Radical Ion Probes. 2. Evidence for the Reversible Ring Opening of Arylcyclopropylketyl Anions. Implications for Mechanistic Studies

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Abstract: Aryl cyclopropyl ketones have frequently been utilized as diagnostic probes for single electron transfer (SET) for a variety of organic transformations. The implicit assumption in these studies is that the formation of rearranged product(s) signals the intermediacy of a ketyl anion. Through a detailed examination of the mechanism, kinetics, and products arising from the decay of several arylcyclopropylketyl anions (generated electrochemically), we have demonstrated that the assumptions made in the use of these substrates as SET probes are tenuous. Radical anions generated from compounds whose only substituents on the cyclopropane ring are either H or CH_3 including phenyl cyclopropyl ketone (**6**), 1-benzoyl-2-methylcyclopropane (**7**), 1-benzoyl-2,2-dimethylcyclopropane (**8**), 1-benzoyl-1-methylcyclopropane (**9**), and *p*-tolyl cyclopropyl ketone (**10**) undergo *slow* and *reversible* ring opening. This preequilibrium is followed by a rate-limiting coupling of the ring-opened and ring-closed species. The direction of equilibrium overwhelmingly favors the ring-closed form. For $\mathbf{6}^{\bullet-}$, the equilibrium constant for ring opening is estimated to be 2×10^{-8} with a maximum rate constant for the forward reaction estimated to be 2 s^{-1} and a minimum rate constant for the reverse direction of 8×10^{7} s^{-1}. Via deuterium labeling coupled with ^2H NMR and GC/MS analysis the major product arising from the dianion is demonstrated to arise via a novel intramolecular hydride-transfer process. The radical anion generated from *p*-cyclopropylacetophenone (**11**) shows no evidence for cyclopropane ring opening. $\mathbf{11}^{\bullet-}$ decays with a bimolecular rate law forming a pinacol dimer. These observations are complemented by results obtained from semiempirical molecular orbital calculations at the AM1 level. Important factors in the design of radical ion probes based upon intramolecular rearrangements are identified and discussed.

Introduction

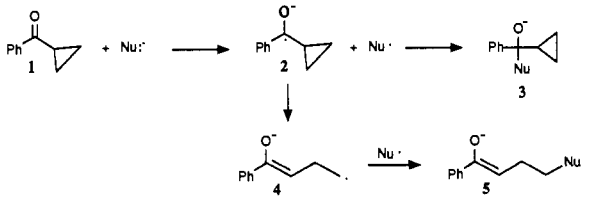
A tremendous amount of activity and interest in mechanistic organic chemistry has been simulated by the recognition of single electron transfer (SET) as an important reaction pathway. Many classical organic reactions previously thought to involve solely conventional polar intermediates are now believed to involve some component of SET. Evidence has been accumulating which provides testimony for the importance of SET in such fundamental organic transformations as electrophilic aromatic substitution, nucleophilic substitution at saturated carbon, and nucleophilic addition to carbonyl compounds.[1]

To illustrate, consider two possible mechanisms for reaction of a nucleophile ($Nu:^-$) and a carbonyl compound: (a) a polar (two-electron) process, $Nu:^- + C{=}O \rightarrow Nu{-}C{-}O^-$, and (b) a single-electron-transfer process, $Nu:^- + C{=}O \rightarrow [Nu^{\bullet}/{}^{\bullet}C{-}O^-] \rightarrow Nu{-}C{-}O^-$. Experiments designed to detect paramagnetic intermediates (i.e., $Nu^{\bullet}$ and/or $^{\bullet}C{-}O^-$) are required to ascertain the importance of the SET pathway. Common approaches include the use of ESR spectroscopy, trapping by radical scavengers, and kinetic isotope effects.[1]

A popular approach for the experimental detection of electron-transfer pathways involves the use of intramolecular rearrangements. If an appropriate "probe" substituent is incorporated into the substrate, the intermediacy of a radical or radical ion is often inferred by the appearance of rearranged products. These "probes" are typically based upon rupture of three- or four-membered rings, cyclizations involving a remote C=C, or geometric (cis → trans) isomerizations.[1]

In the case of free radicals, rearrangement probes have enjoyed remarkable success because several radical rearrangements are well-documented[2,3] and in several instances their absolute rate constants are known. Griller and Ingold have coined the term "free radical clocks" to describe such rearrangements, because absolute rate constants for competing bimolecular processes can be determined from simple product analyses.[4]

Scheme I



For radical ions, however, this level of dependability and sophistication has not yet been attained. In most mechanistic studies it is simply *assumed* that structural features which lead to rearrangement of free radicals will also lead to rearrangement of radical ions. A specific example involves phenyl cyclopropyl ketone, which has frequently been used to study reactions of a variety of nucleophiles with carbonyl compounds.[5-28] In several

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(2) Wilt, J. W. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. I, pp 334-501.
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(15) House, H. O.; Prabhu, A. V.; Wilkins, J. M.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 3067. In this paper, half-lives for $\mathbf{6}^{\bullet-}$ and $\mathbf{8}^{\bullet-}$ were reported with the implicit assumption that an EC mechanism was operating. Our results demonstrate that this assumption is incorrect and that these radical anions decay by a more complicated mechanism.
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(17) Hall, S.; Sha, C.; Jordan, F. *J. Org. Chem.* **1976**, *41*, 1494.
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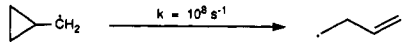
of these studies, phenyl cyclopropyl ketone is purported to be a probe for SET, with the assumption that incorporation of the cyclopropyl group will lead to rearranged reaction products if the SET pathway is operating (Scheme I).

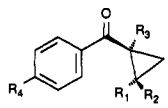
The implicit assumption is that relief of cyclopropane ring strain will provide the thermodynamic and kinetic driving force for radical-anion rearrangement (**2** → **4**) in analogy to the cyclopropylcarbinyl radical (eq 1).[4,29] The validity of this assumption is uncertain.



(1)

There are several conflicting reports in the literature regarding the integrity of a cyclopropyl ring in ketyl radical anions. Dissolving metal reduction of aliphatic cyclopropyl ketones yields ring-opened products, a process generally ascribed to ring opening of a ketyl anion.[30-34] However, dicyclopropylketyl anion is apparently sufficiently stable such that its ESR spectrum can be recorded without any reported difficulty.[35] The half-lives of several arylcyclopropylketyl anions, studied by cyclic voltammetry, have been reported and their decays ascribed to ring opening.[15] However, exhaustive electrolysis of phenyl cyclopropyl ketone yields the corresponding pinacol without cyclopropane ring opening.[36] Dissolving metal reduction of phenyl cyclopropyl ketone yields benzylcyclopropane.[37]

Because of the disparity of these observations and because cyclopropyl ketones have been utilized as SET probes in several mechanistic studies, we began a detailed study of the chemistry of cyclopropylketyl anions, the preliminary results of which have been reported in an earlier paper.[38] Specifically, we suggested that cyclopropylcarbinyl type rearrangements of ketyl anions generated by one-electron reduction of phenyl cyclopropyl ketones **6–8** are reversible. In this paper, we report our findings regarding the chemistry of radical anions generated from **6–11** and provide additional evidence which demonstrates that these compounds are unsuitable probes for SET.



6 ($R_1 = R_2 = R_3 = R_4 = H$)
7 ($R_1 = CH_3$; $R_2 = R_3 = R_4 = H$)
8 ($R_1 = R_2 = CH_3$; $R_3 = R_4 = H$)
9 ($R_1 = R_2 = R_4 = H$; $R_3 = CH_3$)
10 ($R_1 = R_2 = R_3 = H$; $R_4 = CH_3$)

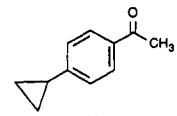


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Table I. Summary of Data Obtained by DCV for Compounds **6–11**

compd	E° (V)[a,b]	$R_{A/B}$[c]	E_a (kcal/mol)[d]	k_{obs} (M^{-1} s^{-1})
6	−2.420	2.0 ± 0.1	9.5 ± 0.2	3.9 ± 0.4
7	−2.435	1.8 ± 0.1	7.7 ± 0.1	13.1 ± 1.5
8	−2.435	2.0 ± 0.1	7.1 ± 0.2	211 ± 30
9	−2.410	*e*		*e*
10	−2.496	2.2 ± 0.1		14.4 ± 3.4
11	−2.482	2.4 ± 0.2		2.8 ± 1.3

[a] 0.5 M n-Bu_4NBF_4, DMF, Au working electrode, 0.1 M Ag^+/Ag reference. [b] $E^\circ = (E_{pa} + E_{pc})/2$ when $I'_{pa}/I'_{pc} = 1.00$. [c] Overall reaction order, see text. [d] Apparent activation energy; temperature varied in the range −10 to +60 °C. [e] Decay too slow for DCV analysis.

Results and Discussion

A. Voltammetry Experiments. The mechanism and kinetics of decay of radical anions generated from **6–11** were studied electrochemically. All voltammetric measurements were performed at 23 °C in anhydrous *N,N*-dimethylformamide (DMF) with 0.5 M tetra-*n*-butylammonium tetrafluoroborate (n-Bu_4NBF_4) as the supporting electrolyte. A gold minidisk served as the working electrode, and the reference electrode was 0.1 M Ag^+/Ag (+0.337 V vs SCE).

A thorough description of the voltammetric techniques utilized in this study (e.g., cyclic and derivative cyclic voltammetry (CV, DCV) and linear sweep voltammetry (LSV)) is available in several reviews.[39] In summary, these methods permit assignment of the rate law for the decay of species generated (reversibly) by heterogeneous electron transfer (Scheme II). Once the rate law is established for the homogeneous reaction, rate constants can be extracted from the experimental data by digital simulation, curve fitting, or the use of published empirical relationships (working curves).

Scheme II

$$A + e^- \rightleftarrows B$$

$$B \xrightarrow{k} \text{products}$$

$$\frac{-d[B]}{dt} = k[A]^a[B]^b$$

1. Derivative Cyclic Voltammetry. The "reaction order approach"[39] provides a means of assessing the rate law for decay of an electrode-generated intermediate (i.e., −d[B]/dt, Scheme II) by observing the variation of the anodic to cathodic derivative current ratio (I'_{pa}/I'_{pc}) as a function of substrate concentration (C_A) and sweep rate (v). A plot of log v_C vs C_A yields a straight line whose slope is related to the combined reaction order in A and B according to eq 2, where v_C represents the sweep rate needed to keep the derivative current ratio at a constant value (typically between 0.3 and 0.7) and $R_{A/B}$ is the combined reaction order in A and B.[39]

$$R_{A/B} = a + b = \delta \log v_C / \delta \log C_A + 1 \qquad (2)$$

Typical reaction order plots for the compounds pertinent to this paper are available as supplementary material. The results of these experiments are summarized in Table I. Radical anions generated from **6–8**, **10**, and **11** all decay with a rate law which is *second order* overall. These results are clearly inconsistent with a simple cyclopropylcarbinyl ring-opening reaction (i.e., an overall first-order process). It was not possible to assign a rate law for the decay of $\mathbf{9}^{\bullet-}$ whose lifetime proved too long for DCV reaction order analysis. Based upon the fact that products analogous to those observed for the bulk electrolysis of **6–8** and **10** are isolated, a similar mechanism for decay is implicated (vide infra). Also, it should be mentioned that $\mathbf{11}^{\bullet-}$ underwent sluggish decay, and

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Table II. LSV Analysis of 1-Benzoyl-2,2-dimethylcyclopropane (8)

rate law	$\delta E_p/\delta \log \nu$ (mV/decade)	$\delta E_p/\delta \log C_A$ (mV/decade)
k[B]	−29.5[a]	0.0[a]
k[B]^2	−19.7[a]	19.7[a]
k[A][B]	−29.5[a]	29.5[a]
obsd	−17.3 ± 0.2	19.4 ± 0.6

[a] Theoretical response, see ref 39.

because of this, the data were obtained at $I'_{pa}/I'_{pc} = 0.82$. Strictly speaking, it is not rigorously correct to apply the reaction order approach when $I'_{pa}/I'_{pc} > 0.7$,[39] and this is the likely reason for the comparatively larger error in the measured reaction order. Nonetheless, the data unambiguously show that the reaction is greater than first order.

