Unusual Redox Behavior in the Photoinduced Electron-Transfer Reactions of Amino Ketones

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Abstract: Irradiation of a wet benzene solution of 1,2-diphenyl-2-piperidino-1-ethanone and 9,10-dicyanoanthracene leads to the formation of benzil and deoxybenzoin. We have interpreted these products as arising from deprotonation leading to net oxidation coupled with reductive elimination. The latter pathway is noteworthy in that we show *reductive elimination* of an electron *donor* can be a chief consequence of photochemical single electron transfer (SET) quenching.

Introduction

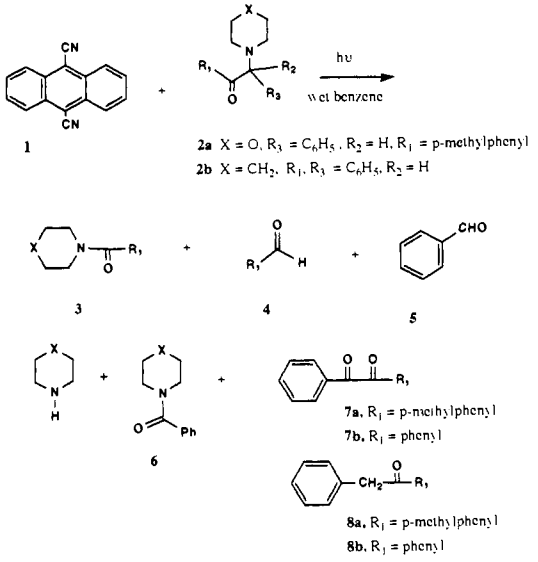
Amines typically react with photoexcited electron acceptors via single electron transfer (SET) quenching, which can culminate in the formation of a rich variety of two-electron redox products.[1,2] In an earlier report, we described novel oxidation products (**3–6**) arising from irradiation of acceptors such as 9,10-dicyanoanthracene (**1**, DCA) in the presence of amino ketones such as **2a**.[3] These products (Scheme I) can be attributed to two general reactions originating from the amino ketone cation radical generated by SET quenching: (1) unassisted fragmentation (products **4** and **5**) and (2) nucleophile-assisted fragmentation (products **3** and **6**). In subsequent studies, especially in investigations with aromatic amino ketones,[4] we have found evidence for two additional pathways: (3) deprotonation leading to net oxidation (**7a**) coupled with (4) reductive elimination (**8a**). The first two pathways have been discussed previously;[3] in the present report we evaluate the latter two which can be major routes to products in a number of cases. The latter pathway and products are noteworthy in that we show that reductive elimination of an electron donor can be a chief consequence of photochemical SET quenching.

Results

In typical experiments, solutions of amino ketones (2×10^{-2} M) and DCA (4×10^{-3} M) in deuterated, undried benzene (or deuterated, undried acetonitrile) are degassed by freeze–pump–thaw cycles, sealed, and irradiated with a high-pressure mercury lamp fitted with a filter to pass light of 400–440 nm. The course of the reaction is followed by NMR, and at the end, the apparatus is opened and the sample analyzed by GC–MS. Products are identified by comparison of their spectral and chromatographic characteristics with authentic samples.

In the case of aliphatic amino ketones such as 3-morpholino-3-methyl-2-butanone and **2a** in benzene, products analogous to **3–6** are the major amino ketone photoproducts arising through SET quenching of DCA or thioindigo.[3] Reduced acceptor products such as $DCAH_2$ are also detected. However, the observation of considerable amounts of diketone (**7a**) (18%) and the reductive deamination product (**8a**) (24%) indicates that other paths for decomposition of the amino ketone cation radical from **2** are active. Examination of the closely related amino ketone **2b** in the same solvent revealed simpler chemistry in that *only* products **7b** and **8b** accumulate and there is little consumption of DCA.[5] Presumably product **7** can arise from deprotonation of the α-hydrogen of the amino ketone cation radical. The resulting iminium radical can generate an iminium ion following one-electron oxidation; hydrolysis gives **7** and morpholine. This pathway is well-established for oxidation of amines not prone to fragmentation.[1] Our first thought about **8** as a major product was that it was arising from a trivial process. Direct irradiation of α-amino ketones results in intramolecular electron transfer and the zwitterion or intramolecular charge-transfer state (ICT) indicated in Scheme II. Proton transfer generates a biradical which can fragment to give **8**.[6-8] Careful control studies indicated that

