1** and **2** are the first reported structures of three-coordinate nickel(II).

The complexes **2** and **4** (Figure 2) are structurally similar to $[\{Co(N(SiMe_3)_2)_2\}_2]$.[7] The dimeric configurations of **2** and **4**, with bridging NPh_2 groups, are in sharp contrast to the published structure of $[\{Co(NPh_2)_2\}_2]$, which was reported to be associated through a Co-Co interaction without amido bridges.[3] The complex **4** has two cobalt atoms separated by 2.566 (3) Å. The average Co-N distances range from 1.89 (terminal) to 2.00 Å (bridging). The magnetic susceptibility of **4** at 298 K is 1.72 μ_B. It is interesting to note that while $[\{Co(N(SiMe_3)_2)_2\}_2]$ and $[\{Co(NPh_2)_2\}_2]$ have similar metal-metal distances they have different degrees of magnetic couplings.[3,7] The magnetic moment of $[\{Co(N(SiMe_3)_2)_2\}_2]$ at 296 K is 4.83 μ_B.[20]

Information on multiple metal-metal bonding in late transition metals is somewhat sparse. However, we hope that a series of formula $[\{M(NPh_2)_2\}_2]$, M = Mn-Ni, can be crystallized which will give magnetic and structural data to yield valuable information on the M-M interactions in the d^{5-9} metals. More comprehensive magnetic and spectroscopic studies on complexes **1** → **4** are under way.[21]

Acknowledgment. We thank the National Science Foundation, Research Corporation, and the Committee on Research of the University of California for financial support.

Supplementary Material Available: Tables of fractional coordinates, thermal parameters, bond distances and angles, and data collection and refinement summaries (15 pages). Ordering information is on any current masthead page.

(14) Covalent radii for four-coordinate Ni are 1.21 Å (Td) and 1.16 Å (Sq): Kilburn, B. T.; Powell, H. M. *J. Chem. Soc. A* **1970**, 1688. For *N*, values of 0.70-0.75 Å are commonly quoted.
(15) Jarchow, O. *Z. Kristallogr., Kristallgeom., Kristallphys., Kristallchem.* **1972**, *136*, 122.
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(19) Bradley, D. C.; Hursthouse, M. B.; Malik, K. M. A.; Möseler, R. *Transition Met. Chem. (Weinheim, Ger.)* **1978**, *3*, 253.
(20) Bradley, D. C.; Fisher, K. J. *J. Am. Chem. Soc.* **1971**, *93*, 2058.
(21) Andersen, R. A.; Berg, D.; Power, P. P., work in progress.

A New Class of Irreversible Inhibitors of Leukotriene Biosynthesis

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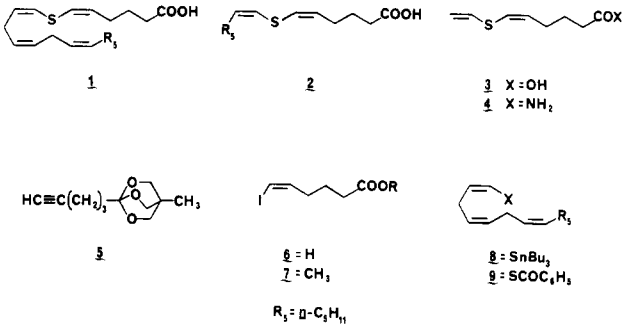
Effective inhibitors of leukotriene[1,2] biosynthesis are of interest for both the understanding and control of various inflammatory and allergic diseases.[3] Recent papers from this laboratory have described rationally devised inhibitors of the first step of leukotriene biosynthesis (a 5-lipoxygenase, 5-LO reaction) which are of competitive[4] and irreversible types.[5] Reported herein is a novel class of potent irreversible 5-LO inhibitors (**1**-**4**) whose activity also provides insight regarding the mechanism of the LO reaction.