Apparent activation energies (E_a) for the decay of several of these radical anions were also determined. At several temperatures, the sweep rate was adjusted to keep the derivative current ratio constant. An Arrhenius type plot of ln (ν_C/T) vs $1/T$ yields a straight line according to eq 3.[39]

$$\ln (\nu_C/T) = (-E_a/RT) + C \quad (3)$$

Representative plots are available as supplementary material; results are summarized in Table I.

2. Linear Sweep Voltammetry. The DCV reaction order approach outlined above provides an overall order for the homogeneous chemical reaction but does not separate the individual reaction orders in A and B. Deconvolution of the individual reaction orders in A and B can be accomplished with linear sweep voltammetry. For voltammetric waves where no reverse current is observed, the variation in the forward peak potential (E_p) as a function of sweep rate and substrate concentration can be related to the individual reaction orders in A and B according to eqs 4 and 5.[39]

$$\delta E_p/\delta \log \nu = -1/(b + 1) \log (RT/nF) \quad (4)$$

$$\delta E_p/\delta \log C_A = (a + b - 1)/(b + 1) \log (RT/nF) \quad (5)$$

LSV results for 1-benzoyl-2,2-dimethylcyclopropane (**8**) are available as supplementary material. A summary of these results compared to those calculated for several possible mechanisms appears in Table II and clearly support a mechanism which is *second order in radical anion* (i.e., an EC_{DIM}-type process; $-d[B]/dt = k_{obs}[B]^2$). Decay kinetics for the other arylcyclopropylketyl anions of interest in this study were too slow for LSV analysis. However, based upon the analogy between the DCV results, exhaustive electrolysis, etc., it seems reasonable to assume that the mechanism for decay of **6**$^{\bullet-}$–**10**$^{\bullet-}$ is similar (vide infra).

3. Rate Constants for Decay of 6$^{\bullet-}$–10$^{\bullet-}$. For the EC_{DIM} mechanism, the rate constant can be calculated according to eq 6, where $\nu_{0.5}$ is the sweep rate at which the derivative current ratio is equal to 0.5.[39]

$$k(EC_{DIM}) = 0.1173(F/RT)\nu_{0.5}/C_A \quad (6)$$

The following procedure was followed to ensure that the "best" value for $\nu_{0.5}$ was used in the calculation of the rate constants. It has been demonstrated that a plot of ln (I'_{pa}/I'_{pc}) vs ln ($1/\nu$) is linear in the region $0.25 \leq I'_{pa}/I'_{pc} \leq 0.70$ for a variety of mechanisms.[39] Consequently, $\nu_{0.5}$ was obtained via a linear least-squares fitting of the voltammetric data for each concentration of substrate. Representative plots are available as supplementary material. The results are summarized in Table I.

B. AM1 SCF-MO Calculations. The enthalpies of ring opening (ΔH_{rc}) for the ketyl anions utilized in this work were calculated utilizing semiempirical molecular orbital theory (AM1 approximation)[40] and are summarized in Table III. Increased substitution of the cyclopropyl group lowers the calculated enthalpy of ring opening, and these values parallel the apparent activation energies observed for the decay of the ketyl anions (Table I). It is noteworthy that for most of these radical anions the ring-opening reaction appears to be *endothermic*. These results suggest that, without radical-stabilizing substituents present on the cyclopropyl group, relief of ring strain does not compensate for the loss of resonance energy in the conversion of the delocalized radical anion to the localized distonic radical anion.

Table III. AM1-Calculated Enthalpy of Ring Opening for Cyclopropyl Ketyl Anions 6$^{\bullet-}$–11$^{\bullet-}$

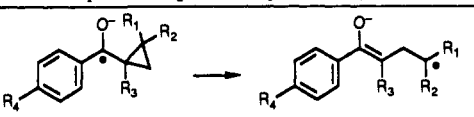
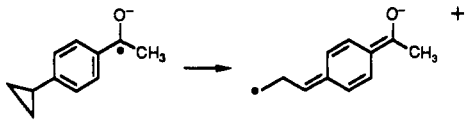
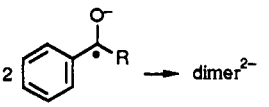
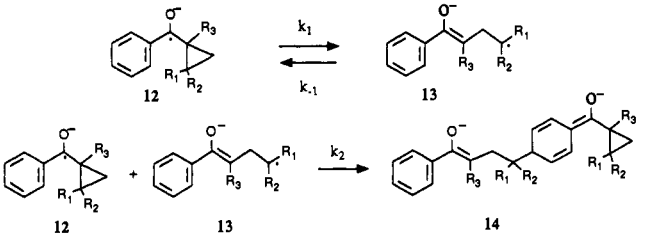
radical anion	R_1	R_2	R_3	R_4	$\Delta H°$ (kcal/mol)
					
6$^{\bullet-}$	H	H	H	H	+7.9
7$^{\bullet-}$	Me	H	H	H	+2.5
8$^{\bullet-}$	Me	Me	H	H	−2.5
9$^{\bullet-}$	H	H	Me	H	+6.2
10$^{\bullet-}$	H	H	H	Me	+7.9
11$^{\bullet-}$					+1.6

Table IV. Relative Stability of Phenylalkylketyl Anions As Assessed by DCV (0.5 M n-Bu_4NBF_4, DMF, Au, C_A = 3.0 mM, ν = 100 mV/s)



R	I'_{pa}/I'_{pc}	R	I'_{pa}/I'_{pc}
CH_3	0.00	$CH(CH_3)_2$	0.96
CH_2CH_3	0.40	$C(CH_3)_3$	1.00

Scheme III



C. Proposed Mechanism for Decay of 6$^{\bullet-}$–10$^{\bullet-}$. From the data in Table I and II, it is evident that radical anions generated from **6**–**10** do not decay via simple rupture of the cyclopropyl ring, as such a process would be expected to exhibit first-order kinetics. At first glance, the experimentally observed second-order kinetics suggest a simple ketyl dimerization reaction: $2R_2C{=}O^{\bullet-} \rightarrow \text{dimer}^{2-}$.[41] However, close examination of the rate constants in Table I reveals that increased alkyl substitution on the cyclopropane ring increases the observed bimolecular rate constant (i.e., **8**$^{\bullet-}$ > **7**$^{\bullet-}$ > **6**$^{\bullet-}$), a trend reflected in the apparent E_a's as well. Such an observation is precisely the opposite of what is typically expected for ketyl dimerizations.[41] For the phenyl alkyl ketone series, increased steric bulk retards the rate of ketyl anion dimerization, as illustrated by the data in Table IV.

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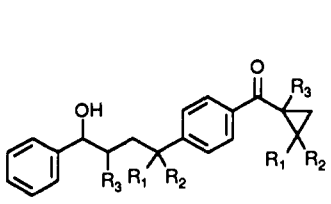
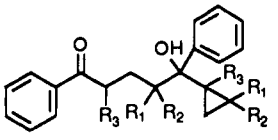
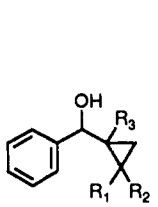
Table V. Yields of Products from the Bulk Electrolysis of **6–9**



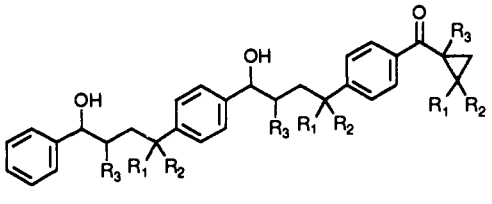
15a–d



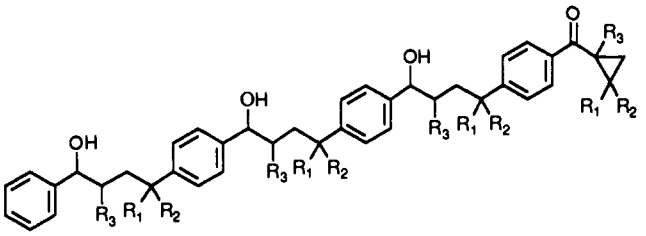
16a–d



17a–d



18a–d



19a–d

starting compd	shorthand designation	R_3	R_2	R_1	yield (%)[a,b] SM[c]	15	16	17	18	19
6	**a**	H	H	H	14	41	7	*d*	11	*d*
7	**b**	H	H	CH_3	17	51	6	*d*	15	5
8	**c**	H	CH_3	CH_3	17	40	*d*	*d*	17	7
9	**d**	CH_3	H	H	10	41	*d*	12	9	*d*

[a] 0.2 M n-Bu_4NBF_4, DMF, Au working electrode. [b] Constant-current electrolyses, 1 equiv of electrons; constant-potential electrolysis yielded similar results. [c] Recovered starting material. [d] None detected.

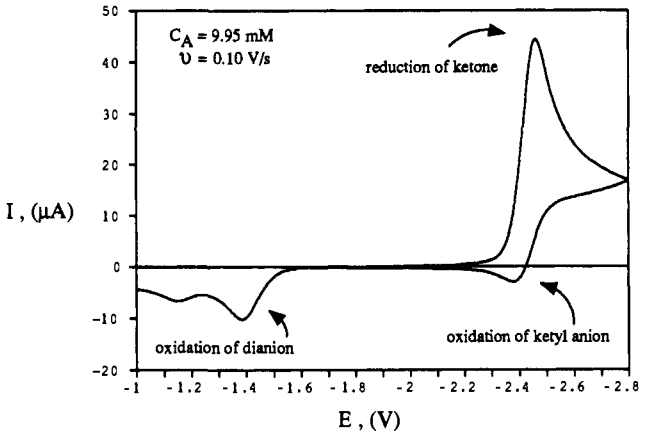


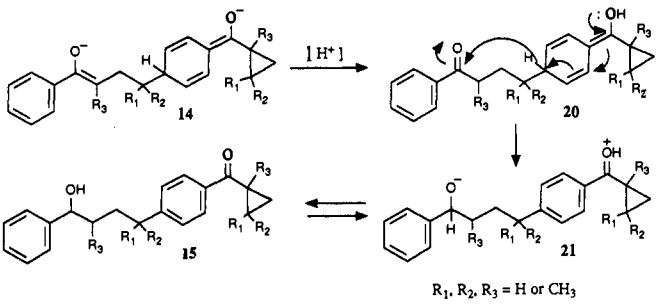
Figure 1. Cyclic voltammogram of 1-benzoyl-2,2-dimethylcyclopropane (**8**).

A mechanism which explains both the observed kinetics and structure/reactivity trends is presented in Scheme III. Radical anion **12** opens *reversibly* to distonic radical **13**, which subsequently couples with **12** to yield dianion **14**. The composite rate constant (k_{obs}) reduces to $(k_1/k_{-1})k_2$ assuming the second step is rate limiting ($k_2[\mathbf{12}] \ll k_{-1}$).

