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Compatible Injection and Detection Systems for Studying the Kinetics of Excess Electron Transfer

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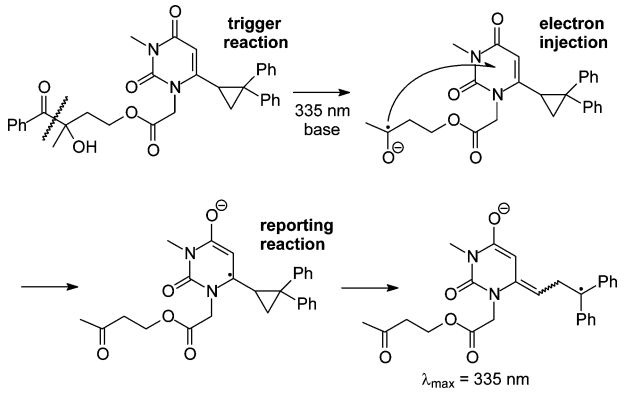
ABSTRACT



A design for fast kinetic studies of electron transfer in radical anions is reported. α-Hydroxy radicals formed by 355 nm laser flash photolysis of α-phenacyl alcohols are deprotonated under basic conditions to give ketyl radical anions that serve as electron injectors in inter- and intramolecular electron-transfer reactions. The 2,2-diphenylcyclopropyl group serves as a reporter. When an electron is injected and transferred such that spin character is adjacent to the reporter, cyclopropyl ring opening gives a readily detected diphenylalkyl radical.

Electron transfer in organic and biological molecules has been a fruitful area of study for years.[1−4] Major research efforts have been devoted to hole transfer (i.e., radical cations) in proteins and DNA molecules,[5−9] and electron transfer in biological radical anions (excess electron transfer or EET) is receiving increasing attention. An intriguing aspect of EET is that radical anions are relatively stable species in aqueous solutions, and EET in DNA has generated interest[9−23] in part because the potential for long-distance electron transfer exists.

Precise kinetic measurements of EET requires an electron injector reaction that serves to start the timing and a

(1) Bixon, M.; Jortner, J. *Adv. Chem. Phys.* **1999**, *106*, 35−202.
(2) Taube, H. *Science* **1984**, *226*, 1028−1036.
(3) Marcus, R. A. *Prix Nobel* **1993**, 67−90.
(4) Winkler, J. R.; Gray, H. B. *Chem. Rev.* **1992**, *92*, 369−379.
(5) Stubbe, J.; Nocera, D. G.; Yee, C. S.; Chang, M. C. Y. *Chem. Rev.* **2003**, *103*, 2167−2201.
(6) Giese, B. *Bioorg. Med. Chem.* **2006**, *14*, 6139−6143.
(7) Barton, J. K. *Pure Appl. Chem.* **1998**, *70*, 873−879.
(8) Schuster, G. B. *Acc. Chem. Res.* **2000**, *33*, 253−260.
(9) (a) Lewis, F. D.; Letsinger, R. L.; Wasielewski, M. R. *Acc. Chem. Res.* **2001**, *34*, 159−170. (b) Lewis, F. D.; Liu, X.; Miller, S. E.; Hayes, R. T.; Wasielewski, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11280−11281.
(10) Voityuk, A. A.; Michel-Beyerle, M. E.; Roosch, N. *Chem. Phys. Lett.* **2001**, *342*, 231−238.
(11) Behrens, C.; Burgdorf, L. T.; Schwogler, A.; Carell, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1763−1766.
(12) Amann, N.; Pandurski, E.; Fiebig, T.; Wagenknecht, H. A. *Chem.−Eur. J.* **2002**, *8*, 4877−4883.
(13) Cichon, M. K.; Haas, C. H.; Grolle, F.; Mees, A.; Carell, T. *J. Am. Chem. Soc.* **2002**, *124*, 13984−13985.
(14) Wagenknecht, H. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 2454−2460.
(15) Breeger, S.; Hennecke, U.; Carell, T. *J. Am. Chem. Soc.* **2004**, *126*, 1302−1303.
(16) Giese, B.; Carl, B.; Carl, T.; Carell, T.; Behrens, C.; Hennecke, U.; Schiemann, O.; Feresin, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1848−1851.
(17) Haas, C.; Kraling, K.; Cichon, M.; Rahe, N.; Carell, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 1842−1844.

