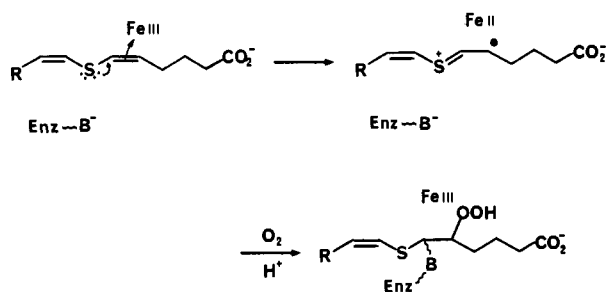


Scheme II



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) enzyme¹¹ 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 , respectively¹³ at 35 °C; $K_m(\text{arachidonate}) = 10 \mu\text{M}$).

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 ($K_i = 4.2 \mu\text{M}$) 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: ¹H 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.

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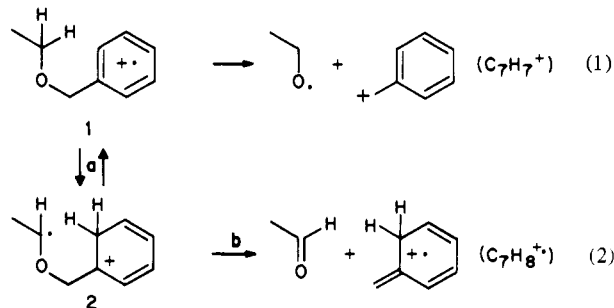
Distonic Radical Ions. Stepwise Elimination of Acetaldehyde from Ionized Benzyl Ethyl Ether

Chrysostomos Wesdemiotis, Rong Feng, and Fred W. McLafferty*

Chemistry Department, Cornell University
Ithaca, New York 14853

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The mass spectral rearrangement via γ -hydrogen transfer to an unsaturated site¹ involves a stepwise mechanism (e.g., **1** \rightarrow **2** \rightarrow C_7H_7^+ , eq 2) according to several theoretical² and experi-



mental³ studies. In sharp contrast, Bowie and co-workers⁴ 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^+ 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 $\sim 1 \text{ kcal mol}^{-1}$ less stable than the distonic radical ion **2**.^{10,12,14} On the other

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(10) Assuming that benzyl ethyl ether and benzyl methyl ether have the same ionization energies (I),^{11a} $\Delta H_f^\circ(\mathbf{1}) = \Delta H_f^\circ(\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2\text{CH}_3)^{11b} + I = -27 + 210 = 183 \text{ kcal mol}^{-1}$.

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(12) $\Delta H_f^\circ(\mathbf{2})$ can be estimated from the sequence $\text{CH}_3\text{CH}_2\text{OCH}_2\text{C}_6\text{H}_5 \rightarrow \text{CH}_3\text{CHOCH}_2\text{C}_6\text{H}_5 \rightarrow \text{CH}_3\text{CHOCH}_2\text{C}_6\text{H}_5^+$ (**2**). Using the C-H bond dissociation energy of $\text{CH}_3\text{CH}_2\text{OCH}(\text{CH}_3)\text{-H}$ (90 kcal mol⁻¹)^{13a} as $D(\text{R-H})$, $\Delta H_f^\circ(\text{CH}_3\text{CHOCH}_2\text{C}_6\text{H}_5) = \Delta H_f^\circ(\text{CH}_3\text{CH}_2\text{OCH}_2\text{C}_6\text{H}_5) + D(\text{R-H}) - \Delta H_f^\circ(\text{H})^{13b} = -27 + 90 - 52 = 11 \text{ kcal mol}^{-1}$. Using the proton affinity of toluene^{13c,d} for that of $\text{CH}_3\text{CHOCH}_2\text{C}_6\text{H}_5$, $\Delta H_f^\circ(\mathbf{2}) = \Delta H_f^\circ(\text{CH}_3\text{CHOCH}_2\text{C}_6\text{H}_5) + \Delta H_f^\circ(\text{H}^+)^{13b} - \text{PA} = 11 + 366 - 195 = 182 \text{ kcal mol}^{-1}$.