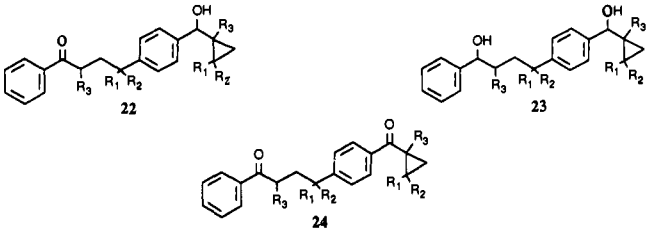
Cyclic voltammetry (CV) experiments on the phenyl cyclopropyl ketones reveal an anodic wave substantially more positive than the ketone/ketyl couple which we have assigned to the oxidation of the dimer dianion. A CV trace of 1-benzoyl-2,2-dimethylcyclopropane (**8**) showing these features is presented in Figure 1. The proposed structure of dimer dianion **14** is based upon the observed products of bulk electrolysis (vide infra).

D. Bulk Electrolysis Experiments. 1. Phenyl Cyclopropyl Ketones 6–9. Bulk electrolyses of **6–9** yielded the products shown in Table V. The "dimerization" step outlined in Scheme III yields initially dianion **14**. Curiously, bulk electrolyses of aryl cyclopropyl ketones **6–9** yield, as the major product, dimeric compounds whose generally structure is represented by **15**. A possible mechanism for the conversion of dianion **14** to **15**, involving an *intramolecular* hydride transfer, is outlined in Scheme IV. Support for this mechanism is provided by the following experimental results.

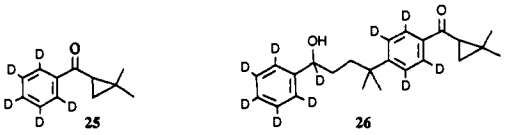
Scheme IV



It is noteworthy that the byproducts of an *intermolecular* reaction (**22–24**) are not observed.



Electrolysis of the d_5 derivative of 1-benzoyl-2,2-dimethylcyclopropane (**25**) resulted in complete deuterium incorporation at the benzylic alcohol carbon in dimer **26**, as assessed by ^1H and ^2H NMR.



To further address the question of intra- vs intermolecular hydride transfer, we performed a coelectrolysis of an equimolar mixture of 1-benzoyl-2,2-dimethylcyclopropane (**8**) and d_5 derivative **25**. The resulting dimeric products were analyzed by mass spectrometry.

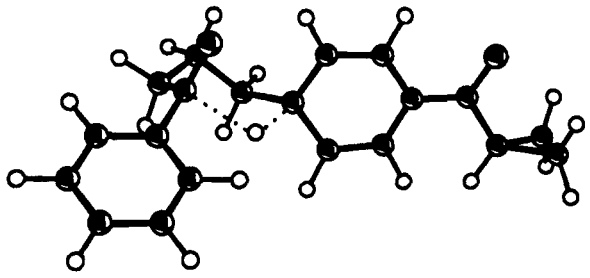
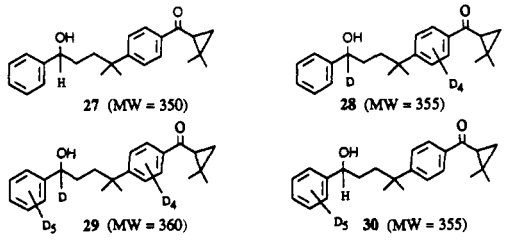
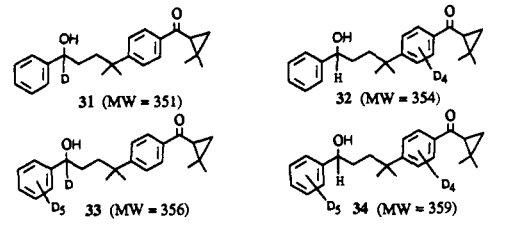


Figure 2. MMX-calculated transition state for intramolecular hydride transfer.

If the hydride transfer is *intramolecular*, four products (**27–30**) with three distinct molecular weights will result. Assuming statistical combination, molecular ion peaks at *m/e* 350, 355, and 360 should be observed in a 1.0:2.0:1.0 ratio.

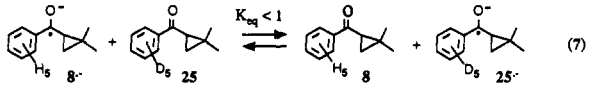


An *intermolecular* process will yield these *plus four additional products* (**31–34**). Again, assuming statistical combination, these eight products will exhibit seven peaks at *m/e* 350, 351, 354, 355, 356, 359, and 360 in a ratio of 1.0:1.3:1.0:2.3:1.7:1.0:1.3 (corrected for the natural isotopic abundance of carbon).



Experimentally, only the three major peaks at *m/e* 350, 355, and 360 in a 1.00:1.4:0.6 ratio are observed, consistent with the intramolecular mechanism depicted in Scheme IV. (The complete listing of peaks in the region *m/e* = 350–360 is available as supplementary material.)

The discrepancy from the statistically predicted ratio can be accounted for assuming the equilibrium constant for eq 7 is less than unity. Similar phenomena have been observed with several



(7)

organic radical anions and their neutral isotopic isomers.[42] Assuming $K_{eq} \approx 0.75$ would result in a predicted ratio of 1:1.5:0.6 for the intramolecular process, remarkably close to the 1.0:1.4:0.6 ratio we observe.

A plausible six-membered transition state for the hydride transfer obtained from molecular mechanics calculations is depicted in Figure 2.

2. *p*-Tolyl Cyclopropyl Ketone (10). Controlled-current electrolysis of **10** (1 equiv of electrons) yielded the products depicted in Figure 3, as well as 22% recovered starting material. Because the para position of the ketyl anion is blocked by a methyl group, decay of this species occurred via coupling at the ortho and carbonyl carbons, presumably via a mechanism analogous to that outlined in Scheme III. The formation of a significant

(42) Stevenson, G.; Sturgeon, B. *J. Org. Chem.* **1990**, *55*, 4090.

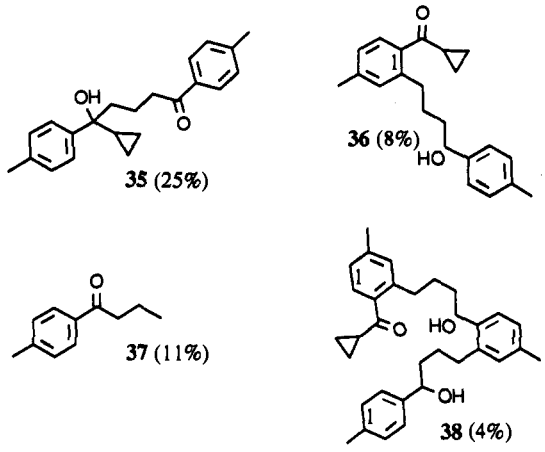
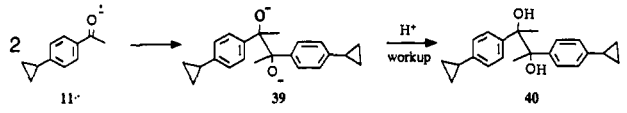
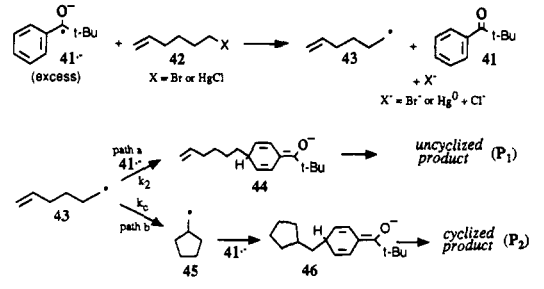


Figure 3. Products/yields arising from the bulk electrolysis of *p*-tolyl cyclopropyl ketone (**10**).

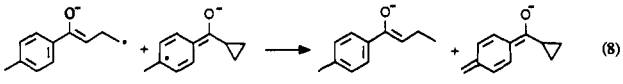
Scheme V



Scheme VI



amount of ring-opened monomer **37** might be explained by the hydrogen atom transfer outlined in eq 8.



(8)

3. *p*-Cyclopropylacetophenone (11). Constant-current electrolysis (1 equiv electrons) of **11** in DMF at gold yielded 22% recovered starting material and pinacol dimer **40**. A simple EC_{DIM} mechanism (Scheme V) explains both the voltammetry and electrolysis results. If cyclopropane ring opening does occur in this system, it must occur at a rate too slow to compete with pinacolization.

E. Estimate of the Absolute Rate Constant k_2 (Scheme III). The experimentally derived rate constants ($k_{obs} = (k_1/k_{-1})k_2$) for the decay of the ketyl anions resulting from the electrochemical reduction of phenyl cyclopropyl ketones **6–8** provide no information on the absolute magnitudes of k_1, k_{-1}, and k_2. The experiments described in this section were designed to approximate k_2, the bimolecular rate constant for coupling of the distonic radical anion **13** with ketyl anion **12** (Scheme III), independently, under conditions which closely match those of our voltammetry experiments (i.e., *n*-Bu_4N^+ counterion, DMF solvent). To accomplish this task, we assumed that the reactivity of the "radical portion" of distonic radical anion **13** was similar to an alkyl radical (i.e., the enolate and radical parts were assumed to be independent).

Electrolytic reduction of pivalophenone (**41**) in DMF/*n*-Bu_4NBF_4 results in formation of a stable ketyl anion (Scheme VI). After electrolysis, a small amount (<0.1 equiv) of Δ^5-hexenylmercuric chloride or Δ^5-hexenyl bromide (**42**) was added. Rapid electron transfer yields the Δ^5-hexenyl radical (**43**). Once formed, **43** undergoes cyclization to the cyclopentylmethyl radical (**45**) with rate constant $k_c = 2 \times 10^5\ s^{-1}$ (25 °C),[43] setting up a

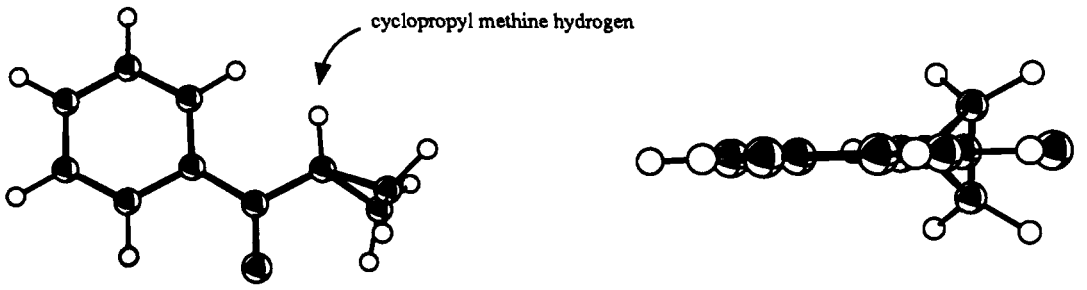


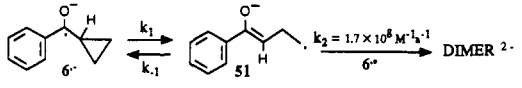
Figure 4. AM1-optimized geometry of phenylcyclopropylketyl anion ($6^{\bullet-}$).

competition which results in the formation of both uncyclized and cyclized products. Reaction products and typical yields observed for these experiments are summarized in Table VI. The concentration of pivalophenone ketyl anion ($41^{\bullet-}$) was monitored (before and after addition of **42**) with a second (voltammetric) electrode by application of the Cottrell equation[44] to current vs time data obtained by potential step methods.