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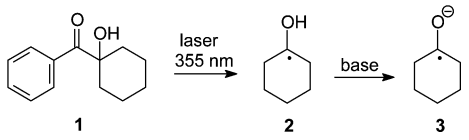
terminator reaction that provides a good detection element. The two elements must be compatible and must operate in an appropriate time domain for ET reactions. In this work, we demonstrate laser flash photolysis (LFP) methods that are designed for direct kinetic studies of EET in the nanosecond and microsecond time ranges in organic and biological molecules.

Two methods for electron injection are photoinduced electron transfer (PET) from a polycyclic aromatic compound and reduction from a photochemically generated α-hydroxy radical. Back electron-transfer reactions are possible in the former case but not in the latter, and Giese, Carell, and co-workers used α-hydroxy radicals for electron injection into DNA.[16] We used α-hydroxy phenyl ketones as precursors in intra- and intermolecular electron transfer (ET) studies. For detection in intramolecular studies, we employed an ultrafast cyclopropylcarbinyl radical ring-opening reaction,[24] which has been used for neutral radicals[25] and radical cations[26] and which was expected to maintain its fast character in a radical anion version.[27]

Intermolecular ET studies employed 1-phenacylcyclohexanol (**1**) as the radical precursor (Scheme 1). Photolysis of

Scheme 1



1 with 355 nm laser light gave the 1-hydroxycyclohexyl radical (**2**) in a fast cleavage reaction ($k \approx 1 \times 10^9$ s^{-1})[28] with $\phi \approx 0.4$.[29] In neutral protic solvent, radical **2** reduced 9-fluorenone to the ketyl radical anion with a rate constant of $k \approx 1 \times 10^8$ M^{-1} s^{-1}. The spectrum of the fluorenone ketyl radical is shown in Figure 1A. Radical **2** did not reduce simple carbonyl compounds, but deprotonation of **2** ($pK_a \approx 12.5$)[30,31] in 1:1 water−acetonitrile containing 0.05 N NaOH

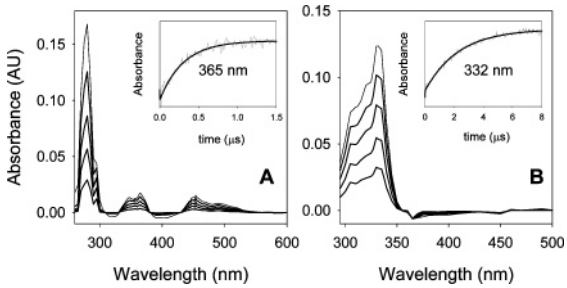
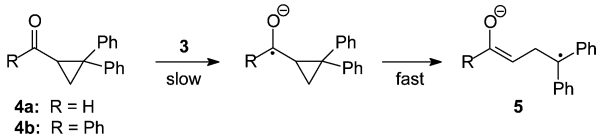


Figure 1. Time-resolved spectra. (**A**) LFP of **1** and 9-fluorenone in 1:1 water−acetonitrile. (**B**) LFP of **1** and **4b** in 1:1 water−acetonitrile with 0.05 N NaOH. The insets show kinetic traces (gray) and fits (black) at one wavelength.

gave the cyclohexanone radical anion (**3**) that was a stronger reducing agent.[32] Ketyl **3** reduced several carbonyl compounds, and the results demonstrate the limits for fast electron injection reactions from this class of initiators. For example, aldehyde **4a** and phenyl ketone **4b** were reduced and subsequently ring opened to give UV-detectable diphenylalkyl radicals **5** (λ_{max} = 335 nm) (Scheme 2, Figure 1B),

Scheme 2



whereas the corresponding methyl ketone (**4**; R = CH_3) did not react with **3**.