The synthesis of 7-thiaarachidonic acid (**1**) was accomplished as follows. The OBO ester of 5-hexynoic acid[6] (**5**) was transformed into the *Z*-iodo olefin methyl ester **7** by the following sequence: (1) metalation with 1 equiv of *n*-butyllithium in tetrahydrofuran (THF) at -10 °C, cooling to -78 °C, and reaction with 1 equiv of iodine to form the iodo acetylene, mp 77-78 °C,

(1) Samuelsson, B. *Science (Washington, D.C.)* **1983**, *220*, 568.
(2) Corey, E. J. *Experientia* **1982**, *38*, 1259.
(3) Lewis, R. A.; Lee, C. W.; Krilis, S.; Corey, E. J.; Austen, K. F. In "Advances in Inflammation Research"; Raven Press: New York, 1984; Vol. 7, p 17.
(4) Corey, E. J.; Cashman, J. R.; Kantner, S. S.; Wright, S. W. *J. Am. Chem. Soc.* **1984**, *106*, 1503.
(5) Corey, E. J.; Lansbury, P. T., Jr.; Cashman, J. R.; Kantner, S. S. *J. Am. Chem. Soc.* **1984**, *106*, 1501 and references cited therein.
(6) (a) Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571. (b) Corey, E. J.; De, B. *J. Am. Chem. Soc.* **1984**, *106*, 2735.

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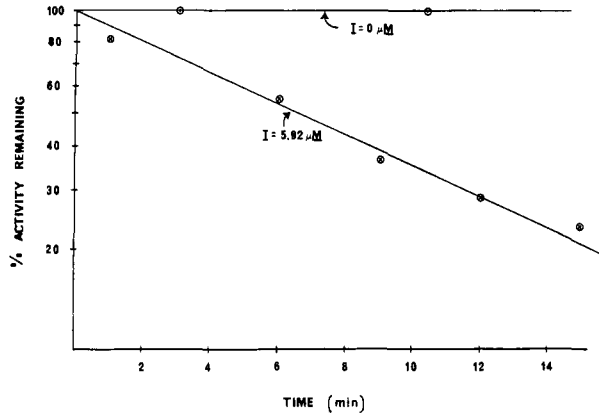


Figure 1. Inactivation of RBL-1 5-LO enzyme in air at 30 °C by 5.92 μM **1** and control (no **1**).

Table I. Irreversible Aerobic Inactivation of Arachidonate 5-Lipoxygenase from RBL-1 Cells

inhibitor	k_{inact}, min^{-1}	K_i, μM	concn range, μM
1	0.63[a]	14.2	2–5
2	0.50[a]	29.0	5–12
3	0.43[a]	6.0	17–82
4	0.39[a]	22.2	3–12
5,6-DHA	0.55[b]	370	60–140
5,6-DHA amide	2.40[b]	29	10–50

[a] At 30 °C. [b] At 22 °C.

(2) hydroboration of the iodoacetylene using 1.1 equiv of dicyclohexylborane in THF (1.5 h at 0 °C and 0.5 h at 23 °C) followed by addition of glacial acetic acid and heating at 65 °C for 3.5 h to replace boron by hydrogen, (3) treatment of this acetic acid solution with water (30 min, 23 °C), extractive isolation, and saponification with 1:1 1 N aqueous lithium hydroxide–dimethoxyethane to give after acidification and extraction the acid **6**, and (4) esterification of **6** by heating with methyl iodide and anhydrous potassium carbonate in acetone at 55 °C for 1 h to form **7**, which was purified by chromatography on silica gel (75% overall from **5**). The vinylstannane **8**[7] was transformed into the corresponding vinyllithium compound (1 equiv of *n*-butyllithium in THF at −78 °C for 10 min, −40 °C for 1.5 h), which was treated sequentially with 1.5 equiv of styrene sulfide[8] (−78 °C for 2.5 h) and benzoyl chloride (1.5 equiv, −78 °C for 0.5 h) to give after extractive isolation and chromatography on silica gel the thiobenzoate **9** (73%). Reaction of **9** at −78 °C in THF with 2.5 equiv of *n*-butyllithium for 1.5 h generated the corresponding (*Z*)-vinyl thiolate which was treated with cuprous iodide (2 equiv) to form the cuprous thiolate. To this thiolate reagent were then added the *Z*-iodo ester **7** and dimethylformamide and the mixture was heated to 100 °C for 2 h (THF was allowed to distill). Extractive isolation and chromatography on silica gel provided the methyl ester of 7-thiaarachidonic acid (83%), which was converted to **1** in >90% yield by saponification using 1:1 1 N lithium hydroxide–dimethoxyethane at 23 °C for 3.5 h, acidification, and extractive isolation.