It is unlikely that any of the observed products arise from addition of the radicals to neutral pivalophenone because addition of alkyl radicals to aromatic ketones has been shown to be slow. For example, $k \approx 80\ M^{-1}\ s^{-1}$ for $CH_3^{\bullet}$ + benzophenone.[45]

From the observed ratio of cyclized and uncyclized products, k_2 was determined to be $1.7 \times 10^8\ M^{-1}\ s^{-1}$. The results for several runs using both the alkenyl bromide and the alkenylmercury chloride are available as supplementary material. Our value of k_2 is similar to the reported rate constant for coupling of lithium benzophenone ketyl anion with a primary alkyl radical in THF ($k_{25°} = 1.5 \times 10^8\ M^{-1}\ s^{-1}$).[46]

Based upon these results, it is now possible to estimate the equilibrium constant for ring opening of the phenylcyclopropylketyl anion.

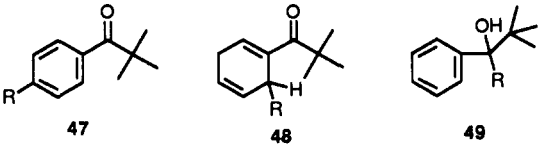


Thus, *ring opening of phenylcyclopropylketyl anion is not only reversible, but the equilibrium favors the ring closed form.* Applying $\Delta G = -RT \ln K$ yields $\Delta G = 10.4$ kcal/mol for ring opening of the phenylcyclopropylketyl anion (at 298 K), a value close to the AM1-calculated value of 7.9 kcal/mol (Table III).

Further, it is now possible to estimate lower and upper limits for k_{-1} and k_1, respectively. Assuming (a) $[6^{\bullet-}] \leq 50$ mM (the maximum concentration of starting cyclopropyl ketone in any of our experiments) and (b) $k_{-1} \geq 10k_2[6^{\bullet-}]$ (the minimum condition for k_2 to be the rate-limiting step), $k_{-1} \geq 8 \times 10^7\ s^{-1}$ and $k_1 \leq 2\ s^{-1}$. Our estimate of k_1 based upon these assumptions is within range of an estimate by Tanner, Chen, and Luelo, who via a different method of radical-anion generation place an upper limit of 12 s^{-1} on k_1 for the phenylcyclopropylketyl anion.[47]

F. Stereoelectronic Factors in the Ring Opening of Cyclopropylketyl Anions. As discussed earlier, it was not possible to study the mechanism and kinetics of electrochemical reduction of α-methylcyclopropyl ketone (**9**) because the resulting radical anion was unexpectedly stable. (At scan rates as low as 10 mV/s, the anodic/cathodic current ratio was unity.) Qualitatively, we estimate that this radical anion decays *at least 2 orders of magnitude slower* than the phenylcyclopropylketyl anion ($6^{\bullet-}$). Controlled-current electrolysis of phenyl α-methylcyclopropyl ketone yields products analogous to that observed for phenyl cyclopropyl ketone. On this basis, we *assume* that the α-methyl derivative decays by the same mechanism as $6^{\bullet-}$–$8^{\bullet-}$ (Scheme III).

Table VI. Products Arising from Coupling of Pivalophenone Ketyl Anion ($41^{\bullet-}$) and the Δ^5-Hexenyl Radical (**43**)



$(CH_2{=}CHCH_2CH_2CH_2CH_2)_2Hg$

50

product	mmol of product (% yield) organomercurial radical source[a]	alkyl bromide radical source[b]
47a	2.84×10^{-3} (30.2)	4.88×10^{-3} (37.9)
47b	4.21×10^{-4} (04.5)	2.76×10^{-4} (02.2)
48a	1.09×10^{-3} (11.6)	2.01×10^{-3} (15.6)
48b	1.94×10^{-4} (02.1)	1.60×10^{-4} (01.3)
49a	*c*	*c*
49b	1.69×10^{-4} (01.8)	9.59×10^{-4} (00.8)
50	1.01×10^{-3} (21.4)	
mass balance (%)	73	58
$P_1^{\infty}/P_2^{\infty}$	5.0	4.9
k_{2av} ($M^{-1}\ s^{-1}$)	1.3×10^8	1.7×10^8

[a] 9.4×10^{-3} mmol of RHgCl added to 25 mL of 10.31 mM ketyl anion ($41^{\bullet-}$). [b] 1.29×10^{-2} mmol of RBr added to 25 mL of 7.03 mM ketyl anion ($41^{\bullet-}$). [c] **48a** and **49a** not separable by GLC. [d] $k_2 = (P_1^{\infty}k_c)/(P_2^{\infty}[41^{\bullet-}])$; $[41^{\bullet-}]$ determined before and after addition of **42**.

Thermodynamic factors do not appear to be responsible for the sluggish decay of the α-methyl-substituted ketyl anion. The AM1-calculated enthalpy of ring opening is about 2 kcal/mol *more favorable* compared to that of the phenylcyclopropylketyl anion (Table III). Consequently, it seems unlikely that a large difference in the equilibrium constant for ring opening is responsible for the stability of the α-methyl derivative. Further, there is no compelling reason to suspect that the rate constant (k_2) for the dimerization of the distonic radical anion with the ring-closed ketyl anion would be significantly different for either **6** or **9** because both involve coupling of a primary radical with a ketyl anion.

We suggest that substitution of the methyl group at the α position induces a change in the rate-determining step from k_2 to k_1. This change in the rate-determining step is likely the result of stereoelectronic factors which retard the rate constants for both cyclopropane ring opening (k_1) and ring closing (k_{-1}).

AM1 calculations suggest that the phenylcyclopropylketyl anion adopts a "bisected" conformation (Figure 4). In this conformation, the π component of the vicinal cyclopropyl bonds (C_1–C_2 and C_1–C_3) is aligned with the adjacent π system, allowing facile ring opening. In contrast, the AM1-optimized geometry for the α-methyl derivative suggests this radical anion adopts a perpendicular conformation (Figure 5). (Introduction of the α-methyl substituent destabilizes the bisected conformation because of steric interactions.) In the perpendicular conformation, the π component of the vicinal cyclopropyl bonds are orthogonal to the π system

(43) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739.
(44) Bard, A. J.; Faulkner, L. R. *Electrochemical Methods: Fundamentals and Applications*; Wiley: New York, 1980.
(45) (a) Smid, J.; Szwarc, M. *J. Am. Chem. Soc.* **1956**, *78*, 3322. (b) Schuler, R.; Kuntz, R. *J. Phys. Chem.* **1963**, *67*, 1004.
(46) Garst, J.; Smith, C. *J. Am. Chem. Soc.* **1976**, *98*, 1520.
(47) Tanner, D. D. Personal communication, University of Alberta.

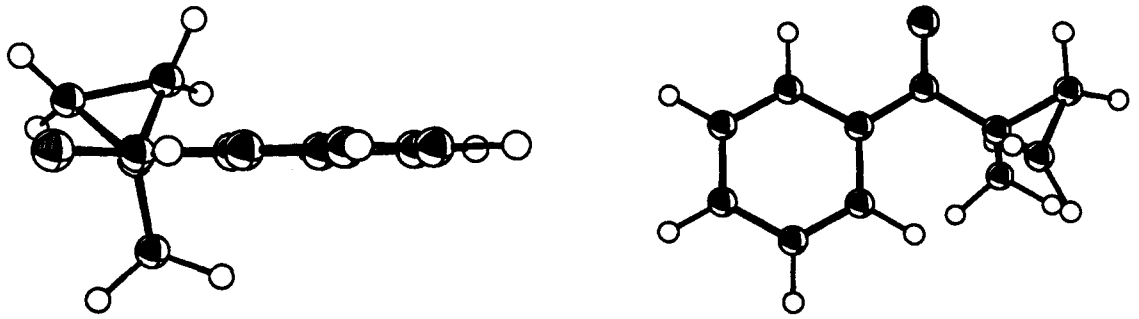
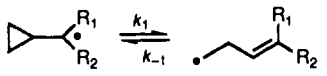


Figure 5. AM1-optimized geometry of (1-benzoyl-1-methylcyclopropyl)ketyl anion ($9^{\bullet-}$).

Table VII. Effect of Substituent on the Rate Constants for Cyclopropylcarbinyl (and Related) Ring Opening



R_1	R_2	k_1 (s^{-1})	k_{-1} (s^{-1})	ref
H	H	1×10^8	5×10^3	*a*
Ph	H	1×10^6	1×10^7	*b*
Ph	O^-	≤2	8×10^7	this work

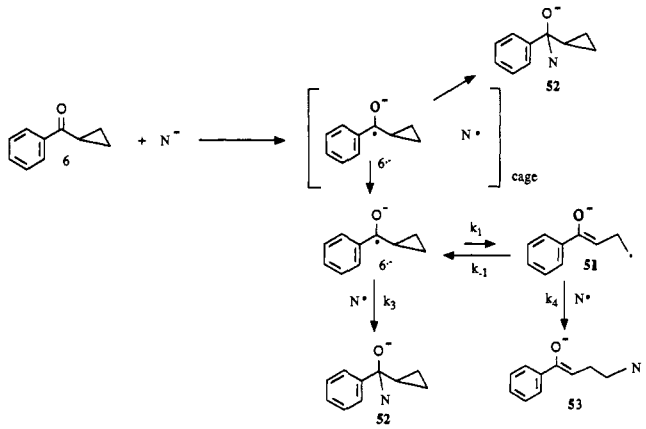
[a] Reference 29. [b] Reference 49.

of the adjacent benzoyl group and the ring opening is expected to be slower. Similar arguments regarding stereoelectronic control have been advanced to explain the regiochemistry of ring cleavage in dissolving metal reductions of rigid cyclopropyl ketones.[48]

G. Effect of α Substituents on the Rate Constant for Ring Opening of the Cyclopropylcarbinyl Radical and Related Systems. Table VII illustrates the effect of α substituents on the rate constants for ring opening of several cyclopropylcarbinyl systems. It is readily apparent the radical-stabilizing substituents (phenyl, O^-) at the α position diminish both the rate constant and equilibrium constant for ring opening, an observation also supported by the enthalpies of ring opening reported in Table III. We therefore conclude that *relief of ring strain associated with cyclopropane ring opening does not compensate for the loss of resonance energy in these systems and that this factor must be addressed in the design of substrates which might be envisioned as possible probes for radical ion intermediates in organic and bioorganic reactions.* One possible strategy to circumvent this problem would involve the placement of radical-stabilizing substituents on the cyclopropane ring (e.g., phenyl). Indeed, preliminary results have shown that, unlike any of the substrates reported herein, the radical anion generated from 1-benzoyl-2-phenylcyclopropane undergoes ring opening with a rate constant $>10^3$ s^{-1} with an AM1-calculated enthalpy of ring opening of −6 kcal/mol.[38,50,51]

H. Use of Phenyl Cyclopropyl Ketone as a SET Probe. The results reported in this paper suggest that phenyl cyclopropyl ketone is unsuitable as a probe substrate for single electron transfer. To illustrate this point, consider the hypothetical SET process depicted in Scheme VII. Reaction of nucleophile N^- with **6** generates a geminate radical anion/radical pair. If combination of these two paramagnetic species occurs before cage escape (picosecond time scale), no ring opening will be observed because the rate constant is too sluggish (time scale on the order of seconds). Even if radical anion $6^{\bullet-}$ escapes the cage and attains full equilibrium with its ring-opened counterpart ($K_{eq} \approx 10^{-8}$), the concentration of the latter species will be too low to be trapped effectively. For example, assuming that the rate constant for reaction of ketyl anion $6^{\bullet-}$ with $N^\bullet$ (k_3) is 10^8 M^{-1} s^{-1} (a reasonable estimate based upon our measured rate constant for reaction of a primary radical with a ketyl anion), in order to see a 1% yield of ring-opened product **53** the rate constant for trapping of distonic radical **51** by $N^\bullet$ (k_4) would have to be 10^{14} M^{-1} s^{-1}—several orders of magnitude greater than the diffusion-controlled limit. *Consequently, based upon our results, we conclude that even if a bonafide single-electron-transfer process were occurring, this experiment would fail to detect it.*

Scheme VII



Conclusions

Without radical-stabilizing substituents on the cyclopropane ring, arylcyclopropylketyl anions undergo a slow and reversible ring-opening reaction and, as a consequence, are not suitable probes for electron-transfer processes. The mitigating factor in these systems is that the loss of resonance energy associated with cyclopropane ring opening is not compensated by the relief of cyclopropane ring strain. While this study has focused its attention on radical anions, similar concerns are likely to pertain to cyclopropylcarbinyl-type rearrangements of radical cations as well. Consequently, we believe these issues must be considered in any study which attempts to probe for the intermediacy of paramagnetic species in chemical reactions based upon intramolecular rearrangements.