Scheme I



Scheme II

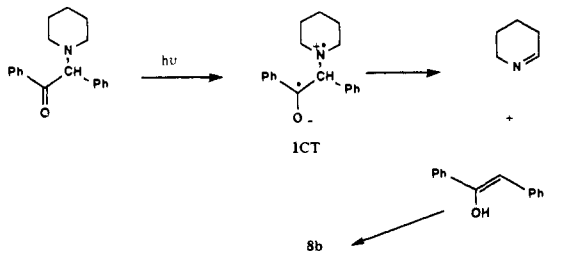


Table I. Product Yields for Amino Ketone Photolysis[a] Sensitized by **1** (DCA) in Benzene-d_6

amino ketone	3	4	5	6	7	8
2a	19	2.5	9	5	18	24
2b					23	60

[a] With **1** at 4×10^{-3} M, amino ketone 2.0×10^{-2} M, carried to about 10% conversion.

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(5) The yield of **8** always exceeds that of **7**, even at very low conversion. This can be partially attributed to the photolability of **7**, which absorbs the irradiating wavelength (400–440 nm), and to the fact that phenacyl radicals (**9**) abstract hydrogen from other sources, e.g., solvent.

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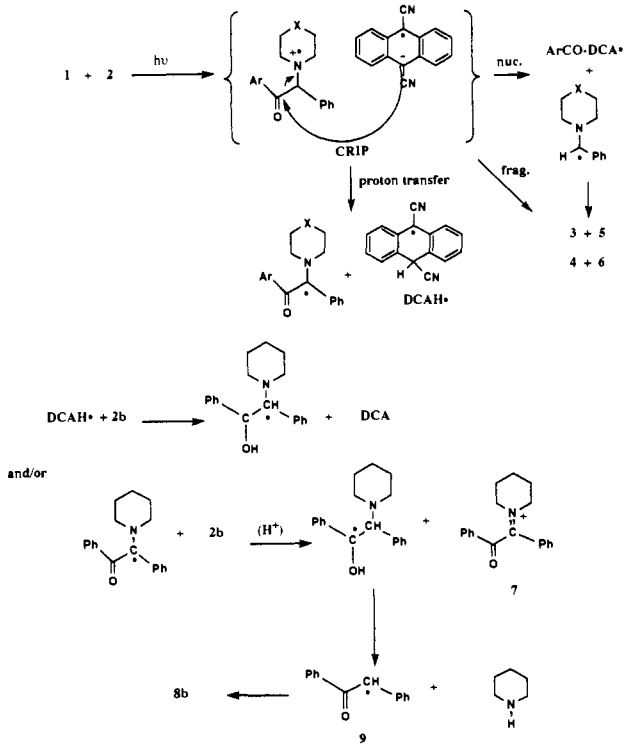
Scheme III



in our experiments the amino ketone should not be excited directly or indirectly. Nonetheless, it was considered possible that the ICT state could be achieved and thus be the precursor of **8**. For **2b** this pathway should also give the oxidation product of piperidine, 3,4,5,6-tetrahydropyridine.[9] This product was synthesized independently and shown to be stable under the reaction conditions. It was not found among the reaction products within the limits of detection by GC–MS when the reaction of **2b** was sensitized by DCA. It thus appears clear that **8** does not arise via the ICT state but as a consequence of the SET quenching of photoexcited DCA by amino ketones **2**.

Since **7b** is a two-electron oxidation product of **2b** and **8b** is a two-electron reduction product, the lack of net consumption of DCA and the production of roughly equivalent amounts of **7b** and **8b**[5] suggest that the overall reaction for DCA/**2b** is a photochemical SET-mediated disproportionation. Irradiation of DCA with **2b** in perdeuterated dioxane leads also to **7b** and **8b** as the predominant products; under these conditions the **8b** produced incorporates 45 atom % deuterium in the α-position. Dioxane is an efficient hydrogen atom donor,[10] and the results are consistent with a hydrogen atom abstraction by a phenacyl type radical **9** as shown in Scheme III. Substitution of 9,10-dimethoxyanthracene (DMA), an efficient excited-state electron donor,[11] for DCA in experiments with **2b** results in relatively clean formation of **8b** with no production of **7b** or the abovementioned fragmentation products. Here electron transfer should occur in the reverse direction, reducing the amino ketone to give the anion radical of **2b**. After protonation the neutral radical could eliminate piperidine as shown in Scheme III to yield the phenacyl radical precursor of **2b**. Reinforcement for this pathway is provided by our observation that tributyltin hydride (an excellent hydrogen atom donor)[12] reduces **2b** to **8b**.