The acid **2** was synthesized by the same methodology starting from (*Z*)-1-(tributylstannyl)-1-heptene.[7] The acid **3** was similarly synthesized starting from vinyllithium.[9]

When substances **1–4** were allowed to interact with the 5-lipoxygenase obtained from rat basophilic leukemic cells (RBL-1) at 30 °C the enzyme was irreversibly inactivated in a time-dependent manner in the presence of oxygen (air) but not in its absence. Control experiments showed that the 5-LO enzyme was completely stable in the presence of air at 30 °C in the absence of compounds **1–4** for time periods more than sufficient for

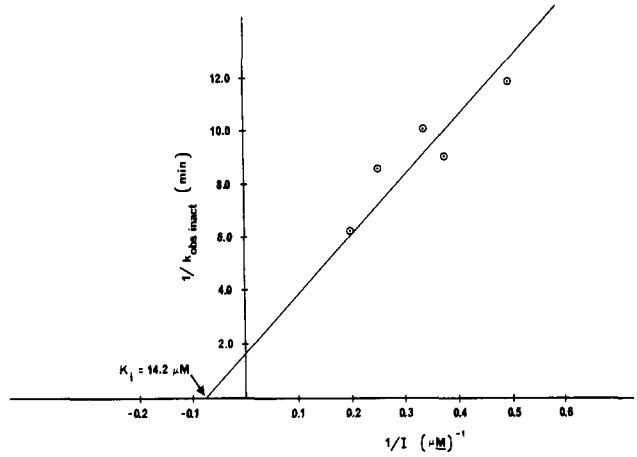


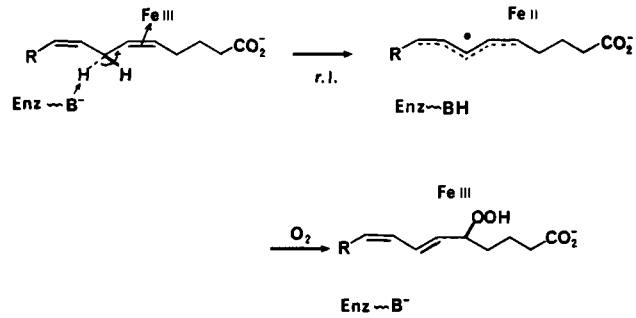
Figure 2. Double-reciprocal analysis of RBL-1 5-LO enzyme inactivation in air at 30 °C by 7-thiaarachidonate (**1**).

Table II. Inhibition of the Oxidation of Arachidonate by the 5-Lipoxygenase from RBL-1 Cells

inhibitor	K_m,[a] μM	K_m(app), μM	K_i,[e] μM
1 sulfoxide	10.0	62.5[b]	5.0
2 sulfoxide	9.9	12.5[c]	16.5
3 sulfoxide	9.9	17.9[d]	36.0

[a] K_m determined by Lineweaver–Burk analysis of the arachidonate → 5-HPETE conversion by RBL-1 5-LO in the absence of inhibitor. K_m(app) determined for the conversion of arachidonate to 5-HPETE in the presence of inhibitor: [b] 39 μM. [c] 23.4 μM. [d] 26.6 μM. [e] K_i determined by Dixon analysis using 6 μM arachidonate.

Scheme I

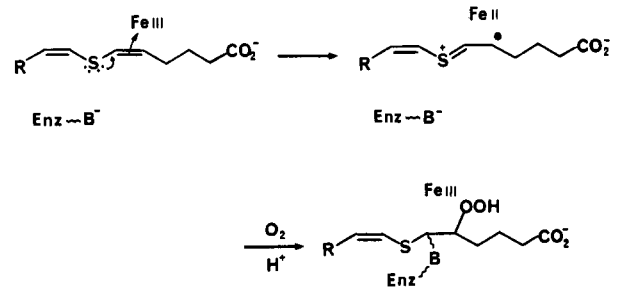


complete deactivation by **1–4**. The procedures for the preparation of the 5-LO enzyme and for measuring the rates of aerobic deactivation by **1–4** were the same as have been described previously.[5,10–12] Figure 1 shows the results of a typical run with 7-thiaarachidonate (**1**) and demonstrates pseudo-first-order kinetics for deactivation of the 5-LO enzyme. Figure 2 summarizes kinetic data for deactivation of the 5-LO enzyme at several different concentrations of **1** leading to a rate constant for deactivation of 0.6 min^{-1} at 30 °C; compounds **2–4** showed strictly comparable kinetic behavior. Table I summarizes the rate constants for irreversible inhibition of the 5-LO enzyme by **1–4** and also com-