Experimental Section

General Considerations. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra (^1H, ^2H, ^{13}C) were obtained on either a 200- or 270-MHz Bruker FT NMR spectrometer. All chemical shift values are reported in δ units relative to Me_4Si (δ = 0.00 ppm) in deuteriochloroform (^2H spectra run in $CHCl_3$). Infrared spectra were recorded on a Perkin-Elmer Model 1600 FT-IR spectrometer, and IR bands are reported in cm^{-1}. Ultraviolet spectra were obtained on a Beckman Du-50 spectrophotometer and are reported with λ in units of nm and ε in units of M^{-1} cm^{-1}. Both low- and high-resolution mass spectral data were obtained from a VG Analytical Model 7070 E-HF double-focusing, magnetic sector, high-resolution mass spectrometer. Electron impact ionization (70 eV) was employed unless otherwise stated. Low-resolution GC/MS was performed on a Hewlett-Packard Model 5890 gas chro-

(48) For a review, see: Boche, G.; Walborsky, H. M. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987.
(49) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Chem. Soc., Chem. Commun.* **1990**, 923.
(50) Tanko, J. M.; Drumright, R. E. Unpublished results at Virginia Polytechnic Institute and State University.
(51) Tanner reports that the rate constants for ring opening are 2×10^6 and 3×10^5 s^{-1} for the cis and trans isomers, respectively, consistent with our published results.[38] However, because stereoisomerization is observed, it appears that this rearrangement is *also* reversible. Tanner, D. D. Personal communication, University of Alberta.

matograph with an HP methylsilicone capillary column (12 m × 0.2 mm) interfaced to an HP 5097B EI mass spectrometer and an HP series computer. Gas chromatographic analyses were performed on a Hewlett-Packard HP 5890 instrument equipped with both FID and TCD detectors and an HP 3393A reporting integrator. Analyses were accomplished on either an Alltech RSL-200 (nonpolar) capillary column (30 m × 0.25 mm) or a Supelco SE-54 (low-polarity) capillary column (15 m × 0.25 mm). Analytical and preparative HPLC separations were accomplished on a Rainin HPXL instrument using a Microsorb C-18 reversed-phase column (analytical, 5 μm, 4.6 mm i.d. × 25 cm; preparative, 5 μm, 21.4 mm i.d. × 25 cm) with acetonitrile/water solvent mixtures. Flash chromatography[52] was performed on silica gel (EM Science, 230–400 mesh) using hexane/ethyl acetate solvent mixtures (weight ratio of silica to substrate ≈200:1). Thin-layer chromatography (TLC) was performed on precoated silica gel 60 F-254 plates purchased from EM Science.

Electrochemical Measurements. Electrochemical experiments were performed using an EG&G Princeton Applied Research Model 273 potentiostat/galvanostat, interfaced (GPIB/IEEE-488) to an IBM PC-XT computer. The triangular waveform for cyclic voltammetry was generated using the Model 273 digital program generator. Data acquisition was accomplished using the Model 273 internal (100-μs) A/D converter. Using the ASYST operating language,[53] on-site software was produced for controlling the potentiostat functions, data transfer to the PC, and subsequent data analysis and storage. This menu-driven software allows the user to run an experiment, store/recall data from a disk file, and perform a variety of data analysis operations including plot (I vs t, I vs E, dI/dt vs t, or I vs E plot superimposed with data from a disk file), data smoothing/filtration, subtraction of data in a disk file from data in memory, and transfer of the data to a Lotus 123 worksheet. Derivative cyclic voltammograms were generated from the raw current vs time data from the potentiostat by interpolating a second-order polynomial through consecutive data points and taking the first derivative of the polynomial. This derivative trace was then digitally filtered, using the "smooth" function in ASYST. Via a fast Fourier transformation, the frequency spectrum of the derivative data array is generated. Convolution of the data is achieved by multiplication of the data spectrum by "the inverse Fourier transform of the 'Blackman window' for convolution weights.[53,54] The cut-off frequency for the low-pass filter (f_0), measured in cycles per point, was set according to the total number of data points (N): $f_0 = 100/N$ (within the range $0.03 \le f_0 \le 0.5$). The total number of data points (which varied with the scan rate and the magnitude of the potential scan) was always set to maximize resolution and was in the range 400 ≤ number of data points ≤ 6144.

Theoretical Considerations. Molecular mechanics calculations were performed using MMX (Serena Software, Bloomington, IN 47402-3076). Semiempirical MO calculations were performed using the AM1 approximation developed by Dewar et al.[40] and implemented through MOPAC 5.0 (QCPE 455). Full geometry optimizations were performed using UHF.

Materials. *n*-Butyllithium, tetra-*n*-butylammonium iodide, bromobenzene-d_5, pivalophenone, phenyl cyclopropyl ketone, 1-bromo-5-hexene, and (bromomethyl)cyclopentane were obtained from Aldrich. Triply distilled mercury was obtained from Bethlehem. *trans*-1-Benzoyl-2-methylcyclopropane (**7**),[55] 1-benzoyl-2,2-dimethylcyclopropane (**8**),[56] 1-benzoyl-1-methylcyclopropane (**9**),[56a,57] *p*-tolyl cyclopropyl ketone (**10**),[58] *p*-cyclopropylacetophenone (**11**),[59] and Δ^5-hexenylmercuric chloride[60] were prepared according to published procedures. Tetra-*n*-butylammonium tetrafluoroborate (n-Bu_4NBF_4) was prepared by treatment of tetra-*n*-butylammonium iodide with aqueous HBF_4 using the method of House.[61] The crude salt was thoroughly dried under vacuum (0.1 mmHg) and then recrystallized four times from ethyl acetate/pentane. After recrystallization, the salt was dried under vacuum (0.1 mmHg). Neutral alumina (activated, neutral, Brockmann I, 150 mesh) was placed under vacuum (0.5 mmHg) and heated with a flame until bumping subsided (15–60 min). *N,N*-Dimethylformamide (DMF, Aldrich HPLC grade, 99+%) was stirred over anhydrous copper(II) sulfate (10 g/L) and activated neutral alumina (30 g/L) under argon for 3 days and then distilled. The middle cut (ca. three-fourths of total volume) was saved and stored over anhydrous $CuSO_4$ under argon. Before use, the DMF was passed through a column of activated neutral alumina (2.5 cm × 20 cm) under positive argon pressure into a receptacle blanketed with argon.

Argon (Airco UN-1006) was passed through an oxygen removal tower (5.4 cm × 84.5 cm, Kontes) packed with 1 kg of BASF oxygen binding catalyst R3-11. The catalyst bed was operated at 125 °C by heating the tower with a heat cord. The argon was then passed through a moisture trap packed with 4-Å molecular sieves.

1-Benzoyl-d_5-2,2-dimethylcyclopropane (25). A 1.94-g (17-mmol) portion of 2,2-dimethylcyclopropanecarboxylic acid was dissolved in 20 mL of dry diethyl ether under Ar. The flask was cooled to −78 °C, and the lithium salt of the acid was generated by slow addition of 7.1 mL (17.85 mmol) of 2.5 M *n*-butyllithium in hexane. In a separate flask 2.50 g (15.4 mmol) of bromobenzene-d_5 was dissolved in 20 mL of dry diethyl ether under Ar. The flask was cooled to −78 °C, and 6.5 mL (16.2 mmol) of 2.5 M *n*-butyllithium in hexane was slowly added with stirring. The reaction mixture was stirred and allowed to warm to 0 °C over the course of 2 h. The resulting (phenyl-d_5)lithium (at 0 °C) was then slowly transferred via a cannula into the lithium salt of 2,2-dimethylcyclopropanecarboxylic acid (at −78 °C). The reaction mixture was allowed to warm to room temperature over the course of 1.5 h and then stirred for 1 h. The flask was cooled to 0 °C and the reaction mixture quenched with 20 mL of saturated aqueous ammonium chloride solution and acidified with concentrated HCl. The organic layer was separated, washed twice with water, dried over magnesium sulfate, and concentrated. Flash chromatography (5% ethyl acetate, 95% hexane) followed by short-path distillation yielded 42% of a colorless oil: bp 52–56 °C, 0.1 mm; ^1H NMR ($CDCl_3$) δ 0.9 (m, 1 H), 1.1 (s, 3 H), 1.35 (s, 3 H), 1.55 (m, 1 H), 2.45 (m, 1 H); ^2H NMR ($CHCl_3$) δ 7.50 (s, 3 D), 8.0 (s, 2 D); IR 2949, 2871, 2280, 1669, 1564, 1458, 1436, 1401, 1181, 1117, 991; MS m/e (relative intensity) 181 (0.9), 180 (6.5), 179 (M^+, 37), 178 (2.6), 177 (2.0), 164 (19), 155 (21), 110 (100).

Voltammetric Measurements (General). Voltammetric measurements were performed on solutions which contained 0.5 M n-Bu_4NBF_4 in DMF. The solutions were prepared by weighing n-Bu_4NBF_4 into a oven-dried volumetric flask and then placing the volumetric flask in a desiccator under vacuum (0.02–0.05 mmHg) for approximately 24 h to remove any last traces of moisture from the electrolyte. The desiccator was then filled with argon and the volumetric flask removed and sealed with a septum. The appropriate quantity of electroactive substrate was then added to the volumetric flask. Purified DMF was percolated under argon through a column of neutral activated alumina (2.5 cm × 20 cm) into the volumetric flask (blanketed with argon). The resulting solution was transferred to an oven-dried voltammetry cell (blanketed with argon and containing $^1/_2$ g of activated neutral alumina) through a short plug of activated neutral alumina under positive argon pressure. The solution was purged with argon and stirred with neutral activated alumina (ca. 0.5 g) 20–30 min. A standard three-electrode voltammetry cell was utilized. The gold working electrode (1.6-mm diameter) was purchased from Bioanalytical Systems (BAS). The working electrode was prepared for use by polishing with alumina slurry as outlined in the BAS electrode polishing kit (Part No. MF-2056). The reference electrode was fabricated by sealing a 5-mm length of 4-mm-diameter porous Vycor rod to a 4-mm-o.d. Pyrex tube with Teflon heat shrink tubing. The other end of the Pyrex tube was attached to a bridge tube with Teflon heat shrink tubing. The electrode case was filled with 0.1 M $AgNO_3$ in acetonitrile, and a silver wire inserted through a septum was placed in contact with the filler solution. A Pt auxiliary electrode was used (separated from the working solution by a Vycor-tipped bridge tube). Positive-feedback iR compensation was set by monitoring the current response (oscilloscope) to a square potential step waveform applied to the electrometer by the potentiostat. iR compensation was increased until the potentiostat began to oscillate and was then backed off to 85% of that value. All experiments were performed at ambient temperature (23 °C) unless otherwise

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stated. Variable-temperature studies were performed using a jacketed electrochemical cell and a variable-temperature circulating bath. The solutions were blanketed (positive pressure) with argon throughout the experimental sequence. Each result represents the numerical average of a minimum of three experiments.

