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Cyclopropylcarbinyl-Type Ring Openings. Reconciling the Chemistry of Neutral Radicals and Radical Anions

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Abstract: Cyclopropylcarbinyl → homoallyl and related rearrangements of radical ions (a) are frequently used as mechanistic "probes" to detect the occurrence of single electron transfer in chemical and biochemical processes, (b) provide the basis for mechanism-based drug design, and (c) are important tools in organic synthesis. Unfortunately, these rearrangements are poorly understood, especially with respect to the effect of substrate structure on reactivity. Frequently, researchers assume that the same factors which govern the reactivity of neutral free radicals also pertain to radical ions. The results reported herein demonstrate that in some cases structure−reactivity trends in radical ion rearrangements are very different from neutral radicals. For radical ions, delocalizations of *both* charge and spin are important factors governing their reactivity.

Introduction

A rigorous understanding of the mechanism and kinetics associated with the unimolecular rearrangements of neutral free radicals has been achieved in the past two decades. Rate constants and, more significantly, activation parameters have become available for rearrangements of many types of neutral radicals. As such, these processes have proven enormously valuable as probes for radical intermediates (i.e., with appropriately designed substrates, the detection of rearranged products signals intermediacy of free radicals) and as radical clocks (i.e., the unimolecular rearrangement is used as a molecular level "stopwatch" to time competing, bimolecular processes of the radical).[1] An understanding of this chemistry has led to well-established synthetic methods based upon neutral radical rearrangements.

There have been numerous studies dealing with bond cleavage in radical ions. The most common and perhaps best understood examples of these are dissociative processes,[2] in which two fragments, a neutral radical and an ion are generated from the parent radical ion (e.g., for a radical anion, $A-B^{\bullet -} \rightarrow A^{\bullet} + B^{-}$ or $A^{-} + B^{\bullet}$).[3−11] There are fewer examples of bond cleavage in radical ions which can be classified as *rearrangements*, i.e., bond breaking leads to a single species, a distonic radical ion (in which the charge and spin reside on the same species).[12−28]

Compared to neutral free radicals, our understanding of the mechanism and kinetics associated with rearrangements of radical ions, and consequently, their use as mechanistic probes or clocks, is in the dark ages. Sometimes the "rearrangement" of a radical ion is more complex than a simple, first-order process (e.g., ring opening radical cations generated from cyclopropyl arenes).[29] In most cases, only a meager amount of

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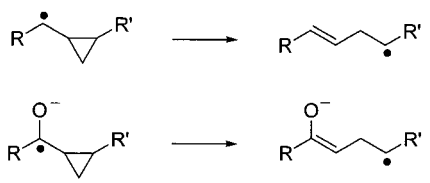
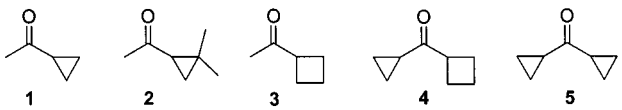


Figure 1. Ring opening of neutral radicals vs radical anions.

kinetic information is available, yet such rearrangements are critically important for both mechanistic and synthetic purposes. Rearrangements of radical anions derived from single electron reduction of ketones (e.g., using reagents such as SmI_2) have proven extremely useful synthetic methods.[30] Radical ion rearrangements are often used to diagnose single electron transfer and the intermediacy of paramagnetic species in numerous chemical processes. (For example, the most compelling arguments that the enzyme monoamine oxidase B processes substrates via a single electron-transfer pathway are based upon the chemistry of a rearrangeable radical cation probe, benzyl cyclopropylamine.[31])

Our studies have focused on the mechanism and kinetics of *rearrangements* of radical anions derived from cyclopropyl ketones. These species undergo a ring opening process directly analogous to the cyclopropylcarbinyl → homoallyl neutral free radical rearrangement (Figure 1), leading to a distonic radical anion. In terms of substituent effects, both systems (Figure 1) behave similarly: (1) Radical-stabilizing groups at the α-carbon (R) decelerate the ring-opening process and (2) radical-stabilizing substituents (e.g., alkyl, phenyl, and vinyl) on the cyclopropyl group (R′) accelerate the reaction, leading to the more substituted (and more stable) radical/radical ion. For both types of process, relief of cyclopropyl ring strain is not the sole mitigating factor associated with the rate of these rearrangements; resonance energy (spin delocalization) in the ring-closed vs ring-opened forms must also be considered.[32−35]

In a recent Communication,[36] we reported that as important as spin delocalization is in determining the rate of radical ion rearrangements, charge delocalization is at least as (and likely a more) important a factor. In our present paper, we test critical assumptions which led to this conclusion, and expand the discussion of structure/reactivity trends in radical anion rearrangements. Experimentally, radical anions generated from aliphatic ketones **1**−**5** were studied by using direct (cyclic voltammetry and preparative electrolysis) and indirect (homogeneous redox catalysis) electrochemical techniques. The results of these experiments were augmented with molecular orbital calculations.



1 **2** **3** **4** **5**

Experimental Section

Materials. *N*,*N*-Dimethylformamide (DMF, EM Science, 98%) was stirred over copper(II) sulfate (Aldrich, 98%) and activated alumina (Aldrich, neutral, Brockman activity I) for >3 days and vacuum distilled immediately before use. Alumina was flame dried under vacuum (until evolution of water vapor ceased) prior to use. 1-Methyl-2-pyrrolidinone (NMP) was vacuum distilled and stored over molecular sieves. Dimethyl sulfoxide (DMSO) was stirred over CaH_2 for several days and vacuum distilled just prior to use. Tetra-*n*-butylammonium perchlorate (TBAP) was prepared by the method of House[37] and recrystallized 4× from ethyl acetate/hexane and vacuum oven dried before use. 1-Acetyl-2,2-dimethyl cyclopropane[38,39] and cyclobutyl cyclopropyl ketone[40] were prepared according to published synthesis. The following compounds were obtained from Aldrich and used as received: Cyclopropyl methyl ketone, cyclobutyl methyl ketone, and dicyclopropyl ketone. All mediators used in this study except fluoranthene (Agros Organics, >98%) and anthracene (Matheson, Coleman & Bell, >98%) were obtained from Aldrich and used as received.

General. GC/MS was performed on a Hewlett-Packard HP 5890 gas chromatograph interfaced to a HP 5970 low-resolution mass spectrometer and a HP series computer. High-resolution mass spectral data were obtained from a VG Analytical model 7070 E-HF double-focusing magnetic sector high-resolution spectrometer with use of electron impact (70 eV) ionization. GC analysis was performed on a Hewlett-Packard 5890A gas chromatograph equipped with an FID detector and an HP 3393A reporting integrator.

Electrochemistry. Electrochemical measurements were performed on an EG&G Princeton Applied Research (EG&G/PAR) model 273 potentiostat/galvanostat interfaced to an MS-DOS computer. The details of this system were described earlier.[33] Voltammetric measurements were performed on solutions which contained 0.5 M tetra-*n*-butylammonium perchlorate (TBAP) in DMF. Solutions were prepared by weighing out 1.71 g of TBAP into a 10 mL volumetric flask. The 10 mL flask along with all other voltammetric cell pieces (with the exception of the working electrode) were treated in a Baxter DP-22 vacuum-drying oven (30−40 mmHg) at 40° C for 1.5 h. Voltammetric cell pieces were then placed immediately in a desiccator to cool. The voltammetric cell was assembled under argon/nitrogen flow. The 10 mL flask containing electrolyte was diluted with purified DMF and added to the voltammetric cell. The completed cell assembly was argon (dry, deoxygenated) purged for approximately 15 min prior to use. The electroactive substance was added to the cell only after clean backgrounds were obtained at each sweep rate used (a maximum cell current <10 uA at υ = 100 mV/s over the potential range −2.7 to −3.2 V was considered acceptable).

A three-electrode voltammetry cell was used. The GCE working electrode (5 mm diameter) was prepared for use by polishing with an alumina slurry to a mirror finish and stored in a desiccator. The Ag/Ag^+ (0.1 M in CH_3CN, 0.337 V vs SCE) reference electrode was freshly prepared. A Pt wire coil was used as the auxiliary electrode. Mechanical stirring was performed between voltammetric runs to clean the working electrode surface. Positive-feedback *iR* compensation was set by monitoring the current response. IR compensation was increased until oscillation and then backed off to 90% of that value. All experiments were performed at ambient temperature.