(7) Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1984**, *25*, 2419.
(8) Guss, C. O.; Chamberlain, D. L. *J. Am. Chem. Soc.* **1952**, *74*, 1342.
(9) In this case the vinyl thiolate obtained from vinyllithium and styrene sulfide was treated directly with cuprous iodide and **7**.

(10) Corey, E. J.; Kantner, S S.; Lansbury, P. T., Jr. *Tetrahedron Lett.* **1983**, *24*, 265.
(11) Corey, E. J.; Shih, C.; Cashman, J. R. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 3851.
(12) For evaluation of time-dependent inhibition of RBL-1 5-LO enzyme by **1–4** a solution of the enzyme was preequilibrated with medium in air at 30 °C after which the inhibitor (**1**, **2**, **3**, or **4**) was added and the deactivation was allowed to proceed with gentle agitation in air for varying periods of time. At the appropriate time tritiated arachidonate was added (32 μCi/mmol, final concentration 100 μM) to the incubation vessel. After 7 min of incubation at 35 °C the 5-LO reaction was quenched with cold methanolic trimethyl phosphite, and the products were isolated by extraction and esterified with ethereal diazomethane. The products were separated by thin-layer chromatography on silica gel using 50:50:1:1 ether–hexane–acetic acid–methanol and the following bands (R_f) were scraped into scintillation vials for counting: 0.77, 0.37, and 0.15 (methyl esters of arachidonate, 5-HETE, and LTB_4, respectively).

Scheme II



parable data for the previously reported irreversible 5-LO inhibitors 5,6-dehydroarachidonate (5,6-DHA) and the corresponding amide (5,6-DHA amide). It is clear that the 7-thia compounds **1–4** are potent irreversible inactivators of the RBL-1 5-LO enzyme.

The effect of the sulfoxides of **1–3** on the arachidonate 5-LO enzyme was also investigated kinetically. These three substances were found to exhibit strictly competitive kinetics and to be purely reversible inhibitors (see Table II).[13]

7-Thiaarachidonate (**1**), **2**, and **3** were also examined as possible inhibitors of the prostaglandin synthetase (cyclooxygenase) enzyme[11] from ram seminal vesicles. In this system **1**, **2**, and **3** were found to be reversible, competitive inhibitors (K_i values 4.5, 6.0, and 61 μM, respectively[13] at 35 °C; K_m(arachidonate) = 10 μM).

We propose the following as a working hypothesis to accommodate the facts now available. Assuming that the catalytically active 5-LO enzyme possesses an Fe(III) unit, as seems to be the case for other LO enzymes that have been purified and studied in detail,[14] one reasonable mechanism for the 5-LO reaction is that shown in Scheme I. B^-, is an LO proton acceptor and Fe(III) is pentacoordinated to the LO with a vacant coordination site near the 5,6-double bond of the substrate. The rate-limiting step, which must involve C–H bond breaking,[5,15] is envisaged as concerted proton transfer to B^- and electron transfer to Fe(III) to generate an intermediate pentadienyl radical,[14a] which is then oxygenated. On the basis of this model the process shown in Scheme II could account for the destruction of 5-LO catalytic activity by **1–4**. Although **1–4** contain no abstractable proton, the high-electron-donating character of the divinyl sulfide unit could allow direct electron transfer to Fe(III) thereby activating **1–4** to react with oxygen even in the absence of abstractable hydrogen. Covalent coupling of enzyme and inhibitor, for example as shown in Scheme II, would lead to irreversible deactivation of the LO enzyme. The failure of the sulfoxides corresponding to **1–3** to cause irreversible 5-LO deactivation can be understood in terms of their relatively low-electron-donating power. The hydroxamate of **3** was found to be a competitive (K_i = 4.2 μM) rather than an irreversible inhibitor of the 5-LO, probably as a result of hydroxamate coordination with the Fe(III) site.[4] Scheme II predicts that 13-thiaarachidonate should irreversibly inhibit both the PG synthetase and the soybean 15-LO enzymes;[16] experiments in this area are under way.[17]

Supplementary Material Available: ^{1}H NMR, IR, UV, and mass spectral data for compounds **1–4**, **7**, and **9** (1 page). Ordering information is given on any current masthead page.