Second-order rate constants for electron transfer from **2** or **3** to the various acceptors were determined from the observed rate constants for a series of reactions under pseudo-first-order conditions using eq 1, where k_{obs} is the observed rate constant, k_0 is a background rate constant, k_{ET} is the second-order electron-transfer rate constant, and [sub] is the concentration of substrate. Kinetic results for reactions of acceptors with **3** and the acceptor reduction potentials[32−34] are listed in Table 1.

$$k_{obs} = k_0 + k_{ET}[sub] \quad (1)$$

Figure 2 shows a plot of the second-order rate constants for reactions of radical anion **3** vs the reduction potentials of oxidants. For the series aldehyde **4a**, phenyl ketone **4b**, acetophenone, benzophenone, and 9-fluorenone, the plot is linear (solid circles). The rate constant for reduction of easily

(18) Ito, T.; Rokita, S. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1839−1842.
(19) Ito, T.; Rokita, S. E. *J. Am. Chem. Soc.* **2004**, *126*, 15552−15559.
(20) Schiemann, O.; Feresin, E.; Carl, T.; Giese, B. *ChemPhysChem* **2004**, *5*, 270−274.
(21) Cai, Z. L.; Sevilla, M. D. *Top. Curr. Chem.* **2004**, *237*, 103−127.
(22) Kaden, P.; Mayer-Enthart, E.; Trifonov, A.; Fiebig, T.; Wagenknecht, H. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1637−1639.
(23) Voityuk, A. A. *J. Chem. Phys.* **2005**, *123*.
(24) Newcomb, M.; Johnson, C. C.; Manek, M. B.; Varick, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10915−10921.
(25) Newcomb, M.; Tanaka, N.; Bouvier, A.; Tronche, C.; Horner, J. H.; Musa, O. M.; Martinez, F. N. *J. Am. Chem. Soc.* **1996**, *118*, 8505−8506.
(26) Horner, J. H.; Bagnol, L.; Newcomb, M. *J. Am. Chem. Soc.* **2004**, *126*, 14979−14987.
(27) Tanko, J. M.; Gillmore, J. G.; Friedline, R.; Chahma, W. *J. Org. Chem.* **2005**, *70*, 4170−4173.
(28) Ruhlmann, D.; Fouassier, J. P.; Schnabel, W. *Eur. Polym. J.* **1992**, *28*, 287−292.
(29) Jockusch, S.; Landis, M. S.; Freiermuth, B.; Turro, N. J. *Macromolecules* **2001**, *34*, 1619−1626.
(30) Laroff, G. P.; Fessenden, R. W. *J. Phys. Chem.* **1973**, *77*, 1283−1288.
(31) Xu, L.; Newcomb, M. *J. Org. Chem.* **2005**, *70*, 9296−9303.
(32) Lilie, V. J.; Beck, G.; Henglein, A. *Ber. Bunsen Phys. Chem.* **1971**, *75*.
(33) Pal, H.; Mukherjee, T.; Mittal, J. P. *Radiat. Phys. Chem.* **1994**, *44*, 603−609.
(34) Barwise, A. J. G.; Gorman, A. A.; Leyland, R. L.; Smith, P. G.; Rodgers, M. A. J. *J. Am. Chem. Soc.* **1978**, *100*, 1814−1820.

Table 1. Second-Order Rate Constants for Electron Transfer from Radical Anion **3** to Various Electron Acceptors[a]

acceptor	k_{ET} (10^8 M^{-1} s^{-1})	E_{red}[b] (V)	ref[c]
HMAQ[d]	29 ± 5	−0.69	33
9-fluorenone	43 ± 3	−1.21	34
benzophenone	2.2 ± 0.2	−1.55	34
acetophenone	1.44 ± 0.05	−1.66	34
4b	1.05 ± 0.07	−1.66	34[e]
4a	0.24 ± 0.03	−1.9	32[e]
4 (R = CH_3)	NR[f]	−2.2	32[e]
1,3-dimethylthymine	0.039 ± 0.004		

[a] Rate constants determined at 22 °C in 1:1 water−acetonitrile mixtures containing 0.05 N NaOH (pH ≈ 13); errors are 2 σ. [b]Half-wave reduction potential vs SCE. [c]Reference for reduction potential. [d]2-(Hydroxymethyl)-anthraquinone. [e]Reduction poetntials for **4** were assumed to be equal to those of the simple models with methyl in place of the cyclopropyl group. [f]No reaction observed.