The GCE working electrodes were prepared as follows. A glassy carbon rod (Alfa Aesar) was cut into several 4−5 mm plugs. Carbon plugs were secured into glass rods with Torrseal−Varian vacuum epoxy resin (Varian vacuum products) being careful not to get epoxy on the reverse of the carbon plug where the electrical connection must be made. Rods were left to cure in air for 2 days. A small amount of silver 2-part

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Scheme 1

$$A + e^- \rightleftharpoons A^{\bullet -} \quad (k_s)$$

$$A^{\bullet -} \longrightarrow B^{\bullet -} \quad (k_o)$$

conductive adhesive (Alfa Aesar) was placed into the glass rods and a short piece of Cu brazing rod was inserted and allowed to cure for 2 days. The electrode surface was polished with alumina slurry (Buehler) starting with 1.0 um grit and decreasing to 0.3 and finally 0.05 um until a mirror finish was obtained. The surface was maintained by polishing routinely with 0.05 um grit polish, rinsing with methanol and water, and wiping lightly.

Preparative electrolyses were performed on solutions which contained 0.2 M TBAP in DMF. Solution preparation and cell handling were performed similarly to that for voltammetry. A conventional H-cell with two compartments separated by a medium glass frit was utilized. Fifty milliliters of electrolyte solution was divided equally between the two compartments of the vacuum oven dried H-cell, and the resulting system was purged with dry, deoxygenated argon for >15 min before use. The electroactive substrate was placed in the working compartment exclusively and electrolysis was conducted as specified in the specific experiments. For constant potential experiments, *iR* compensation was set as in voltammetric experiments. A gold foil working electrode was utilized. All electrolysis experiments were performed at ambient temperature. Reaction progress was monitored by GC where necessary. Solution workup consisted of quenching the cathodic compartment with ca. 1 mL of 5% H_2SO_4, adding ca. 50 mL of water, and extracting with 4 × 50 mL of ether. Ether layers were combined, washed with water and saturated NaCl, dried over $MgSO_4$, and concentrated. Products of bulk electrolysis were all known compounds. Yields were determined by GC vs an appropriate internal standard.

Molecular Orbital Calculations. MO calculations were performed by using the density functional (B3LYP)[41,42] and/or the Hartree−Fock theory[43] as implemented through Titan (Wave function Inc., Irvine, CA, and Schrödinger Inc., Portland, OR). Geometry optimizations were performed with the 6-31+G*[44,45] basis set; single point calculations were subsequently performed at the 6-311+G*[44,45] level to obtain the pertinent energies and charge/spin densities. Vibrational frequencies were calculated to verify that transition states were successfully located.

Electrochemical Simulations. Digital simulations of cyclic voltammograms were performed with Digisim 2.1 (Bioanalytical Systems Inc., 2701 Kent Ave. W. Lafayette, IN 47906) and working curves were generated from simulated responses with use of TableCurve 2D (Jandel Scientific Software: 2591 Kerner Blvd., San Rafael, CA 94901).

Results

Cyclic and Linear Sweep Voltammetry. Direct electrochemical techniques such as cyclic and linear sweep voltammetry (CV and LSV, respectively) are incredible tools for studying the chemistry of radical ions.[46,47] As applied to this study, a cyclopropyl ketone (**A**, Scheme 1) is reduced at an electrode surface generating its radical anion $\mathbf{A}^{\bullet -}$; k_S is the heterogeneous rate constant for this step. This radical anion undergoes subsequent ring opening yielding $\mathbf{B}^{\bullet -}$ with the rate constant k_o. Either of these steps may be rate limiting, depending on the structure of the substrate.

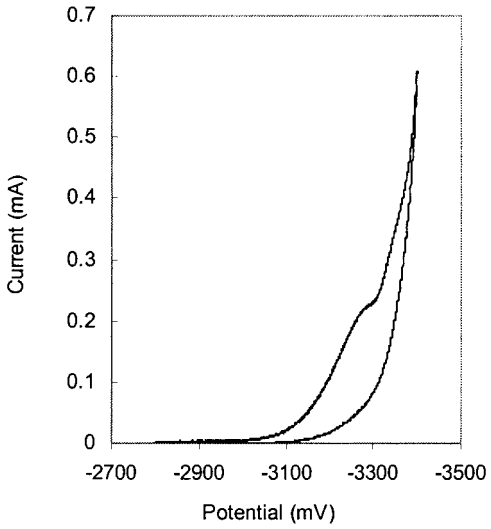

Figure 2. Cyclic voltammogram of methyl cyclopropyl ketone (**1**, ν = 100 mV/s, 0.003 M).

These techniques typically examine the effect of sweeprate and substrate concentration on the electrochemical response. When the chemical step is rate limiting, it is possible to obtain information such as the formal reduction potential of the substrate, the rate law for the chemical step (usually first order in these systems), and the rate constant k_o. When heterogeneous electron transfer is rate limiting, it is possible to measure k_S and the transfer coefficient α.[46,47]

Very quickly, it became obvious that cyclic and linear sweep voltammetry are not effective tools for studying the radical anions generated from **1**−**5**. This point was graphically illustrated by examining the cyclic voltammogram of cyclopropyl methyl ketone (Figure 2). The small wave attributable to the reduction of substrate was superimposed on a large background current attributable to solvent/electrolyte decomposition. Only at low concentrations and slow sweep rates was it possible to generate the small voltammetric response shown. As concentration or sweep rate increased, the peak potential was quickly shifted into the background response. Because of these complications, a thorough linear sweep voltammetry study (i.e., examining peak potential as a function of sweeprate and substrate concentration) was not feasible.

Crudely, the broadness of the peak ($E_{p/2} - E_p$ ~106 mV, where E_p and $E_{p/2}$ are the peak- and half-peak potentials, respectively) suggests that the homogeneous electron-transfer step (k_S) is rate limiting. On this basis, the transfer coefficient (α) can be estimated according to eq 1 ,[47] yielding $\alpha \approx 0.45$.

$$\alpha = \frac{RT}{F}\frac{1.85}{E_{p/2} - E_p} \qquad (1)$$

The transfer coefficient is a measure of transition state location. For systems in which electron transfer and bond-breaking occur, α can be used as a diagnostic tool to determine whether these two processes occur in a manner that is stepwise or concerted (i.e., dissociated electron transfer).[2] The observed value of α near 0.5 is supportive of a stepwise pathway, suggesting that $\mathbf{A}^{\bullet -}$ exists as a discrete intermediate.

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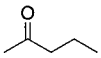
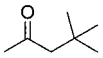
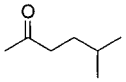
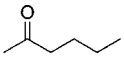
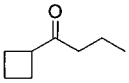
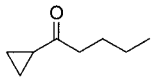
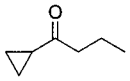
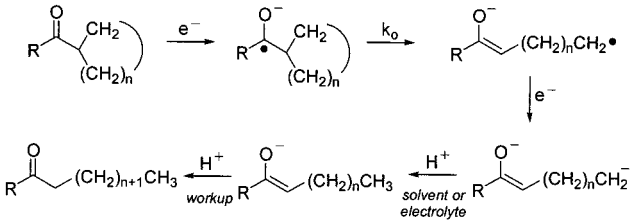
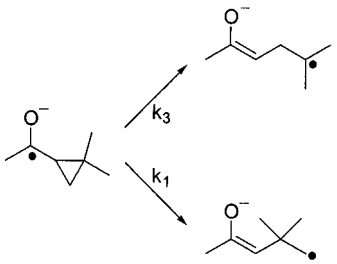
Table 1. Products Arising from the Electrochemical Reduction of **1** → **5**

Substrate	Conditions	Results
1	mediated (biphenyl)	 (34%), addition products (4%), unreacted **1** (60%)
2	direct (constant current, several runs)	 (3%),  (7 - 8%), recovered **2** (80 - 90%)
3	mediated (biphenyl)	 (24%), addition products (3%), recovered **3** (83%)
4	mediated (biphenyl)	 (19%),  (not detected), recovered **4** (71%)
5	direct (constant current)	 (28%), recovered **5** (52%)

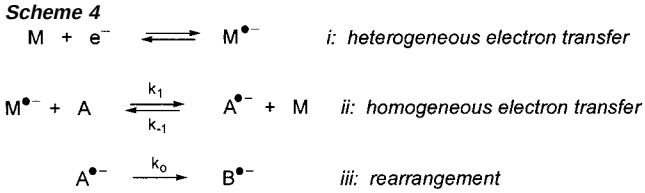
Scheme 2



Scheme 3



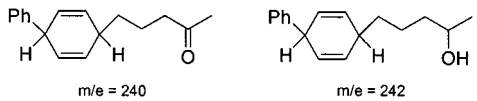
Scheme 4



Preparative-Scale Electrolyses/Product Analysis. In all cases, preparative-scale electrolyses of **1**−**5** gave ring-opened products (Table 1), consistent with the ECE mechanism depicted in Scheme 2. Depending on the specific substrate, the electrolyses were conducted either directly at a gold electrode or indirectly with biphenyl as an electron-transfer mediator.