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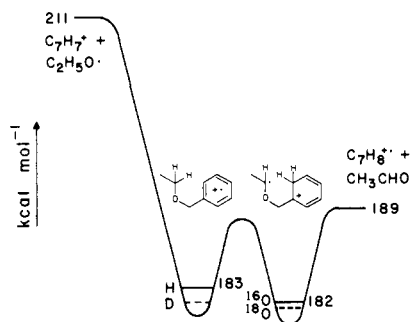


Figure 1. Potential energy diagram for acetaldehyde loss from benzyl ethyl-1,1- d_2 ether.

hand, this is not true for the closely similar $\text{CH}_3(\text{CH}_2)_3\text{C}_6\text{H}_5^+$ (3), which is more stable than its distonic isomer $\text{CH}_3\text{CHCH}_2\text{CH}_2\text{C}_6\text{H}_6^+$ (4) by $\sim 12 \text{ kcal mol}^{-1}$.¹⁵ Despite this, the formation of C_7H_8^+ from 3 apparently proceeds through a stepwise mechanism.^{3b}

Ion isomerizations such as $1 \rightarrow 2$ and $3 \rightarrow 4$ can be studied by comparing mass spectra from 70-eV electron ionization (EI)¹⁷ and spectra from collisionally activated dissociation¹⁸ (CAD). EI spectra show ion dissociations occurring in $\ll 1 \mu\text{s}$, while CAD spectra represent dissociations induced in ions that have had a much longer time (25 μs for the 10-keV ions used here)¹⁹ to isomerize. C_7H_7^+ (eq 1) and C_7H_8^+ (eq 2) represent the major fragment ions in both the EI and CAD spectra of benzyl ethyl ether and *n*-butylbenzene;²¹ isomerization of 1 to 2, or of 3 to 4, should increase the formation of C_7H_8^+ relative to C_7H_7^+ . Consistent with the greater stability of 3 vs. 4 for *n*-butylbenzene this time delay makes little difference, with $[\text{C}_7\text{H}_8^+]/[\text{C}_7\text{H}_7^+] = 0.6$ for EI and 0.8 for CAD. However, for benzyl ethyl ether the similar EI value of 0.8 increases to 6 for CAD, indicating that a substantial proportion of the 1 ions have isomerized to 2 before undergoing CAD. The $[\text{C}_7\text{H}_8^+]/[\text{C}_7\text{H}_7^+]$ value of this CAD spectrum is reduced to 4 by reducing the ionizing electron energy to 15 eV, apparently lowering the proportion of 1 ions formed with sufficient energy to isomerize to 2 in 25 μs .

In further support of the intermediacy of 2, the spontaneous dissociation of metastable benzyl ethyl-1,1- d_2 ether ions of $\sim 25\text{-}\mu\text{s}$ lifetime yields $[(\text{M} - \text{C}_2\text{H}_4\text{O})^+]/[(\text{M} - \text{C}_2\text{H}_3\text{DO})^+] = 2.4\%$ (10% for 2-keV ions, lifetime $\sim 60 \mu\text{s}$). Also for these data a stepwise exchange involving the reversible isomerization $1 \rightleftharpoons 2$ (eq 3) appears to be the only logical explanation.

Finally, the unusual isotope effects of Bowie et al.⁴ could also be consistent with a stepwise mechanism. If (Figure 1) the transition-state energy for $1 \rightarrow 2$ is slightly less than that for 2

(14) We calculate $1 \rightarrow \text{C}_7\text{H}_8^+$ (eq 2) to be 6 kcal mol⁻¹ endothermic overall; $\Delta H_f^\circ(\text{CH}_3\text{CHO}) = -40 \text{ kcal mol}^{-1}$ ^{11b} and $\Delta H_f^\circ(\text{C}_7\text{H}_8^+) = 229 \text{ kcal mol}^{-1}$ (Burgers, P.C.; Terlouw, J. K.; Levens, K. *Org. Mass Spectrom.* 1982, 17, 295).