(13) K_i values were determined by Dixon analysis, see: Dixon, M. *Biochem. J.* **1953**, *55*, 170.

(14) (a) DeGroot, J. J. M. C.; Veldink, G. A.; Vliegenthart, J. F. G.; Boldingh, J.; Wever, R.; van Gelder, B. F. *Biochem. Biophys. Acta* **1975**, *377*, 71. (b) Slappendel, S.; Malmström, B. G.; Petersson, L.; Ehrenberg, A.; Veldink, G. A.; Vliegenthart, J. F. G. *Biochem. Biophys. Res. Commun.* **1982**, *108*, 673. (c) Greenwald, J. E.; Alexander, M. S.; Fertel, R. H.; Beach, C. A.; Wong, L. K.; Bianchine, J. R. *Ibid.* **1980**, *96*, 817.

(15) (a) Corey, E. J.; Lansbury, P. T., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 4093. (b) Vliegenthart, J. F. G.; Egmond, M. R.; Veldink, G. A.; Boldingh, J. *Biochem. Biophys. Res. Commun.* **1973**, *54*, 1178.

(16) See: Corey, E. J.; Park, H. *J. Am. Chem. Soc.* **1982**, *104*, 1750.

(17) This work was assisted financially by grants from the National Institutes of Health and the National Science Foundation. We are indebted to Drs. R. A. Lewis and K. F. Austen of the Harvard Medical School for supplies of RBL-1 cell extracts.

Distonic Radical Ions. Stepwise Elimination of Acetaldehyde from Ionized Benzyl Ethyl Ether

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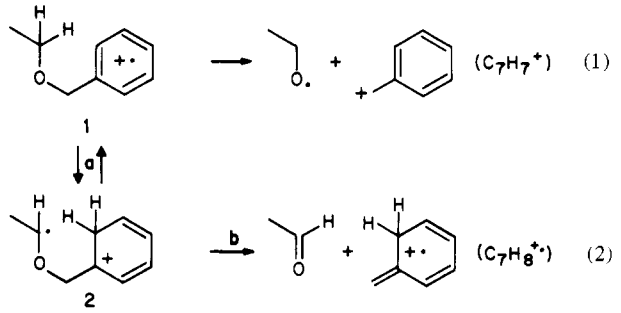
The mass spectral rearrangement via γ-hydrogen transfer to an unsaturated site[1] involves a stepwise mechanism (e.g., **1** → **2** → $C_7H_8^{+\cdot}$, eq 2) according to several theoretical[2] and experimental[3] studies. In sharp contrast, Bowie and co-workers[4] recently concluded that this rearrangement loss of CH_3CHO from ionized benzyl ethyl ether is instead concerted,[5] on the basis of their observation of significant isotope effects for both the C–H bond broken in step a (eq 2) and the C–O bond broken in step b. This conclusion is of special interest in light of recent arguments that multibond breaking (and/or making) reactions cannot normally be synchronous.[6,7] Here we present multiple evidence that $C_7H_8^{+\cdot}$ formation from **1** (eq 2) indeed proceeds by a stepwise mechanism involving the distonic radical ion[8,9] **2** as a stable intermediate.



Distonic radical ions have their charge and radical sites separated;[8] they are often more stable than their conventional isomers with the charge and radical at a common site. Thermochemical calculations show that the benzyl ethyl ether ion **1** is ~1 kcal mol^{-1} *less* stable than the distonic radical ion **2**.[10,12,14] On the other

(1) McLafferty, F. W. *Anal. Chem.* **1956**, *28*, 306; **1959**, *31*, 82. Kingston, D. G. I.; Bursey, J. T.; Bursey, M. M. *Chem. Rev.* **1974**, *74*, 215.