In the mediated approach, byproducts resulting from addition of the ring-opened, distonic radical anions to the radical anion of the mediator may result (e.g., $R^{\bullet -} + M^{\bullet -} \rightarrow R-M^{-2}$). For example, in the mediated reduction of primary alkyl halides (which produce primary radicals via $R-X + e^- \rightarrow R^{\bullet} + X^-$), only 5% of the reaction with biphenyl radical anion involves addition.[48] Hence, for substrates expected to produce a 1° distonic radical anion (e.g., **1**, **3**, **4**, and **5**), biphenyl is used as an electron-transfer mediator with the expectation that products arising from addition to the mediator would be minor.

Accordingly, for **1**, after passage of 1 equiv of electrons in the presence of biphenyl and acidification, 2-pentanone was obtained in 34% yield, with 60% unreacted starting material. A tiny quantity of addition products was detected by ^{1}H NMR and GC/MS but they were not individually isolated. ^{1}H NMR indicates a substituted biphenyl and a cleaved cyclopropane ring. Although potential structures such as these are suggested, no effort was made to discern the regiochemistry.



In contrast to 1° radicals, addition is more competitive with electron transfer in the reaction of 3° radicals with biphenyl radical anion; 70% of the reaction of ^{t}Bu$^{\bullet}$ + Ph−Ph$^{\bullet -}$ involves addition.[48] Because the radical anion generated from 1-acyl-2,2-dimethylcyclopropane (**2**$^{\bullet -}$) can open either to the primary (k_1) or tertiary (k_3) distonic radical anions shown in Scheme 3, the reduction of **2** is carried out directly (in the absence of a mediator) to avoid the formation of addition products. On the basis of the observed regiochemistry of the products (Table 1), ring opening occurs with only slight preference for the more-substituted (stable) distonic radical anion ($k_3/k_1 \cong 2.5$).

Indirect Electrochemistry. Homogeneous redox catalysis is a powerful technique for studying the chemistry of highly reactive intermediates produced via electron transfer.[49−53] Consider the reactions depicted in Scheme 4. Rather than substrate **A**, an electron-transfer mediator or catalyst **M** is reduced at the electrode surface. For this to occur, the mediator must be more easily reduced than the substrate, (i.e., $E^{\circ}_{A/A^{\bullet -}} < E^{\circ}_{M/M^{\bullet -}}$). Reduction of the substrate occurs in solution (homogeneous) via electron transfer from the reduced form of the mediator (**M**$^{\bullet -}$).

(48) Andrieux, C. P.; Gallardo, I.; Savéant, J.-M.; Su, K.-B. *J. Am. Chem. Soc.* **1986**, *108*, 638−647.
(49) Andrieux, C. P.; Hapiot, P.; Savéant, J.-M. *Chem. Rev.* **1990**, *90*, 723−738.
(50) Andrieux, C. P.; Blocman, C.; Dumas-Bouchiat, J. M.; M'Halla, F.; Savéant, J. M. *J. Electroanal. Chem.* **1980**, *113*, 19−40.
(51) Savéant, J. M.; Su, K. B. *J. Electroanal. Chem.* **1985**, *196*, 1−22.
(52) Andrieux, C. P.; Savéant, J.-M. *J. Electroanal. Chem.* **1986**, *205*, 43−59.
(53) Nadjo, L.; Savéant, J. M.; Su, K. B. *J. Electroanal. Chem.* **1985**, *196*, 23−34.

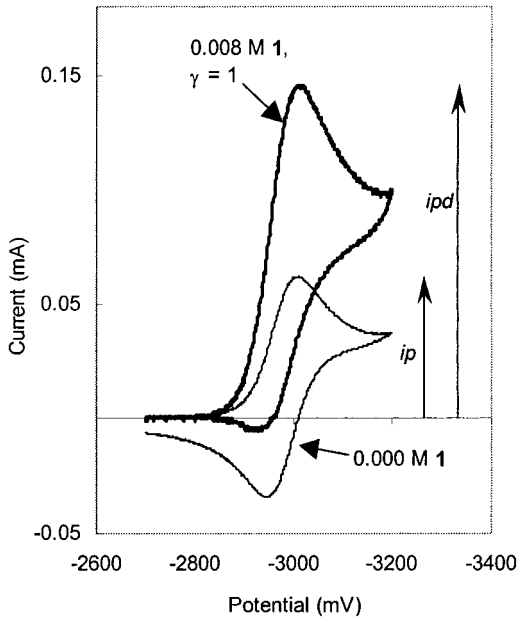


Figure 3. Cyclic voltamogram of biphenyl in the absence and presence of methyl cyclopropyl ketone (**1**, $\nu = 100$ mV/s).

In this manner, the reference is taken away from the electrode and placed on the reversible 1e$^-$ reduction of a compound with a known $E°$. Effects of substrate addition on this reversible electron transfer are manifested experimentally by an increase in peak current and a loss of reversibility (if catalysis is occurring). The key experimental observable is the current ratio i_p/i_{pd}, where i_p and i_{pd} are the voltammetric peak currents of the mediator in the presence and absence of the substrate, respectively, at a particular value of γ (the ratio of the substrate to mediator concentrations, $C°_A/C°_M$). Figure 3 depicts the effect of added cyclopropyl methyl ketone (**1**) on the cyclic voltammogram of biphenyl.

Savéant et al. introduce the dimensionless rate constants λ_1, λ_{-1}, and λ_0 defined below (eqs 2−4, where ν is the sweep rate in V s^{-1} and R, T, and F are the ideal gas constant, temperature, and Faraday's constant, respectively). Published working curves are available which depict the current ratio i_p/i_{pd} (a) as a function of $\log(\lambda_1)$ when the electron-transfer step (k_1) is rate limiting or (b) as a function of $\log(\lambda_0\lambda_1/\lambda_{-1})$ when the chemical step (k_0) is rate limiting.[50]

$$\lambda_1 = \frac{k_1 C°_M}{\nu}\frac{RT}{F} \quad (2)$$

$$\lambda_{-1} = \frac{k_{-1} C°_M}{\nu}\frac{RT}{F} \quad (3)$$

$$\lambda_0 = \frac{k_0}{\nu}\frac{RT}{F} \quad (4)$$

As noted above, kinetic control may be governed by either the homogeneous electron-transfer step (k_1) or the chemical step (k_0, Scheme 4). If the rate of the chemical step is faster than back electron transfer ($k_0 > k_{-1}$ [M]), then the electron-transfer step is rate limiting and k_1 can be determined. If the chemical step is slow relative to back electron transfer ($k_0 < k_{-1}$ [M]), the chemical step is rate limiting with the electron-transfer step as a rapid preequilibrium. Under these conditions the composite rate constant k_0k_1/k_{-1} can be determined. Because $\log(K_1) = -F(E°_{M/M^{\bullet-}} - E°_{A/A^{\bullet-}})/(2.303RT)$, k_0 can be extracted if the reduction potential of the substrate is known.