reduced 2-(hydroxymethyl)anthraquinone (open square) falls off the linear portion of the plot because it is at the diffusion-control limit and possibly in the Marcus inverted region. *N*,*N*-Dimethylthymine reacted relatively slowly with ketyl **3**, $k = 3.9 \times 10^6$ M^{-1} s^{-1}. Extrapolation of the correlation line to the observed rate constant for the thymine derivative (open circle) gives an estimated reduction potential for *N*,*N*-dimethylthymine of −2.11 V vs SCE in water−acetonitrile at pH ≈ 13, and the E_{red} of thymine in DNA is expected to be more favorable due to intramolecular H-bonding. Steenken reported an $E_{red} = -1.34$ V for thymine in neutral aqueous solution,[35] which likely is the value for the protonated base. Giese and co-workers showed that electron injection into DNA from α-hydroxy radicals was efficient,[16] and our results demonstrate that the ketyl radical anion injects an electron into the thymine derivative fast enough for LFP kinetic studies.

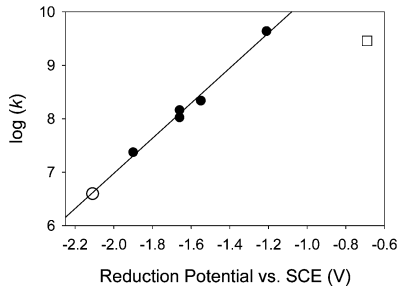
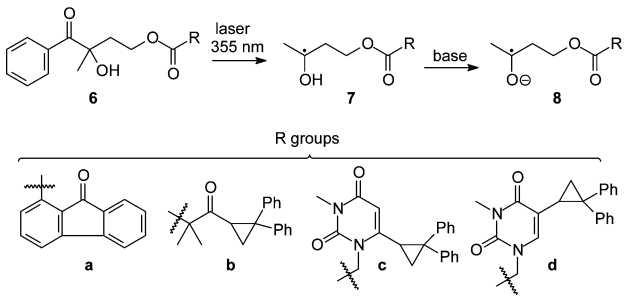


Figure 2. Second-order rate constants for reactions of **3** with carbonyl compounds in 1:1 water−acetonitrile with 0.05 N NaOH. The regression fit is for the rate constants shown with the solid black symbols. The rate constant for HMAQ (open square) was not included in the fit. The symbol for *N*,*N*-dimethylthymine (open circle) was placed at the position on the regression line for the measured rate constant.

Intramolecular electron-transfer reactions were studied with derivatives of 3-phenacyl-1,3-butanediol (**6**), where the precursor moiety for the injector is connected to potential oxidants via a tether at C1 (Scheme 3). LFP of precursors **6**

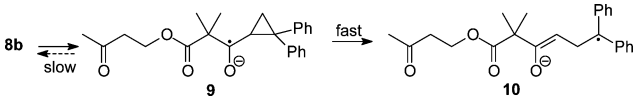
Scheme 3



gave α-hydroxy radicals **7** that could be deprotonated in basic media to give ketyl radical anions **8**. As expected from the intermolecular results, ET from the neutral radical center to the fluorenone moiety in **7a** was fast, $k = (4 \pm 1) \times 10^7$ s^{-1} in various solvents, but internal ET was not observed for other neutral radicals **7**.

Production of α-hydroxy radicals **7** in 1:1 water−acetonitrile containing 0.05 N NaOH gave ketyls **8**. For the diphenylcyclopropane derivative **8b**, rate-limiting intramolecular ET gave ketyl **9**, which opened rapidly to the distonic radical anion **10** (Scheme 4) that was identified by its

Scheme 4



characteristic UV−vis spectrum with $\lambda_{max} = 332$ nm (Figure 3A). Assuming the ET reaction was rate limiting (see below), the rate constant for the effectively isoenergetic reaction of