(2) Boer, F. P.; Shannon, T. W.; McLafferty, F. W. *J. Am. Chem. Soc.* **1968**, *90*, 7239.

(3) (a) Smith, J. S.; McLafferty, F. W. *Org. Mass Spectrom.* **1971**, *5*, 483. (b) Wesdemiotis, C.; Schwarz, H.; Borchers, F.; Heimbach, H.; Levsen, K. *Z. Naturforsch.* **1978**, *33B*, 1150. (c) McAdoo, D. J.; McLafferty, F. W.; Hudson, C. E.; Parks, T. E. *Org. Mass Spectrom.* **1984**, *19*, 353.

(4) Stone, D. J. M.; Bowie, J. H.; Underwood, D. J.; Donchi, K. F.; Allison, C. E.; Derrick, P. J. *J. Am. Chem. Soc.* **1983**, *105*, 1688.

(5) Both substituent effects and the structure of the product ion show that the hydrogen does not transfer to the α-carbon.[4]

(6) Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 209.

(7) For other unimolecular ion decompositions involving stepwise mechanisms, see: (a) Tumas, W.; Foster, R. F.; Pellerite, M. J.; Brauman, J. I. *J. Am. Chem. Soc.* **1983**, *105*, 7464. (b) Mandelbaum, A. *Mass Spectrom. Rev.* **1983**, *2*, 223. Turecek, F.; Hanus, V. *Ibid.* **1984**, *3*, 85.

(8) Yates, B. F.; Bouma, W. J.; Radom, L. *J. Am. Chem. Soc.* **1984**, *106*, 5805.

(9) Wesdemiotis, C.; Danis, P. O.; Feng, R.; Tso, J.; McLafferty, F. W. *J. Am. Chem. Soc.*, submitted for publication.

(10) Assuming that benzyl ethyl ether and benzyl methyl ether have the same ionization energies (**I**),[11a] $\Delta H_f°(\mathbf{1}) = \Delta H_f°(C_6H_5CH_2OCH_2CH_3)^{11b} + I = -27 + 210 = 183$ kcal mol^{-1}.

(11) (a) Shudo, K.; Kobayashi, T.; Utsunomiya, C. *Tetrahedron* **1977**, *33*, 1721. (b) Benson, S. W. "Thermochemical Kinetics"; Wiley-Interscience: New York, 1976.

(12) $\Delta H_f°$ (**2**) can be estimated from the sequence $CH_3CH_2OCH_2C_6H_5 \rightarrow CH_3{\cdot}CHOCH_2C_6H_5 \rightarrow CH_2{\cdot}CHOCH_2C_6H_6^+$ (**2**). Using the C–H bond dissociation energy of $CH_3CH_2OCH(CH_3)$–H (90 kcal mol^{-1})[13a] as D(R–H), $\Delta H_f°(CH_3{\cdot}CHOCH_2C_6H_5) = \Delta H_f°(CH_3CH_2OCH_2C_6H_5) + D$(R–H) – $\Delta H_f°(H{\cdot})^{13b} = -27 + 90 - 52 = 11$ kcal mol^{-1}. Using the proton affinity of toluene[13c,d] for that of $CH_3{\cdot}CHOCH_2C_6H_5$, $\Delta H_f°(\mathbf{2}) = \Delta H_f°(CH_3{\cdot}CHOCH_2C_6H_5) + \Delta H_f°(H^+)^{13b} - PA = 11 + 366 - 195 = 182$ kcal mol^{-1}.

(13) (a) Burrows, H. D.; Formosinho, S. J. *J. Chem. Soc., Faraday Trans. 2* **1977**, *73*, 201. (b) Rosenstock, H. M.; Draxl, K. Steiner, B. W.; Herron, J. T. *J. Phys. Chem. Ref. Data* **1977**, *6*, Suppl. 1. (c) Hehre, W. J.; McIver, R. T., Jr.; Pople, J.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1974**, *96*, 7162. (d) Taft, R. W. In "Proton Transfer Reactions"; Caldin, E., Gold, V., Eds.; Chapman and Hall: London, 1975.

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