Though similar in appearance, different working curves pertain to these two conditions, and it is critical to accurately assess whether the kinetics are governed by the electron transfer or chemical step. For rate-limiting electron transfer, the current ratio is a function of γ and λ_1, the latter of which is related to the mediator concentration (eq 2). For the rate-limiting chemical step, i_p/i_{pd} is a function of γ and $\lambda_0\lambda_1/\lambda_{-1}$, and is *concentration independent* at constant γ (eqs 2−4). Thus, the distinguishing characteristic between these two rate-limiting conditions is the effect of mediator concentration ($C°_M$) on i_p/i_{pd} at constant γ and ν. The peak current ratio varies as a function of mediator concentration only when the electron-transfer step is rate limiting.[50]

The reduction of **1**−**5** by several mediators was studied. Because of the limited quantity of these substrates available, it was more economical to examine the current ratio i_p/i_{pd} as a function of sweep rate and mediator concentration at constant excess factor γ (published working curves present i_p/i_{pd} as a function of γ at constant sweeprate). As revealed in eqs 2−4, at constant γ, *i_p/i_{pd} is a function of $\log(C°_M/\nu)$ (when electron transfer is rate limiting) or i_p/i_{pd} is a function of $\log(1/\nu)$ when the chemical step is rate limiting*. Our approach was to obtain the voltammograms of several mediators in the absence and presence of **1**−**5**. By comparing plots of [i_p/i_{pd} vs $\log(1/\nu)$] and [i_p/i_{pd} vs $\log(C°_M/\nu)$] obtained at different concentrations of mediator (γ constant), any concentration dependence was readily apparent.

For **1** (using naphthalene as a mediator), the plot of i_p/i_{pd} vs $\log(1/\nu)$ (Figure 4a) at various substrate concentrations ($\gamma = 1.00$) appears as three discrete lines. When substrate concentration is factored out (i.e., a plot of i_p/i_{pd} vs $\log(C°_M/\nu)$), the data converge onto a single curve (Figure 4b) clearly showing i_p/i_{pd} is concentration dependent, and thus establishing that electron transfer is rate limiting. For **1**, **2**, **4**, and **5**, over the range of mediators examined, i_p/i_{pd} is found to vary as a function of mediator concentration (at constant γ), indicating that electron transfer is rate limiting for all these substrates with all mediators. (All the pertinent plots are available in the Supporting Information.)

The kinetics of these systems are further complicated by a competing bimolecular reaction between $\mathbf{M}^{\bullet-}$ and the ring-opened product $\mathbf{B}^{\bullet-}$ (i.e., addition, vide infra). Coupling reactions between alkyl radicals and aromatic anion radicals are known to be fast and nearly diffusion-controlled. This competition (Scheme 5) between addition to the mediator (k_{add}) and the second electron reduction (k_{et}) must be considered in the overall reaction profile and introduces a new kinetic parameter ρ, where $\rho = k_{et}/(k_{add} + k_{et})$. The parameter ρ reflects the fraction of $\mathbf{B}^{\bullet-}$ which adds to the mediator. A treatment of this problem and the appropriate theoretical working curves have been published by Savéant.[51]

As noted, published working curves dealing with addition to the catalyst expressed i_p/i_{pd} as a function of γ.[51] In these experiments, because i_p/i_{pd} was measured at various sweep rates at constant γ, it was necessary to derive the appropriate working curves (42 plots of i_p/i_{pd} vs $\log(\lambda_1)$ at $\gamma = 1.00$ and $\gamma = 10$ for

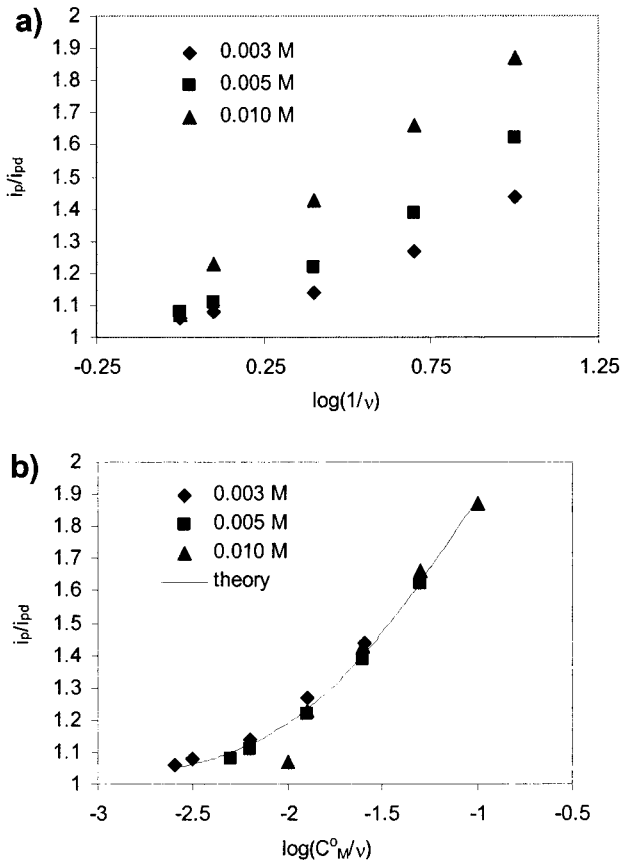
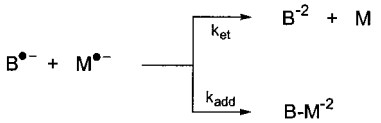


Figure 4. Mediated reduction of methyl cyclopropyl ketone (**1**) by naphthalene ($\nu = 0.1-1.0$ V s^{-1}, $\gamma = 1.00$).

Scheme 5



$\rho = 0.00$ to 1.00 in 0.05 increments) via digital simulation. These working curves were subsequently fit to a polynomial of the form $y = (a + cx + ex^2 + gx^3 + ix^4)/(1 + bx + dx^2 + fx^3 + hx^4 + jx^5)$, where the coefficients $a-j$ were determined for each working curve. Via nonlinear regression, the experimental data [i_p/i_{pd} vs log(C^o_M/ν)] were fit to the polynomial form of the working curves, $y = f(x + x')$, and the adjustable parameter $x' = \log(k_1RT/F)$ was determined. The parameter ρ was determined by the working curve that gave the best fit to the experimental data, and k_1 was determined from x'. A representative fit of the experimental data is provided in Figure 4b.

For **1**, **2**, **4**, and **5**, derived values of k_1 and ρ for the mediators studied are summarized in Table 2. Kinetically, the fact that electron transfer is rate-limiting for these four substrates means $k_0 > k_{-1}$[**M**]. A lower limit on the rate constant k_0 can be established by estimating the quantity k_2[**M**]. The lowest concentration of mediator used in these experiments is 0.001 M; assuming the reverse electron-transfer rate constant k_{-1} is approximately diffusion-controlled, k_0 is estimated to be greater than 10^7 s^{-1} (k_{-1} [M] = (10^{10} M^{-1} s^{-1})(0.001 M) = 10^7 M^{-1} s^{-1}).

The indirect reduction of cyclobutyl methyl ketone (**3**) was examined with naphthalene and biphenyl as mediators. As described above, the current ratio i_p/i_{pd} was examined as a function of sweep rate and mediator concentration at constant excess factor, $\gamma = 1$.

A plot of [i_p/i_{pd} vs log($1/\upsilon$)] and [i_p/i_{pd} vs log(C^o_M/υ)] for the reduction of **3** by naphthalene radical anion is presented in Figure 5, parts a and b. Comparing these two, it is apparent that there is no concentration effect on the peak current ratio, and that the kinetics are governed by the chemical step (ring opening) rather than electron transfer.

The composite rate constant ($k_{obs} = K_1k_0$) was determined from theoretical working curves. Though similar in appearance, different working curves pertained to the two limiting conditions. Again, it was necessary to derive the appropriate working curves as described earlier. A representative fit of the experimental data is provided in Figure 5a.

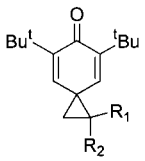
Discussion

Estimates of the Reduction Potentials of 1, 2, 4, and 5 with Marcus Theory. In accordance with Marcus theory, the relationship between k_1 and the free energy of electron transfer ($\Delta G^\circ = F(E_{M/M^{\bullet-}} - E_{A/A^{\bullet-}})$) is described by eq 5 .[54] For this

$$\frac{1}{k_1} = \frac{1}{k_d} + \frac{1}{K_dZ\exp\left(\frac{-\lambda}{4RT}(1 + \Delta G^\circ/\lambda)^2\right)} + \frac{1}{k_d\exp(-\Delta G^\circ/RT)} \quad (5)$$

analysis, it is assumed $k_d = 1 \times 10^{10}$ M^{-1} s^{-1} (the diffusion-controlled rate constant in DMF), $K_d = 0.16$ M^{-1}, and the frequency factor $Z = 6 \times 10^{11}$ s^{-1}. The rate constants in Table 2 are fit to eq 5 via nonlinear regression analysis, with $E^o_{A/B}$ and λ as the only adjustable parameters. An excellent fit is achieved in all cases (pertinent plots are included in the Supporting Information). The results are summarized in Table 3.