Bulk Electrolyses (General). All experiments were performed on solutions which contained 0.2 M n-Bu_4NBF_4 in DMF. A conventional H-cell, with the two compartments separated by a medium glass frit (22 mm in diameter), was utilized. The blank solutions were prepared as described above. Fifty milliliters of the electrolyte solution was partitioned equally between the two compartments of the electrolysis cell under argon. The electroactive substrate was added to the cathodic compartment, and both anodic and cathodic compartments were purged for at least 30 min with argon before electrolysis. A 0.127 mm × 25 mm × 25 mm piece of gold foil served as the working electrode. All electrolysis experiments were performed at ambient temperature (23 °C). Constant-current electrolyses were performed at currents from 35 to 50 mA. Constant-potential electrolyses were performed at potentials approximately 300 mV beyond the cyclic voltammetry peak potential. Positive-feedback iR compensation for controlled-potential electrolyses was set as described earlier. After electrolysis, the cathodic compartment was quenched (5% aqueous HCl) and the contents were poured into 30–40 mL of water and extracted four times with 20-mL portions of diethyl ether. The organic layers were combined and washed three times with water, dried over magnesium sulfate, and evaporated. The products were then separated by flash column chromatography and characterized. Product yields and spectral data are summarized below.

A. Phenyl Cyclopropyl Ketone (6). A 148-mg (1.01-mmol) portion of **6** was electrolyzed at 35 mA for 45 min (0.97 equiv of electrons), giving the following.

(1) 21 mg (14%) of recovered starting material.

(2) 61 mg (41%) of dimer **15a**: ^{1}H NMR ($CDCl_3$) δ 0.95 (m, 2 H), 1.15 (m, 2 H), 1.5–1.8 (m, 4 H), 2.0 (s, 1 H), 2.6 (m, 3 H), 4.6 (m, 1 H), 7.25 (m, 7 H), 7.85 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 11.29 (CH_2), 16.91 (CH), 27.15, 35.67, and 38.47 (CH_2), 74.34 (CHO), 125.77, 127.56, 128.18, and 128.47 (CH), 135.83, 144.67, 147.64 (C), 200.15 (C=O); IR 3448, 3028, 2938, 2860, 1664, 1606, 1568, 1385, 1230, 994, 701; MS m/e (relative intensity) 294 (M^+, 11), 276 (48), 253 (10), 172 (80), 160 (100), 104 (95), 79 (45); HRMS for $C_{20}H_{22}O_2$, calcd 294.161 980 2, found 294.158 203, error 12.8 ppm.

(3) 11 mg (7%) of dimer **16a**: ^{1}H NMR ($CDCl_3$) δ 0.2–0.5 (m, 4 H), 1.3 (m, 1 H), 1.6–2.1 (m, 5 H), 2.95 (t, 2 H, J = 6.1 Hz), 7.2–7.6 (m, 8 H), 7.95 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 0.78, 1.57, and 18.68 (CH_2), 22.19 (CH), 38.68, and 41.88 (CH_2), 75.01 (CO), 125.71, 126.74, 128.65, and 132.99 (CH), 137.28, and 146.51 (C), 200.34 (C=O); IR 3476, 3008, 2931, 1678, 1597, 1580, 1446, 754, 599; MS m/e (relative intensity) 276 ($M^+ - H_2O$, 14), 253 (8), 171 (14), 147 (68), 129 (35), 105 (100), 91 (22), 77 (57).

(4) 16.5 mg (11%) of trimer **18a**: ^{1}H NMR ($CDCl_3$) δ 0.95 (m, 2 H), 1.15 (m, 2 H), 1.5–1.9 (m, 10 H), 2.65 (m, 5 H), 4.6 (m, 2 H), 7.1–7.4 (m, 11 H), 7.95 (m, 2 H); IR 3417, 3026, 2936, 2859, 1657, 1606, 1568, 1385, 1230, 993, 758, 700; MS m/e (relative intensity) 424 ($M^+ - H_2O$, 7), 406 ($M^+ - 2H_2O$, 27), 289 (40), 247 (25), 160 (48), 129 (95), 117 (98), 91 (100), 69 (75).

B. *trans*-1-Benzoyl-2-methylcyclopropane (7). A 166-mg (1.03-mmol) portion of **7** was electrolyzed at 35 mA for 47 min (0.99 equiv of electrons), giving the following.

(1) 29 mg (17%) of recovered starting material.

(2) 85 mg (51%) of dimer **15b**: ^{1}H NMR ($CDCl_3$) δ 0.85 (m, 1 H), 1.25 (m, 6 H), 1.4–1.8 (m, 6 H), 2.1 (s, 1 H), 2.35 (m, 1 H), 2.8 (m, 1 H), 4.6 (m, 1 H), 7.3 (m, 7 H), 7.9 (m, 2 H); ^{13}C NMR δ 18.44 (CH_3), 20.08 (CH_2), 21.18 (CH), 22.35 (CH_3), 26.47 (CH), 34.16, 37.20 (CH_2), 40.15 (CH), 74.70 (CH), 126.02, 127.28, 127.67, 128.46, and 128.61 (CH), 136.35, 144.85, and 152.70 (C), 199.87 (C=O); IR 3448, 3028, 2967, 2928, 2868, 1660, 1605, 1569, 1493, 1331, 1228, 1182, 850, 700; MS m/e (relative intensity) 322 (M^+, 4), 304 (26), 267 (9), 161 (100), 145 (85), 117 (45), 107 (50), 79 (55); HRMS for $C_{22}H_{26}O_2$, calcd 322.193 280 3, found 322.1920, error 4.0 ppm.

(3) 10 mg (6%) of dimer **16b**.

(4) 34 mg (15%) of trimer **18b**.

(5) 9 mg (5%) of tetramer **19b**.

Spectral data for **16b**, **18b**, and **19b** are available as supplementary material.

C. 1-Benzoyl-2,2-dimethylcyclopropane (8). Electrolysis of 158 mg (0.91 mmol) of **8** at 35 mA for 42 min (1 equiv of electrons) yielded the following.

(1) 27 mg (17%) of recovered starting material.

(2) 63 mg (40%) of dimer **15c**: ^{1}H NMR ($CDCl_3$) δ 0.9 (m, 1 H), 1.1 (s, 3 H), 1.30 (two close singlets, 6 H), 1.35 (s, 3 H), 1.4–1.6 (m, 5 H), 2.0 (s, 1 H), 2.45 (m, 1 H), 4.55 (m, 1 H), 7.2–7.4 (m, 7 H), 7.9 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 18.55 (CH_3), 21.92 (CH_2), 26.53 (C), 27.07, 28.73, and 28.20 (CH_3), 32.85 (CH), 34.19 (CH_2), 37.87 (C), 40.04 (CH_2), 74.99 (CH), 125.92, 127.57, 127.94, and 128.49 (CH), 136.70, and 154.11 (C), 198.30 (C=O); IR 3450, 3030, 2959, 2868, 1659, 1609, 1560, 1455, 1391, 1272, 1222, 1188, 1103, 1047, 997, 906, 857, 801, 759, 695; MS m/e (relative intensity) 350 (M^+, 35), 332 (12), 281 (30), 263 (12), 215 (100); HRMS for $C_{24}H_{30}O_2$, calcd 350.224 580 5, found 350.225 220, error 1.8 ppm.

(3) 28 mg (17%) of trimer **18c**.

(4) 13 mg (7%) of tetramer **19c**.

Spectral data for **18c** and **19c** are available as supplementary material.

D. 1-(Benzoyl-d_5)-2,2-dimethylcyclopropane (25). A 150-mg (0.84-mmol) portion of **25** was electrolyzed at 35 mA for 25 min (0.64 equiv of electrons), giving the following.

(1) 35 mg (23%) of recovered starting material.

(2) 36 mg (24%) of dimer **29**: ^{1}H NMR ($CDCl_3$) δ 0.9 (m, 1 H), 1.1 (s, 3 H), 1.30 (two close singlets, 6 H), 1.35 (s, 3 H), 1.4–1.6 (m, 5 H), 1.9 (m, 1 H), 2.45 (m, 1 H); ^{2}H NMR ($CHCl_3$) δ 4.45 (s, 1 D), 7.2–7.4 (s, 7 D), 7.9 (s, 2 D); IR 3447, 2951, 2869, 2276, 2113, 1663, 1577, 1540, 1458, 1418, 1387, 1182, 1116, 1089, 991; MS m/e (relative intensity) 360 (M^+, 55), 342 (22), 291 (45), 219 (100).

(3) 20 mg (13%) of trimer **18c**-d_{15}.

(4) 9 mg (6%) of tetramer **19c**-d_{20}.

Spectral data for **18c**-d_{15} and **19c**-d_{20} are available as supplementary material.

E. Coelectrolysis of 1-Benzoyl-2,2-dimethylcyclopropane (8) and 1-(Benzoyl-d_5)-2,2-dimethylcyclopropane (25). Portions of 70.2 mg (0.39 mmol) and 68.5 mg (0.39 mmol) of **8** and **25**, respectively (total 0.78 mmol), were electrolyzed for 36 min at 35 mA (1 equiv of electrons), giving the following.

(1) 19 mg (ca. 14%) of recovered starting material (mixture of H/D).

(2) 38 mg (ca. 27%) of dimer **15c** (mixture of H/D): MS m/e (relative intensity) 350 (1.000), 351 (0.290), 352 (0.061), 353 (0), 354 (0.088), 355 (1.430), 356 (0.377), 357 (0.079), 358 (0.026), 359 (0), 360 (0.597), 361 (0.184), 362 (0.035); MS m/e (relative intensity) of fully hydrido dimer 350 (1.000), 351 (0.274), 352 (0.044); MS m/e (relative intensity) of fully deuteriated dimer 360 (1.000), 361 (0.365), 362 (0.068).

(3) 27 mg (ca. 19%) of trimer **18c** (mixture of H/D).

(4) 11 mg (8%) of tetramer **19c** (mixture of H/D).

F. *p*-Tolyl Cyclopropyl Ketone (10). A 153-mg (0.95-mmol) portion of **10** was electrolyzed at 35 mA for 44 min (1.01 equiv of electrons), giving the following.

(1) 22 mg (22%) of recovered starting material.

(2) 17 mg (11%) of *p*-tolyl propyl ketone (**37**): ^{1}H NMR ($CDCl_3$) δ 1.0 (t, 3 H, J = 8.3 Hz), 1.8 (m, 2 H), 2.4 (s, 3 H), 2.95 (t, 2 H, J = 8.2 Hz), 7.25 (d, 2 H, J = 12.0 Hz), 7.85 (d, 2 H, J = 12.0 Hz); ^{13}C NMR ($CDCl_3$) δ 13.87 (CH_3), 17.92 (CH_2), 21.53 (CH_3), 40.43 (CH_2), 128.18 and 129.19 (CH), 134.81, 143.50 (C), 201.32 (C=O); IR 3031, 2962, 2930, 2874, 1683, 1607, 1573, 1457, 1409, 1366, 1274, 1223, 1208, 1181, 1000, 897, 809, 748; MS m/e (relative intensity) 162 (12), 147 (15), 119 (100), 91 (47), 65 (22).