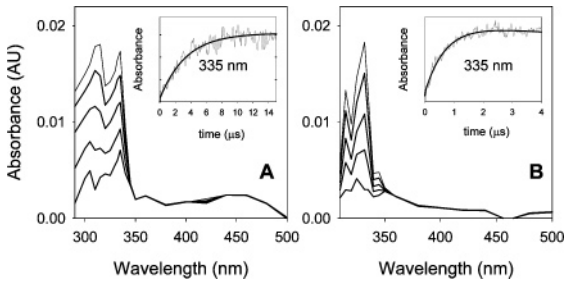


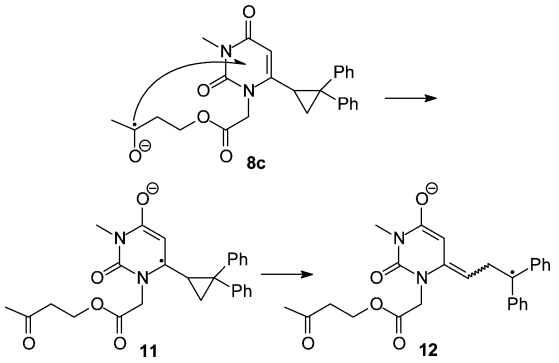
Figure 3. Time-resolved spectra. (**A**) Growth of **10** following LFP of precursor **6b**. Note that reaction of **8b** with excess precursor gives the background signal with λ ≈ 315 nm; see Supporting Information. (**B**) Growth of **12** following LFP of **6c**. The insets show the kinetic traces at 335 nm (gray) and the least-squares first-order fits (black).

(35) Steenken, S.; Telo, J. P.; Novais, H. M.; Candeias, L. P. *J. Am. Chem. Soc.* **1992**, *114*, 4701−4709.

9 was $k = (2.8 \pm 0.1) \times 10^5\ s^{-1}$, giving an intrinsic barrier of $\Delta G^{\ddagger} \approx 10$ kcal/mol for ET over the estimated (from molecular modeling) 9.5 Å distance separating the injector and cyclopropylketone moieties in **8b**.

Ketyl radical anions **8c** and **8d** tested the use of the reporter group in a DNA base. Photolysis of **6c** in neutral acetonitrile gave **7c** that showed no signal growth in the range 300−350 nm. In the basic water−acetonitrile mixture, ketyl radical **8c** was formed, and a signal for the diphenylalkyl radical grew in with a rate constant of $k = (1.4 \pm 0.1) \times 10^6\ s^{-1}$ (Figure 3B).

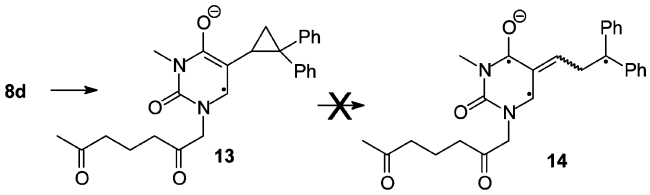
Scheme 5



In the reaction of **6c** (Scheme 5), electron injection from the ketyl moiety of **8c** to the uracil group gave **11**. The diphenylcyclopropyl reporter moiety in **11** is connected to C6 of the uracil, which is a high-spin density position for the radical anion, and ring opening of the cyclopropyl group in **11** gave **12** that was evident from its UV−vis spectrum in Figure 3B. The ET reaction that converts **8c** to **11** is exergonic, and the rate constant for ET in **8c** should be greater than that for ET in **8b**. The 5-fold increase in rate observed for **8c** compared to **8b** confirms rate-limiting ET reactions followed by fast reporting reactions.

When precursor **6d** was studied, no signal at 335 nm was observed from a diphenylalkyl radical under any conditions. In basic media, radical anion **8d** undoubtedly was formed,

Scheme 6



and ET from the ketyl to the uracil moiety in **8d** to give species **13** (Scheme 6) would be expected to have about the same rate constant as the ET in **8c** that gave **11**. The absence of a diphenylalkyl radical signal indicates that the reporting reaction in **13** was too slow to observe. The cyclopropyl reporting group in **13** is bonded to C5 of uracil, a low-spin density site for the radical anion, and ring opening would give a high-energy, cross-conjugated species **14**. Taken together, the results with **8c** and **8d** demonstrate the requirement for proper placement of the reporting element at a position of high-spin character in the penultimate radical anion product.

Our results demonstrate requisite components for kinetic studies of EET in the nanosecond and microsecond time frames. α-Hydroxy radicals can be produced by 355 nm laser light, a wavelength where proteins and DNA are transparent. Electron injection can be obtained with high efficiency from ketyl radical anions, and electron injection from α-hydroxy radicals under general base catalysis conditions was demonstrated by Giese.[16] Readily reduced moieties such as fluorenone can serve as thermodynamic traps, whereas fast ring opening of a cyclopropylcarbinyl system provides a kinetic trap, and both types of product radical anions are readily detected.

Acknowledgment. We thank the National Science Foundation for support.

Supporting Information Available: Synthetic details and NMR spectra for precursors **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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