Values derived for the reorganization energy (λ) of these compounds are consistent with an electron-transfer reaction from an aromatic hydrocarbon to an aliphatic ketone, suggesting that there is not an additional contributor (such as bond lengthening or bond angle deformation) to the overall reorganization energy. The λ values summarized in Table 3 are somewhat higher than those which we observed previously for the reduction of **6**−**8** by similar aromatic hydrocarbons ($\lambda \approx 15-20$ kcal/mol) and merit further comment.



6: $R_1 = R_2 = H$ ($E^o = -2.599$ V)
7: $R_1 = H$, $R_2 = CH_3$ ($E^o = -2.588$ V)
8: $R_1 = R_2 = CH_3$ ($E^o = -2.557$ V)

Eberson has summarized the structural and environmental effects on λ.[54] Spiro compounds **6**−**8** are highly conjugated substrates, and the charge gained in producing the radical anion can be accommodated over a large volume. This results in little reorganization energy to reach the transition state. In the aliphatic cyclopropyl substrates, charge is more highly localized in the radical anion than the neutral ketones, and a higher solvent reorganization energy would be required.

Structural effects on the Reduction Potential of Aliphatic Ketones. Within experimental error, the reduction potentials

(54) Eberson, L. *Electron-transfer reactions in organic chemistry*; Springer-Verlag: Berlin, 1987; Vol. 25.

Table 2. Rate Constants for Homogeneous Electron Transfer (k_1) Between the Reduced Form of the Mediator ($M^{\bullet-}$) and Cyclopropyl Ketones **1**, **2**, **4**, and **5**

		1		**2**		**4**		**5**	
mediator	$E°$ (V)[a]	k_1 ($M^{-1}s^{-1}$)[b]	ρ^c	k_1 ($M^{-1}s^{-1}$)[b]	ρ^c	k_1 ($M^{-1}s^{-1}$)[b]	ρ^c	k_1 ($M^{-1}s^{-1}$)b	ρ^c
naphthalene	−2.901	$4.2(2) \times 10^2$	0.60	$5.9(2) \times 10^2$	0.45	$1.3(1) \times 10^3$	.70	$4.0(1) \times 10^2$	0.75
3,6-dimethylphenanthrene	−2.937	$1.3(1) \times 10^3$	1.00	$8.1(6) \times 10^2$	0.90	$4.2(4) \times 10^3$	1.00	$1.5(2) \times 10^3$	1.00
1,3-dimethylnaphthalene	−2.971	$3.5(2) \times 10^3$	0.95	$2.2(1) \times 10^3$	0.55	$7.4(9) \times 10^3$	1.00	$2.4(1) \times 10^3$	1.00
biphenyl	−2.977	$2.1(1) \times 10^3$	0.95	$2.4(2) \times 10^3$	0.65	$6.5(2) \times 10^3$	0.95	$2.6(2) \times 10^3$	1.00
1-methoxynaphthalene	−2.988	$5.2(2) \times 10^3$	1.00	$2.8(2) \times 10^3$	0.80	$1.5(1) \times 10^4$	1.00	$5.2(4) \times 10^3$	1.00
2,7-dimethoxynaphthalene	−3.027	$9.6(3) \times 10^3$	1.00	$8.0(3) \times 10^3$	0.30			$6.7(5) \times 10^3$	1.00
o-methoxybiphenyl	−3.086	$3.4(1) \times 10^4$	0.95	$3.6(1) \times 10^4$	0.50				

[a] vs 0.1 M $AgNO_3$/Ag. [b] Numeral in parentheses is the error in the last digit. [c] (± 0.05) for all ρ.

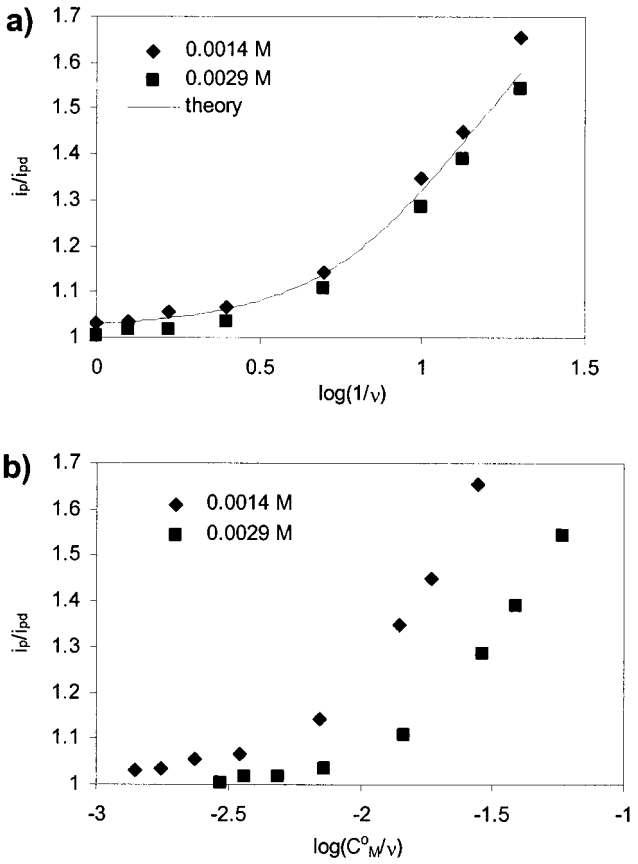


Figure 5. Mediated reduction of cyclobutyl methyl ketone (**3**) by naphthalene (DMF, GCE, 0.5 M TBAP, $\nu = 0.05-1.0$ V s^{-1}, $\gamma = 1.00$).

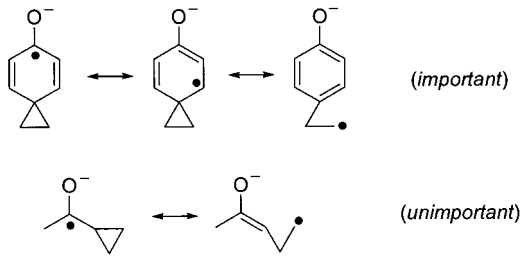
Table 3. Reduction Potentials and Reorganization Energies for **1**, **2**, **4**, and **5** Derived from Marcus Theory

compd	$E°$ (V)[a]	λ (kcal/mol)
1	−3.215 (±0.068)	28 ± 4
2	−3.196 (±0.067)	30 ± 4
4	−3.205 (±0.106)	26 ± 6
5	−3.188 (±0.145)	31 ± 7

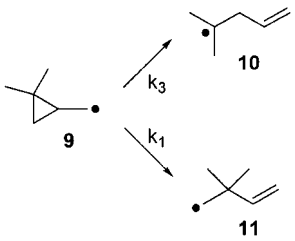
of aliphatic ketones **1**, **2**, **4**, and **5** are identical. Consistent with this conclusion is the fact that rate constants for electron transfer between these substrates and $M^{\bullet-}$ are also nearly identical (Table 2). These results suggest that (a) alkyl substituents on the cyclopropyl group do not perturb $E°$ and (b) that the difference in $E°$ between methyl-, cyclopropyl-, and cyclobutyl-substituted aliphatic ketones is (within experimental error) undetectable.

This conclusion offers an interesting comparison to the substituent effect on the reduction potential of spirocyclohexadienones **6**−**8**, where it was observed that increased methyl substitution on the cyclopropyl group slightly stabilizes the radical anion.[35] For the spirocyclohexadienones, the substituent effect is readily explained on the basis of an aromatic resonance form, which is expected to be an important contributor to the resonance hybrid. For radical anions generated from aliphatic cyclopropyl ketones, the contribution of the nonbonded resonance form is apparently minor (Scheme 6).