(15) $\Delta H_f^\circ(3) = 197 \text{ kcal mol}^{-1}$.¹⁶ $\Delta H_f^\circ(\text{CH}_3\text{CHCH}_2\text{CH}_2\text{C}_6\text{H}_5) = \Delta H_f^\circ(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5)$ ¹⁶ + $D(\text{R}-\text{H}) - \Delta H_f^\circ(\text{H})$ ^{13b} = $-3 + 95 - 52 = 40 \text{ kcal mol}^{-1}$, if $D(\text{R}-\text{H})$ is the same as for $(\text{CH}_3)_2\text{CH}-\text{H}$.^{11b} $\Delta H_f^\circ(4) = \Delta H_f^\circ(\text{CH}_3\text{CHCH}_2\text{CH}_2\text{C}_6\text{H}_5) + \Delta H_f^\circ(\text{H}^+)$ ^{13b} - $\text{PA} = 40 + 366 - 197 = 209 \text{ kcal mol}^{-1}$, assuming that the proton affinities of $\text{CH}_3\text{CHCH}_2\text{CH}_2\text{C}_6\text{H}_5$ and *n*-butylbenzene are the same.^{13cd} The formation of C_7H_8^+ from 3 is endothermic by 37 kcal mol⁻¹: $\Delta H_f^\circ(\text{C}_7\text{H}_8^+) + \Delta H_f^\circ(\text{CH}_3\text{CH}=\text{CH}_2)$ ^{11b} - $\Delta H_f^\circ(3)$ ¹⁶ = $229 + 5 - 197 = 37 \text{ kcal mol}^{-1}$.

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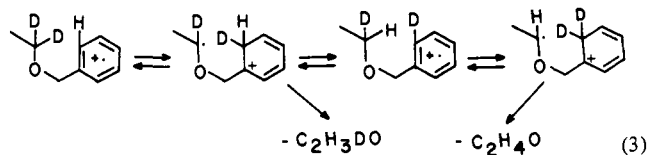
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(21) For both 1 and 3 the formation of C_7H_7^+ (eq 1) requires more energy than formation of C_7H_8^+ (eq 2).



\rightarrow products (the latter reaction should have the looser transition state), both reactions should be subject to an isotope effect.²²

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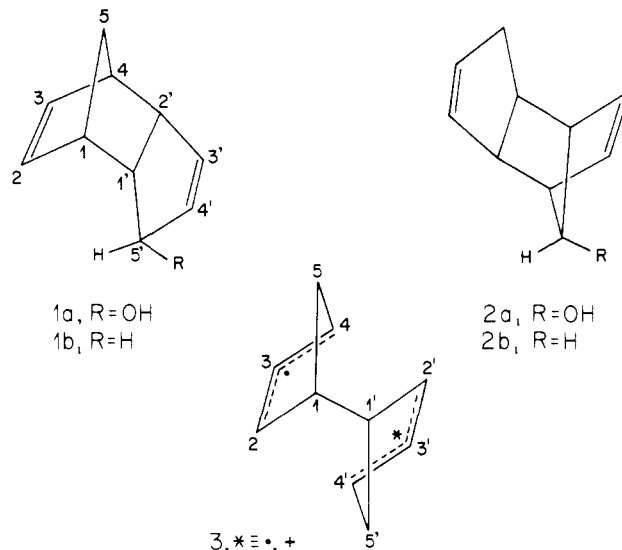
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Radical Cation of Dicyclopentadiene. Evidence for a Singly Bridged Structure

Heinz D. Roth* and Marcia L. M. Schilling

AT&T Bell Laboratories
Murray Hill, New Jersey 07974
Received October 2, 1984

Twenty-five years ago, Woodward and Katz reported the remarkable rearrangement of α -1-hydroxydicyclopentadiene (1a) to *syn*-8-hydroxydicyclopentadiene (2a) which occurs with com-



plete stereochemical selectivity and with complete retention of optical integrity.¹ These observations were interpreted as "evidence which shows with special clarity that the thermal dissociation of dicyclopentadiene derivatives takes place in two discrete and experimentally separable stages".¹ This interpretation implies the involvement of a doubly allylic species, 3, or of its mechanistic equivalent as an intermediate or transition state. In the paper presented here, we discuss evidence for a radical cation of the general structure type, 3, discussed by Woodward and Katz.

We studied the reaction of photoexcited chloranil with *endo*-dicyclopentadiene (1b) and observed strong nuclear spin polarization effects for the hydrocarbon. As in many other systems,²⁻⁴

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