(3) 38 mg (25%) of dimer **35**: ^{1}H NMR ($CDCl_3$) δ 0.35 (m, 2 H), 0.45 (m, 2 H), 1.3 (m, 1 H), 1.6–2.1 (m, 5 H), 2.3 (s, 3 H), 2.4 (s, 3 H), 2.95 (t, 2 H), 7.1–7.4 (m, 6 H), 7.8 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 0.66 and 1.36 (CH_2), 18.63 (CH_2), 20.94, and 21.59 (CH_3), 21.99 (CH), 38.47 and 41.83 (CH_2), 74.80 (CH), 125.52, 128.17, 128.72, and 129.18 (CH), 134.60, 136.06, 143.33, and 143.63 (C), 199.98 (C=O); IR 3476, 3005, 2922, 2870, 1677, 1607, 1572, 1512, 1453, 1407, 1181, 1020, 807; MS m/e (relative intensity) 322 (0.8), 304 (10), 281 (4), 185 (35), 158 (55), 143 (86), 119 (100), 105 (40), 91 (80).

(4) 12 mg (8%) of dimer **36**: ^{1}H NMR ($CDCl_3$) δ 0.9–1.1 (m, 2 H), 1.2–1.4 (m, 2 H), 1.6–1.8 (m, 5 H), 2.2–2.4 (m, appears to be two closely spaced singlets masking a multiplet, 7 H), 2.75–2.85 (m, 2 H), 4.7 (m, 1 H), 7.1–7.3 (m, 6 H), 7.65 (d, 1 H); IR 3473, 3007, 2925, 2858, 1671, 1609, 1513, 1457, 1377, 1219, 1063, 1034, 990, 817; MS m/e (relative intensity) 322 (0.8), 304 (9), 174 (65), 161 (100), 119 (82), 105 (30), 91 (45), 77 (21).

(5) 7 mg (4%) of trimer **38**: ^{1}H NMR ($CDCl_3$) δ 0.8–1.3 (m, 4 H), 1.4–1.8 (m, 10 H), 2.3–2.5 (m, 10 H), 2.6–2.9 (m, 4 H), 4.65 (m, 2 H), 7.0–7.4 (m, 9 H), 7.9 (d, 1 H); IR 3456, 2929, 2857, 1676, 1608, 1512, 1452, 1408, 1379, 1263, 1219, 1181, 816, 732.

G. 1-Benzoyl-1-methylcyclopropane (9). A 157-mg (0.98-mmol) portion of **9** was electrolyzed 45 min at 35 mA (1 equiv of electrons), giving the following.

(1) 15 mg (10%) of recovered starting material.

(2) 65 mg (41%) of dimer **15d**: ^{1}H NMR ($CDCl_3$) δ 0.65 (m, 2 H), 0.85 (d, 3 H), 1.1 (m, 2 H), 1.35 (m, 4 H, looks like singlet of 3 H masking multiplet of 1 H), 1.7 (m, 2 H), 1.9 (s, 1 H), 2.55 (m, 2 H), 4.5 (m, 1 H), 7.0–7.3 (m, 7 H), 7.65 (d, 2 H); ^{13}C NMR ($CDCl_3$) δ

14.49 (CH_3), 14.80 (CH_2), 22.09 (CH_3), 24.35 (C), 33.40 and 34.41 (CH_2), 39.65 and 77.93 (CH), 126.32, 127.33, 128.18, and 128.58 (CH), 134.97, 143.43, and 146.85 (C), 203.58 (C=O); IR 3463, 3084, 3060, 3023, 2964, 2931, 2875, 1670, 1606, 1568, 1452, 1333, 1216, 1176, 1026, 988, 702; MS *m/e* (relative intensity) 322 (4.5), 304 (2.5), 267 (6), 174 (100), 118 (45), 107 (50); HRMS for $C_{22}H_{26}O_2$, calcd 322.193 280 3, found 322.1962, error 9.0 ppm.

(3) 19 mg (12%) of (1-methylcyclopropyl)phenylcarbinol (**17d**): ^{1}H NMR ($CDCl_3$) δ 0.3 (m, 2 H), 0.6 (m, 2 H), 0.9 (s, 3 H), 1.8 (s, 1 H), 4.1 (s, 1 H), 7.1–7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 11.20 (CH_2), 18.33 (CH_3), 21.84 (C), 79.74 (CH), 126.22, 127.16, 127.97, 128.26, 128.57; IR 3442, 3064, 2961, 1450, 1026, 725, 700; MS *m/e* (relative intensity) 162 (1.5), 161 (2.8), 160 (2.0), 134 (100), 91 (25).

(4) 14 mg (9%) of trimer **18d**: ^{1}H NMR ($CDCl_3$) δ 0.65 (m, 2 H), 0.85 (m, 6 H), 1.2 (m, 2 H), 1.35 (m, 5 H), 1.6–1.9 (m, 6 H), 2.55 (m, 4 H), 4.5 (m, 2 H), 7.0–7.3 (m, 11 H), 7.7 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.41, 14.60, 14.89, 22.11, 25.39, 29.69, 30.10, 33.09, 33.46, 34.43, 34.78, 35.04, 35.22, 38.79, 39.69, 40.93, 77.98, 126.07, 126.37, 127.28, 128.19, 128.59, 129.27, 140.85, 141.16, 143.64; IR 3444, 3060, 3026, 2963, 2931, 2874, 1665, 1606, 1452, 1333, 1216, 1177, 1027, 988, 758, 702; MS *m/e* (relative intensity) 466 ($M^+ - H_2O$, 3), 448 ($M^+ - 2H_2O$, 6), 360 (7), 174 (100), 145 (40), 131 (35), 105 (42), 91 (65).

H. *p*-Cyclopropylacetophenone (11). A 160-mg (1.0-mmol) portion of **11** was electrolyzed for 46 min at 35 mA (1 equiv of electrons), giving the following.

(1) 35 mg (22%) of starting material.

(2) 65 mg (40%) of dimer **40**: ^{1}H NMR ($CDCl_3$) δ 0.65 (m, 4 H), 0.95 (m, 4 H), 1.45 (s, 6 H), 1.90 (m, 2 H), 2.6 (s, 2 H), 6.95 (d, 4 H, J = 11.5 Hz), 7.1 (d, 4 H, J = 11.5 Hz); ^{13}C NMR ($CDCl_3$) δ 9.17 (CH_2), 14.96 (CH), 25.03 (CH_3), 78.75 (C), 124.36, and 127.27 (CH), 140.62 and 142.62 (C); IR 3456, 3081, 3001, 2935, 2872, 1613, 1514, 1459, 1371, 1193, 1144, 1069, 922, 903, 830, 733; MS *m/e* (relative intensity) 322 (0.2), 304 (0.3), 286 (0.5), 261 (24), 161 (100).

Competition Experiments to Determine Rate Constant for Coupling of a Primary Alkyl Radical with a Ketyl Anion. The electrochemical cell for these experiments was analogous to the previously described electrolysis experiments. A mercury pool was used as a working electrode instead of a gold flag. In addition, a platinum voltammetry electrode (0.5-mm diameter) was inserted into the cathodic compartment. In voltammetry mode, the 0.5-mm Pt electrode was used as the working electrode and the Hg pool as the auxiliary electrode. Positive-feedback *iR* compensation was set as described earlier.

The anodic compartment was charged with 25 mL of 0.2 M *n*-Bu_4NBF_4 in DMF and the cathodic compartment charged with an identical solution also containing a known concentration of pivalophenone. The cell was stirred and purged with argon for 30 min and then blanketed with argon. The potential of the voltammetry electrode was stepped to −2.9 V (pivalophenone E^0 = −2.48 V (Ag/Ag^+)), and the current decay was monitored as a function of time in order to measure the constant term ($nFAD_0^{1/2}/\pi^{1/2}$) in the Cottrell equation.[44] Because the initial concentration of pivalophenone is known, a plot of $i(t)$ vs $1/t^{1/2}$ yields a line from which the constant term of the Cottrell equation can be computed. (Cottrell equation: $i(t) = [nFAD^{1/2}/\pi^{1/2}][C_0^*/t^{1/2}]$. Note that the diffusion coefficient D_0 is taken to be the same for both pivalophenone and its ketyl anion.) The stirring and purging was restarted, and the electrode leads were switched to electrolysis mode. Constant-current electrolysis (50 mA) was performed to generate pivalophenone ketyl anion. The cell was then switched back to voltammetry mode. The potential of the Pt voltammetry electrode was stepped to −1.9 V and current decay monitored as a function of time to give an upper limit for the ketyl anion concentration. A small amount ($\leq 1/20$ equiv) of 1-bromo-5-hexene or 5-hexenylmercuric chloride dissolved in 1 mL of DMF was then added dropwise to the cathodic compartment with vigorous stirring and purging. After addition was complete, the potential of the voltammetry electrode was stepped to −1.9 V and current decay monitored as a function of time to give a lower limit for the ketyl anion concentration.

The cathodic compartment was quenched with 5% aqueous HCl and poured into water. A known amount of diphenyl ether was added and the solution extracted four times with 20-mL portions of diethyl ether. The organic layers were combined, washed three times with water, and dried over magnesium sulfate. The product distribution was assessed by GC. Response factors for independently synthesized authentic samples (vide infra) were determined relative to diphenyl ether.

Independent Synthesis of Pivalophenone Ketyl Anion/Free Radical Coupling Products. Constant-current electrolyses of pivalophenone were performed in an H-cell with a gold electrode as described above. During the course of the electrolysis either 1-bromo-5-hexene or (bromomethyl)cyclopentane in 2 mL of DMF was slowly added dropwise. Addition of the bromide was controlled so that the ketyl anion color (reddish black) was never fully dissipated. After the electrolysis/addition was complete, the cathodic compartment was quenched with 5% aqueous HCl and poured into water. The aqueous layer was extracted four times with 25-mL portions of diethyl ether. The organic layers were combined, washed three times with water, dried over magnesium sulfate, and concentrated. The crude reaction mixtures were separated by preparative HPLC.

A. Coupling of Pivalophenone Ketyl Anion and Δ^5-Hexenyl Radical. Pivalophenone (252 mg, 1.56 mmol) was electrolyzed for 72 min at 35 mA (1 equiv of electrons). After 10 min of electrolysis, addition of 140 mg (0.86 mmol) of 1-bromo-5-hexene in 2 mL of DMF was added slowly during the remainder of the electrolysis. The cathodic compartment was quenched, worked up, and chromatographed (80% acetonitrile, 20% water) to yield the following.

(1) 17 mg (8%) of **49a**: ^{1}H NMR ($CDCl_3$) δ 0.8 (s, 9 H), 1.0–1.4 (m, 4 H), 1.5–2.2 (m, 5 H), 4.85 (m, 2 H), 5.7 (m, 1 H), 7.1–7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 23.48 (CH_2), 25.82 (CH_3), 29.58, 33.64, and 34.57 (CH_2), 38.48, and 80.99 (C), 114.27 (CH_2), 126.15, 127.09, 127.55, 138.89 (CH), 143.34 (C); IR 3608, 3061, 3023, 2959, 2872, 1640, 1603, 1493, 1481, 1496, 1446, 1393, 1366, 1262, 1108, 1071, 909, 805, 757, 709; MS (GC/MS) *m/e* (relative intensity) 231 (M^+-15, 0.8), 189 (34.14), 171 (3.16), 133 (6.06), 105 (100), 91 (9.43), 77 (16.65).