Scheme 6



Scheme 7



Rate Constants for Ring Opening of Radical Anions Derived from Aliphatic Cyclopropyl and Cyclobutyl Ketones. The rate-limiting step in the electron transfer-mediated reduction of cyclopropyl ketones **1**, **2**, **4**, and **5** is the electron-transfer step (k_1). These observations permit us to assign a lower limit to the rate constant for ring opening of radical anions derived from aliphatic cyclopropyl ketones (k_0) of 10^7 s^{-1} (vide supra). There is good reason to suspect that ring opening may be considerably faster than the cyclopropylcarbinyl *neutral* radical.

For $\mathbf{2}^{\bullet-}$, ring opening occurs with only slight preference for the more-substituted (stable) distonic radical anion (Scheme 3). On the basis of the yield of products observed in the preparative-scale electrolysis, $k_3/k_1 \cong 2.5$. (Dauben and Wolf obtained similar results ($k_3/k_1 \cong 3.1$) in 1970 with Li/NH_3 as the reducing agent.[38]) For comparison, the dimethyl-substituted neutral radical **9** leads to 3° and 1° radicals **10** and **11** in a 6.7:1 ratio (Scheme 7).[55] The low selectivity of both these processes suggests an early transition state for ring opening. The extremely low selectivity observed for ring opening of $\mathbf{2}^{\bullet-}$ compared to neutral

(55) Beckwith, A. L. J.; Bowry, V. W. *J. Org. Chem.* **1989**, *54*, 2681−2688.

Table 4. Composite Rate Constant for Ring Opening of Cyclobutyl Methyl Ketone

mediator (M)	$E^{o}_{M/M^{\bullet-}}$ (V)[a]	ρ[b]	k_{obs} (s^{-1})	k_0 (s^{-1})[c]
naphthalene	−2.901	0.50	$2.1(\pm0.1) \times 10^{-1}$	$2.5(\pm1.4) \times 10^{4}$
biphenyl	−2.977	0.90	$4.0\ (\pm\ 0.2) \times 10^{0}$	$2.5(\pm1.4) \times 10^{4}$

[a] vs 0.1 M $AgNO_3$/Ag. [b] ±0.05. [c] Calculated assuming $E^{o}_{3/3^{\bullet-}} = -3.201 \pm 0.012$ V vs 0.1 M $AgNO_3$/Ag.

radical **9** suggests the former may be more reactive. If this reactivity/selectivity argument is valid, the rate constant for ring opening of these radical anions is expected to be of similar magnitude, perhaps even greater, than the structurally related neutral free radicals. Convincing evidence that this is the case comes from studying a slower rearrangement (e.g., a cyclobutyl ketyl anion).

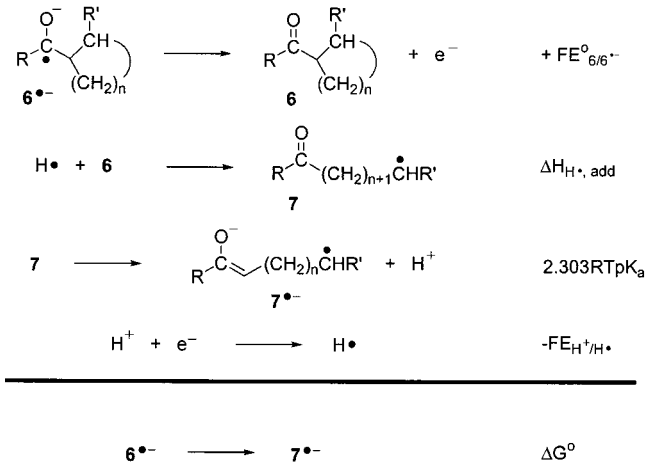
After observing that for radical anions generated from aliphatic cyclopropyl ketones ring opening was apparently so rapid that electron transfer was rate limiting (vide supra), we decided to study cyclobutyl ketone **3** in the hope that ring opening would be slower and, hopefully, rate limiting. For neutral free radicals, the cyclobutylcarbinyl radical ring opens 5 orders of magnitude slower than the cyclopropyl carbinyl radical.[56−58] (The proposition that three-membered-ring cleavage in these radical anions is substantially faster than four-membered-ring cleavage is confirmed, qualitatively at least, by the preparative-scale electrolysis of **4**—only products arising from cleavage of the cyclopropane ring are detected, Table 1).

For the mediated reduction of **3**, ring opening was indeed the rate-limiting step, and *composite* rate constants were determined with use of naphthalene and biphenyl as electron-transfer mediators, $k_{obs} = (k_1/k_{-1})k_0 = K_1k_0$ (Table 4). The equilibrium constant for electron transfer was related to the difference in reduction potential of the mediator and the substrate ($\log(K_1) = -F(E^{\circ}_{M/M^{\bullet-}} - E^{o}_{A/A^{\bullet-}})/(2.303RT)$); unfortunately, the latter value was unknown. In our Communication,[36] we assumed that the reduction potentials of **3** and **1** were similar.

We can now address this assumption more confidently. In analogy to **1** and **2**, electron transfer is rate-limiting in the mediated reduction of **4** and **5**. As a consequence, rate constants for electron transfer with several mediators are determined (Table 2), and reduction potentials are estimated by using Marcus theory (Table 3). Compared to **1**, introduction of a second cyclopropyl group (**5**) or a cyclobutyl group (**4**) has no detectable effect on the kinetics or thermodynamics (i.e., E°) of the electron transfer. With any given mediator, the rate constants for electron transfer for all of these compounds are identical, as are the derived reduction potentials. Thus, a cyclopropyl (or cyclobutyl) group has no measurable effect on the stability of the radical anion.

Of course, the best comparison would be the reduction potential of **1** vs that of acetone. While this cannot be achieved experimentally, this issue can be addressed computationally. Hartree−Fock calculations reveal (a) that the energies of the LUMO of **1** and acetone are nearly identical (acetone, 1.75 eV; **1**, 1.74 eV). Likewise, the ionization potentials (HOMO energy) of $\mathbf{1}^{\bullet-}$ and $Me_2C{=}O^{\bullet-}$ are very close, 1.60 and 1.56 eV,

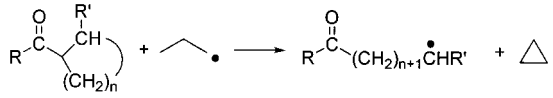
Scheme 8



respectively. Thus, the calculations support the proposition that the cyclopropyl group does not significantly stabilize these radical anions. With the assumption that the reduction potential of **3** is -3.201 ± 0.012 V (the average of compounds **1**, **2**, **4**, and **5**), the derived rate constant for ring opening of $\mathbf{3}^{\bullet-}$ is $2.5 \times 10^4\ s^{-1}$.

Cyclopropane Ring Opening of Radical Anions: Thermochemical Considerations. The free energy of ring opening of several radical anions pertinent to this study were determined by using eq 6, which is derived from the thermochemical cycle depicted in Scheme 8. The quantities needed to solve for ΔG° are (1) $E^{o}_{A/A^{\bullet-}}$, the reduction potential of ketone **6**, (2) $E^{o}_{H^{+}/H^{\bullet}}$, the reduction potential of H^+ (−2.38 V vs NHE DMSO—corrected to 0.1 M Ag^+/Ag reference, and assumed to be unchanged in DMF),[59] (3) the pK_a of **7** (assumed to be the same as the corresponding ketone in DMSO),[60] and (4) $\Delta H_{H\bullet,add}$ (the enthalpy of $H^{\bullet}$ addition to ketone **6**. $\Delta H_{H\bullet,add}$ was calculated (B3LYP/6-31G*) based upon the isodesmotic reaction in eq 7 and referenced to the experimental value of ΔH° for the addition of $H^{\bullet}$ to cyclopropane (derived from experimental heats of formation).

$$\Delta G^{\circ} = F(E^{o}_{A/A\bullet-} - E^{o}_{H+/H\bullet}) + 2.303RTpK_a + \Delta H^{o}_{H\bullet,add} \quad (6)$$



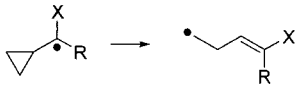
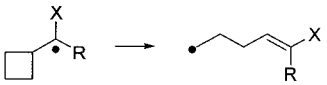
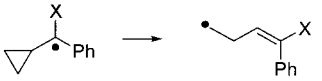
(7)

This procedure is attractive because the calculations are based partly on experimental solution-phase measurements for the charged species, and they should adequately account for the effect of solvent and electrolyte. The results are summarized in Table 5.

Ring Opening: Cyclopropyl vs Cyclobutyl. The results summarized in Table 5 indicate that the driving force for ring opening of the cyclopropyl group of $\mathbf{1}^{\bullet-}$ is nearly the same as that for the ring opening of the cyclobutyl group of $\mathbf{3}^{\bullet-}$. Kinetically, however, ring opening of $\mathbf{1}^{\bullet-}$ is at least 3 orders of magnitude faster than that of $\mathbf{3}^{\bullet-}$. A similar situation pertains to ring opening of the neutral free radicals: Ring opening of the cyclopropylcarbinyl radical is exothermic by 2−4 kcal/mol

(56) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc. Perkin Trans. 2* **1980**, 1083−1092.
(57) Ingold, K. U.; Maillard, B.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1981**, 970−974.
(58) Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1989**, 173−177.
(59) Parker, V. D. *J. Am. Chem. Soc.* **1992**, *114*, 7458−7462.
(60) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463.

Table 5. Kinetic and Thermodynamic Data for Rearrangement of Structurally similar Neutral Free Radicals and Radical Anions

Rearrangement	X = R = H			X = O^-, R = CH_3	
	ΔE^o (kcal/mol)[a]	ΔH^o or ΔE^o (kcal/mol)[b]	k (25°, s^{-1})	ΔG^o (kcal/mol)	k (25°, s^{-1})
	-2.3	-2.3 (th)[c] -1.5 → -4.6 (ex)[d]	1.0×10^{8} [e]	-4.2	$> 10^7$
	-7.0		6.8×10^{8} [f] ($3^o/1^o$ = 6.7)[f]	-8.5	$> 10^7$ ($3^o/1^o$ = 2.5)
	-1.6	-4.4 (ad)[g]	4.7×10^{3} [g, h]	-4.5	2.5×10^4
	+5.8	+5.8 (th)[c] +2.7 (ex)[i]	6×10^{4} [c,j]	+9.9	< 2[k]
	+5.8		3.6×10^{8} [l]	-2.3	$\approx 10^7$ [m] 2.9×10^6 [n] 3×10^5 [o]

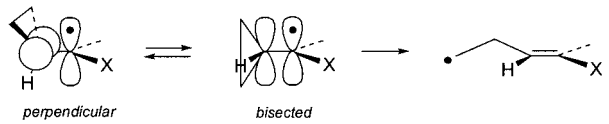
[a] Calculated (B3LYP/6-31G*) this work. [b] Literature (th = theory, B3LYP/6-31G*, ex = experiment, ad = additivity rules). [c] Reference 66. [d] See ref 67 for a summary and discussion. [e] References 68−70. [f] Reference 55. [g] Reference 58. [h] See also references 56 and 57. [i] ΔG°, estimated from forward and reverse rate constants in ref 71. [j] References 71 and 72. [k] References 32 and 33. [l] Reference 73.[73] [m] Reference 34. [n] Reference 74. [o] M. Chahma, J. Tanko (Unpublished results at VPI&SU).

and occurs with a rate constant of 1.0×10^8 s^1. The driving force for ring opening of the cyclobutylcarbinyl is similar, but the rate constant is 5 orders of magnitude lower. Thus, it would be incorrect to conclude that the sluggish rates of ring opening of the cyclobutyl species are attributable to differences in the relief of ring strain. Indeed, the strain energiesy of cyclopropane and cyclobutane are nearly identical, 27.5 vs 26.5 kcal/mol,[61] respectively.

The rapid rate of ring opening associated with cyclopropylcarbinyl radicals can be attributed to the unique conjugative properties of the cyclopropyl vs cyclobutyl groups[62] and the resulting differences in the extent of spin delocalization in the radical anions and transition states for ring opening.

In the case of the neutral radicals, EPR studies reveal that both the cyclopropylcarbinyl[63−65] and cyclobutylcarbinyl[57] systems adopt the bisected conformation vs perpendicular conformation. The reactive conformation for ring opening is the bisected conformation, because the overlap between the cycloalkyl HOMO and the radical center is maximal (Scheme 9). DFT calculations show that for these radicals, a greater amount of spin density is transferred to the cyclopropyl group compared to the cyclobutyl group. (The spin densities at the CH_2 are 0.860 and 0.905 for the cyclopropylcarbinyl and cyclobutylcarbinyl radicals, respectively.) This difference in spin delocalization is reflected in the energetics: For cyclopropyl, the bisected conformation is favored over the perpendicular by 3.3 kcal/mol (a value similar to the rotational barrier of 2.7 kcal/mol measured by EPR);[64] for cyclobutyl, the difference is only 1.1 kcal/mol.

Scheme 9



The calculated barriers and transition state geometries for ring opening of the cyclopropylcarbinyl and cyclobutylcarbinyl radicals obtained in this study compare favorably to previously reported values. For cyclopropylcarbinyl and cyclobutylcarbinyl ring opening, the calculated barriers are 8.6 and 14.2 kcal/mol, respectively. Furthermore, as noted by Dolbier, bond breaking is considerably more advanced in the transition state for ring opening of the cyclobutylcarbinyl radical, where the length of the rupturing C−C bond (2.05 Å) is significantly greater than that for the cyclopropylcarbinyl radical (1.91 Å). This difference is also manifested in the calculated spin densities: There is considerably greater spin density at the developing radical center in the transition state of the cyclobutylcarbinyl radical (0.520) compared to the cyclopropylcarbinyl (0.469).

In the case of the three- vs four-membered ring radical anions ($\mathbf{1}^{\bullet-}$ vs $\mathbf{3}^{\bullet-}$), the situation though similar, is not identical. Consistent with the observed reduction potentials, DFT calculations provide no indication that the cyclopropyl group significantly stabilizes ketyl radical anions. For $\mathbf{1}^{\bullet-}$, the bisected and perpendicular conformations are nearly degenerate (≤0.2 kcal/mol difference in energy). For $\mathbf{3}^{\bullet-}$, the perpendicular conformation is lower in energy by about 1.0 kcal/mol. In the bisected conformation, the spin densities at the $C{=}O^{\bullet-}$ are nearly identical for $\mathbf{1}^{\bullet-}$ and $\mathbf{3}^{\bullet-}$, 0.703 and 0.698, respectively.

As expected, the calculated barrier for ring opening of $\mathbf{3}^{\bullet-}$ (7.5 kcal/mol) is higher than that of $\mathbf{1}^{\bullet-}$ (3.3 kcal/mol), though

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(62) Tidwell, T. T. *Conjugative and substitutent properties of the cyclopropyl group*; Rappoport, Z., Ed.; John Wiley & Sons: Ltd.: New York, 1987; pp 565−632.
(63) Kochi, J. K.; Krusic, P. J.; Eaton, D. R. *J. Am. Chem. Soc.* **1969**, *91*, 1879−1881.
(64) Walton, J. C. *Magn. Reson. Chem.* **1987**, *25*, 998−1000.
(65) Bauld, N. L.; McDermed, J. D.; Hudson, C. E.; Rim, Y. S.; Zoeller, J., Jr.; Gordon, R. D.; Hyde, J. S. *J. Am. Chem. Soc.* **1969**, *91*, 6666−6676.

it must be stressed that these values pertain to a gas-phase calculation and the experimental results are from a study in solution. As is the case for neutral radicals, the extent of bond cleavage is greater in the transition state for ring opening of the four- vs three-membered ring: The lengths of the rupturing C−C bond and spin densities (at the developing radical center) are 2.04 Å and 0.398 for $\mathbf{3}^{\bullet-}$, compared to 1.83 Å and 0.333 for $\mathbf{1}^{\bullet-}$. The bond length differences and spin densities suggest a more delocalized, resonance-stabilized transition state for rupture of the three- vs four-membered ring.

Consequently, we suggest that the reason cleavage of a cyclopropyl group is so much faster than that of a cyclobutyl group (in both radicals and radical anions) is that for the cyclopropyl systems (a) the more reactive bisected conformation is preferred and (b) because the transition state for rupture of the three-membered ring is stabilized to a greater extent (via spin delocalization).