(2) 15 mg (7%) of **48a**: ^{1}H NMR ($CDCl_3$) δ 1.1–1.4 (m, 15 H), 1.95 (m, 2 H), 2.75 (m, 2 H), 3.25 (m, 1 H), 4.85 (m, 2 H), 5.7 (m, 3 H), 6.4 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.20, and 26.92 (CH_2), 28.60 (CH_3), 29.10, 33.72, and 34.97 (CH_2), 35.20 (CH), 43.95 (C), 114.19 (CH_2), 122.24, 129.75, 130.37, and 139.04 (CH), 140.14 (C), 209.83 (C=O); IR 3076, 3028, 2930, 2859, 1661, 1640, 1630, 1477, 1461, 1418, 1394, 1366, 1262, 1155, 910; UV (methanol) 244 (2516); MS (GC/MS) *m/e* (relative intensity) 247 (0.71), 246 (M^+, 5.15), 245 (7.96), 189 (29.56), 163 (15.77), 145 (9.20), 129 (20.79), 105 (49.32), 91 (100), 77 (31.63), 57 (82); HRMS for $C_{17}H_{26}O$, calcd 246.198 365 7, found 246.196 077, error 9.3 ppm.

(3) 48 mg (23%) of **47a**: ^{1}H NMR ($CDCl_3$) δ 1.3–1.5 (m, 11 H, singlet for *tert*-butyl masking multiplet), 1.6 (m, 2 H), 2.05 (m, 2 H), 2.6 (t, 2 H, J = 6.9 Hz), 4.95 (m, 2 H), 5.8 (m, 1 H), 7.15 (d, 2 H, J = 8.3 Hz), 7.65 (d, 2 H, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 28.09 (CH_3), 28.40, 30.44, 33.49, 35.59, and 114.43 (CH_2), 122.48, 127.95, and 128.26 (CH), 138.57, 145.99 (C); IR 3076, 3026, 2969, 2931, 2858, 1672, 1640, 1607, 1477, 1461, 1412, 1394, 1366, 1277, 1196, 1172, 962, 910, 762, 708; MS *m/e* (relative intensity) 245 (0.7), 244 (M^+, 3.5), 187 (100), 91 (65), 77 (21), 57 (60); HRMS for $C_{17}H_{24}O$, calcd 244.182 715 6, found 244.181 885, error 3.4 ppm.

B. Coupling of Pivalophenone Ketyl Anion and Cyclopentylcarbinyl Radical. Pivalophenone (244 mg, 1.50 mmol) was electrolyzed for 69 min (1 equiv of electrons). After 10 min of electrolysis, addition of 135 mg (0.83 mmol) of (bromomethyl)cyclopentane in 2 mL of DMF was added slowly during the remainder of the electrolysis. The cathodic compartment was quenched, worked up, and chromatographed (80% acetonitrile, 20% water) to yield the following.

(1) 20 mg (10%) of **49b**: ^{1}H NMR ($CDCl_3$) δ 0.8 (s, 9 H), 1.0–1.8 (m, 11 H), 2.3 (m, 1 H), 7.1–7.5 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 25.90 (CH_3), 34.26 and 34.84 (CH_2), 36.53 (CH), 38.63 (C), 40.59 (CH_2), 81.53 (C), 126.07, 126.93, and 127.64 (CH), 144.05 (C); IR 3630, 3086, 3058, 3022, 2955, 2870, 1600, 1446, 1393, 1365, 1071, 757, 709; MS (GC/MS) *m/e* (relative intensity) 231 (M^+-15, 0.5), 189 (100), 121 (20), 105 (32), 91 (15), 77 (30), 57 (45).

(2) 22 mg (10%) of **48b**: ^{1}H NMR ($CDCl_3$) δ 0.7–1.8 (m, 20 H), 2.8 (m, 2 H), 3.3 (m, 1 H), 5.65 (m, 1 H), 5.9 (m, 1 H), 6.4 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.18 (CH_2), 28.63 (CH_3), 32.23, 33.79, (CH_2), 34.75, 37.39 (CH), 42.62 (CH_2), 43.87 (C), 121.85, 129.88, and 130.13 (CH), 141.00 (C), 209.76 (C=O); IR 3030, 2956, 2860, 1661, 1630, 1476, 1460, 1418, 1394, 1365, 1261, 1155, 1024, 801, 708; UV (methanol) 242 (1820); MS (GC/MS) *m/e* (relative intensity) 247 (0.45), 246 (2.77), 189 (4.45), 164 (12.42), 107 (100), 93 (4.59), 77 (10.22), 57 (21.88); HRMS for $C_{17}H_{26}O$, calcd 246.198 365 7, found 246.199 417, error 4.3 ppm.

(3) 58 mg (29%) of **47b**: ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9 H), 1.4–1.8 (m, 8 H), 2.05 (m, 1 H), 2.6 (d, 2 H, J = 9.1 Hz), 7.15 (d, 2 H, J = 10.2 Hz), 7.65 (d, 2 H, J = 10.2 Hz); ^{13}C NMR ($CDCl_3$) δ 24.91 (CH_2), 28.18 (CH_3), 32.50 (CH_2), 41.65 (CH), 41.95 (CH_2), 44.06 (C), 128.24 and 128.40 (CH), 135.70 and 145.82 (C); IR 2962, 2869, 1675, 1607, 1476, 1458, 1411, 1261, 1098, 1019, 801; MS (GC/MS) *m/e* (relative intensity) 245 (0.12), 244 (M^+, 0.64), 201 (0.84), 187 (100), 119 (6.08), 91 (14.19), 77 (2.22), 57 (5.76); HRMS for $C_{17}H_{24}O$, calcd 244.182 715 6, found 244.180 450, error 9.3 ppm.

C. Di-5-hexenylmercury (50). Pivalophenone (255 mg, 1.57 mmol) was electrolyzed for 60 min at 35 mA (0.83 equiv of electrons). After electrolysis, 171.5 mg (0.54 mmol) of 5-hexenylmercuric chloride was added (neat) to the cathodic compartment. The reaction was stirred for

5 min under argon, quenched with 5% aqueous HCl, worked up, and flash chromatographed with 5/95 ethyl acetate/hexane to yield 84 mg (42%) of di-5-hexenylmercury (**50**): ^{1}H NMR ($CDCl_3$) δ 1.05 (t, 4 H, J = 8.1 Hz), 1.45 (m, 4 H), 1.85 (m, 4 H), 2.05 (m, 4 H), 4.95 (m, 4 H), 5.80 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 28.30, 33.70, 34.68, 44.07, and 114.06 (CH_2), 139.33 (CH); IR 3075, 2921, 2845, 1640, 1458, 994, 908; MS (chemical ionization) m/e (relative intensity) 369 (7.5), 368 (6.7), 367 (27.0), 366 (15.1), 365 (19.8), 364 (13.5), 363 (7.1), 117 (100).

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Registry No. 6, 3481-02-5; **6**$^{\bullet-}$, 127793-45-7; **7**, 126525-21-1; **7**$^{\bullet-}$, 127909-63-1; **8**, 5685-43-8; **8**$^{\bullet-}$, 127793-46-8; **9**, 26921-44-8; **9**$^{\bullet-}$, 138354-12-8; **10**, 7143-76-2; **10**$^{\bullet-}$, 138354-13-9; **11**, 6921-45-5; **11**$^{\bullet-}$, 138354-14-0; **15a**, 138354-22-0; **15c**, 127793-52-6; **15d**, 138354-28-6; **16a**, 127793-49-1; **16b**, 127793-51-5; **17d**, 116215-96-4; **18a**, 138354-23-1; **18b**, 138354-15-1; **18c**, 138354-17-3; **18c**-d_{15}, 138354-19-5; **18d**, 138354-29-7; **19b**, 138354-16-2; **19c**, 138354-18-4; **19c**-d_{20}, 138354-20-8; **25**, 138354-21-9; **29**, 138354-24-2; **35**, 138354-25-3; **36**, 138354-26-4; **37**, 4160-52-5; **38**, 138354-27-5; **40**, 138354-30-0; **41**, 938-16-9; **41**$^{\bullet-}$, 54978-96-0; **42**, 2695-47-8; **43**, 16183-00-9; **45**, 23907-66-6; **47a**, 138354-33-3; **47b**, 138354-36-6; **48a**, 138354-32-2; **48b**, 138354-35-5; **49a**, 138354-31-1; **49b**, 138354-34-4; **50**, 39179-43-6; Δ^5-hexenylmercuric chloride, 63668-13-3.

Supplementary Material Available: DCV reaction order plots for decay of **6**$^{\bullet-}$, **7**$^{\bullet-}$, **8**$^{\bullet-}$, **10**$^{\bullet-}$, and **11**$^{\bullet-}$, plots for the determination of the apparent activation energy for decay of **6**$^{\bullet-}$, **7**$^{\bullet-}$, and **8**$^{\bullet-}$, plots of peak potential (E_p) vs log C_A and E_p vs ln ν for **8**, plots of $\nu_{0.5}$ vs ln ($1/\nu$) for decay of **6**$^{\bullet-}$, **7**$^{\bullet-}$, **8**$^{\bullet-}$, and **10**$^{\bullet-}$, predicted and observed mass spectral peak intensities for the coelectrolysis of **25** and **8**, results of Δ^5-hexenyl radical competition experiments using 1-bromo-5-hexene and 5-hexenylmercuric chloride as radical sources, and spectral data for **16b**, **18b**,**c**, **19b**,**c**, **18c**-d_{20}, and **19c**-d_{20} (11 pages). Ordering information is given on any current masthead page.

Design, Synthesis, and Kinetic Evaluation of a Unique Class of Elastase Inhibitors, the Peptidyl α-Ketobenzoxazoles, and the X-ray Crystal Structure of the Covalent Complex between Porcine Pancreatic Elastase and Ac-Ala-Pro-Val-2-Benzoxazole

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Abstract: Peptidyl α-ketobenzoxazoles **1** and **2** are potent, competitive, reversible inhibitors of the serine proteinases HLE and PPE. These inhibitors were designed to inactivate the enzyme by interacting with both the serine hydroxyl group and the histidine imidazole ring of the catalytic triad. The X-ray crystal structure determination of **2** bound to PPE confirms the covalent attachment of the inhibitor's carbonyl carbon atom to the hydroxyl group of the active site Ser-195. The nitrogen atom of the benzoxazole ring participates in a hydrogen-bonding interaction with His-57. This is the first example of a reversible inhibitor designed to take advantage of the binding opportunities afforded by both the serine and the histidine of the catalytic triad in serine proteinases.

Introduction

Elastases (EC 3.4.21.11) are possibly the most destructive enzymes in the body, having the ability to degrade virtually all connective tissue components. Uncontrolled proteolytic degradation by elastases has been implicated in a number of pathological conditions. Pancreatic elastase can cause the fatal disease pancreatitis,[1] while leukocyte elastase has been implicated in acute respiratory distress syndrome,[2] rheumatoid arthritis,[3] atherosclerosis,[4] pulmonary emphysema,[5] and other inflammatory disorders.[6] Emphysema is believed to result from an imbalance between human leukocyte elastase (HLE)[7] and its endogenous inhibitor, α_1-proteinase inhibitor. One approach to controlling the progression of emphysema is to supplement the elastase inhibitor capacity of the lung with low molecular weight inhibitors of HLE. Peptidyl trifluoromethyl ketones,[8-10] peptidyl boronic acid esters,[11] and β-lactams[12] have emerged as leading candidates to demonstrate the utility of proteinase inhibitors for the treatment of emphysema.[13]

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(7) Abbreviations: HLE, human leucocyte elastase; PPE, porcine pancreatic elastase; Box, 2-benzoxazolyl; DBKA, peptidyl α,α-difluoro-β-keto amide; Ac, acetyl; Cbz, benzyloxycarbonyl; TFMK, trifluoromethyl ketone; TEA, triethylamine; THF, tetrahydrofuran; DMSO, dimethyl sulfoxide; WSCDI, 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride; HOBT, 1-hydroxybenzotriazole hydrate; TFA, trifluoroacetic acid; DMF, dimethylformamide; MeO, methoxy; Suc, succinyl; pNA, *p*-nitroanilide; rms, root mean square; FR, flow rate.
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