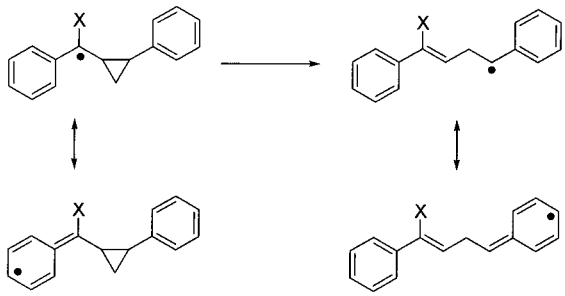
Comparison of Neutral Radicals and Structurally Related Radical Anions. Table 5 summarizes the pertinent kinetic and thermodynamic data for ring opening of several neutral free radicals and radical anions. Our new results dispel the prior belief that ring opening of the radical anions was considerably slower because of the thermodynamic stability of ketyl radicals compared to structurally related alkyl radicals.

The data in Table 5 reveal that as a result of α-phenyl substitution, ring opening of both the neutral radicals and radical anions becomes less favorable kinetically and thermodynamically. Placement of a radical-stabilizing substituent on the cyclopropane ring has the opposite effect: Ring opening becomes more favorable thermodynamically and kinetically. These observations are readily explicable on the basis of resonance: α-substitution stabilizes the ring-closed from; substituents on the cyclopropyl ring stabilize the ring-opened form (or more appropriately, the transition state leading to the ring-opened form, Scheme 10).

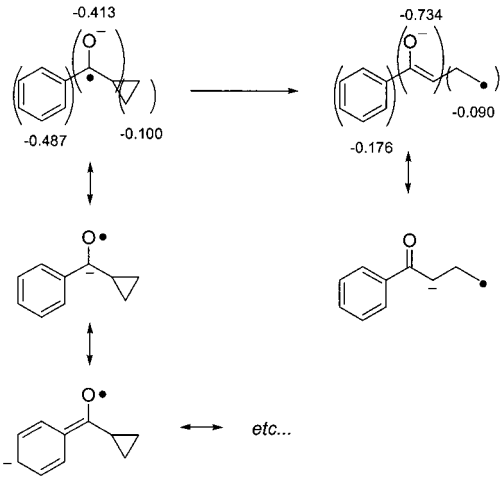
For radical anions generated from aromatic ketones, ring opening of the neutral radical is considerably faster than that of the radical anions (i.e., replacement of H by O^- makes ring opening less favorable and diminishes the rate.)

However, for radical anions derived from aliphatic ketones, the opposite scenario pertains. The energetics of ring opening for the neutral radicals and radical anions are quite similar (Table 5). Where numbers are available (e.g., the cyclobutyl system), the rate constant for ring opening of the radical anion is comparable to, or slightly faster than, that of the structurally related neutral free radical. Unquestionably, the difference between radical anions generated from aliphatic vs aromatic ketones is the ability of the aromatic ring to stabilize the negative charge via resonance (Scheme 11). In the ring-closed form, the

Scheme 10



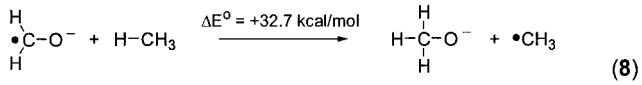
Scheme 11



negative charge can be delocalized into the aromatic ring. Upon ring opening, this stabilization is lost because the charge becomes more localized. The numbers in Scheme 11 are the Mulliken charges associated with various regions of the molecule (obtained from Hartree−Fock calculations).

The lower rate of ring opening of radical anions derived from aromatic ketones is not attributable to the intrinsic stability of ketyl radicals (in general). Rather, it is the fact that aromatic ketyls are especially stable, and the important consideration is the delocalization of negative charge (rather than spin) into the aromatic ring. Our results suggest that aliphatic ketyls are at least (and likely more) as reactive as alkyl radicals in β-scission-type reactions (vide infra). At first glance, this conclusion may seem surprising because radicals are generally stabilized by electron-donating groups (e.g., based upon the C−H bond strengths of methane vs methanol, an OH group stabilizes a radical to the tune of about 7 kcal/mol). Why is it that a deprotonated OH group (i.e., O^-), which is even *more* electron donating, not more able to stabilize radicals?

Indeed, considering the isodesmotic reaction depicted in eq 8 (ΔE^o obtained from B3LYP/6-311+G* calculations on the pertinent species), this supposition appears reasonable: A radical stabilization energy (RSE) of 33 kcal/mol can be attributed to the O^- group relative to hydrogen.



(**8**)

However, "stabilization" depends on the reference reaction used for comparison. Consider eq 9, which depicts an isodesmotic reaction to evaluate and compare the ability of ethyl radical vs acetaldehyde radical anion to undergo β-scission

(66) Halgren, T. A.; Roberts, J. D.; Horner, J. H.; Martinez, F. N.; Tronche, C.; Newcomb, M. *J. Am. Chem. Soc.* **2000**, *122*, 2988−2994.
(67) Smith, D. M.; Nicolaides, A.; Golding, B. T.; Radom, L. *J. Am. Chem. Soc.* **1998**, *120*, 10223−10233.
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(71) Beckwith, A. L. J.; Bowry, V. W. *J. Am. Chem. Soc.* **1994**, *116*, 2710−2716.
(72) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Chem. Soc., Chem. Commun.* **1990**, 923−925.
(73) Hollis, R.; Hughes, L.; Bowry, V. W.; Ingold, K. U. *J. Org. Chem.* **1992**, *57*, 4284−4287.
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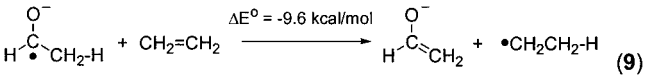
(through loss of H•). In this case, the results suggest that the O^- group actually destabilizes a radical center (relative to hydrogen) by nearly 10 kcal/mol.



(9)

The difference in these two analyses is that eq 8 considers only the interaction of O^- with a radical center (vs a methyl group), where eq 9 compares the interaction of O^- with a radical center vs a carbon−carbon double bond. The implication is that O^- stabilizes the C═C to a greater extent than a radical center, and for that reason, β-scission is thermodynamically more favorable for aliphatic ketyl anions compared to alkyl radicals. (An equivalent, and we suspect indistinguishable, argument is that it is actually O^- which is stabilized more by a C═C than an adjacent radical center.) In either case, the final result is identica The reason β-scission is more favorable for aliphatic ketyl anions (compared to alkyl radicals) is that introduction of the O^- group leads to more resonance stabilization in the products than in the reactants.

Closing Remarks

In summary, stabilization of both charge and spin are important factors pertaining to substituent effects on the rates of radical anion rearrangements. Ring opening of radical anions generated from aromatic ketones is slower than that of the corresponding neutral free radicals because the aromatic ring stabilizes the negative charge in the ring-closed, but not the ring-opened form. In contrast, for radical anions generated from aliphatic ketones, ring opening is significantly faster than that for the structurally related neutral free radical (and possibly more favored thermodynamically). The high reactivity of aliphatic ketyl anions toward β-scission arises because the resonance stabilization between an O^- group and a double bond (i.e., the enolate in the products) is greater than that of an O^- group with the radical center (i.e., $C{=}O^{\bullet -}$ in the reactants).

Although this work has focused specifically on radical anion rearrangements, there is little doubt that many of the same considerations pertain to rearrangements of radical cations. The chemistry of radical ions is perhaps more complex than is generally appreciated; however, it is important to emphasize that they do not appear to defy established principles of organic reactivity. The complexity arises from the fact that these species are both radicals and ions, and their chemistry is reminiscent of both types of reactive intermediates. Indeed, as more systems are studied and patterns regarding the role played by stabilization (or destabilization) of charge and spin are revealed, it is likely that an excellent understanding of the chemistry of this unique class of reactive intermediates will be achieved.

Acknowledgment. Financial support from the National Science Foundation (CHE-9732490) is gratefully acknowledged.

Supporting Information Available: Plots of i_p/i_{pd} vs $\log(1/\nu)$ and vs $\log(C_M^o/\nu)$ for all substrate/mediator combinations studied and results of MO calculations pertaining to cyclopropylcarbinyl and cyclobutylcarbinyl radicals and related radical anions (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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