Discussion

These experiments taken together lend support for the mechanism shown in Scheme III. Initial SET quenching of DCA by **2** in benzene solvent produces a contact radical ion pair (CRIP). Nucleophilic and fragmentation processes lead to products **3–6** as previously studied.[3,4] Proton transfer leads to a radical pair. In the case of **2b**, the proton-transfer step apparently occurs to the exclusion of the other processes for reasons that we do not yet understand. We chose to study **2b** because of this simplification. Further oxidation of the neutral radical derived by SET oxidation of **2b** leads to the two-electron oxidation product **7**. Reduction of a second molecule of **2b** by either DCAH• or the iminium radical generates an anion radical of **2b** or its corresponding protonated neutral radical, which can eliminate piperidine and generate the phenacyl radical **9** which serves as a precursor for deoxybenzoin, **8b**. The observation of photochemical SET-sensitized disproportionation in these studies is closely analogous to other true electron-transfer-sensitized reactions such as the cyanoaromatic-mediated addition of alcohols to alkenes and related fragmentation processes.[13–15] The type of reaction reported here should occur fairly generally for substrates which can be both easily reduced and oxidized in SET processes, particularly in cases where these semireduced and semioxidized species rapidly convert to stable even-electron products. What is novel about the present findings is that a reductive elimination can occur under conditions where the first step of the sequence is a one-electron oxidation.

The process can be viewed as a kind of "chemical sensitization" in which potential two-electron oxidants (excited DCA) and two-electron reductants (the amino ketone) generate powerful redox reagents after SET. The chemistry that follows is ground-state chemistry. Numerous examples of the consequences of this kind of chemistry exist.[16] There are also examples of the elimination mechanism we have suggested for the formation of the radical **9**. The radiolysis of the amino acid serine generates a radical center next to the OH functional group. That radical then eliminates ammonia.[17a,18] Radicals derived from β-amino alcohols behave similarly.[17b]

Experimental Section

General. The apparatus for a typical irradiation consisted of an NMR tube grafted onto a reservoir cell. The solution to be irradiated was vacuum degassed with three or more freeze–pump–thaw cycles to a residual pressure of 3×10^{-6} Torr or less and sealed in glass. The sample in the NMR tube was irradiated with a high-pressure mercury arc lamp equipped with a filter to allow light above 400 nm to pass. The course of the photolysis was followed by NMR spectroscopy, and finally the tube was opened and subjected to GC–MS analysis. GC–MS data were obtained on a 5890 Hewlett-Packard GC with a 5790 HP series mass selective detector. NMR spectra were obtained at 300 MHz on a QE-300 GE-Nicolet spectrometer. Deuterated solvents were used as received. The 2,3,4,5-tetrahydropyridine was synthesized according to the literature.[19] DCA was recrystallized twice from pyridine before use. A sample of 9,10-diethoxyanthracene was a gift from Dr. Samir Farid and was used as received. All reaction products were identified by comparison of NMR and GC–MS spectral data with those of authentic samples.

2-Piperidino-1,2-diphenyl-1-ethanone was prepared by adding 50 g of benzoin to a solution of 36.5 g of thionyl chloride in 150 mL of freshly distilled DMF that was cooled with ice. The solution was allowed to warm and was stirred for 3 h and then treated with 100 mL of water and 100 mL of methylene chloride. The organic layer was washed with water, dried ($MgSO_4$), and evaporated. Recrystallization from ethanol gave 46 g of desyl chloride (mp 61–63 °C). A solution of 10.0 g (43.0 mmol) of desyl chloride and 16.5 mL (167 mmol) of piperidine in 70 mL of anhydrous ether stood for 18 h, was washed with water several times,

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dried (Na_2SO_4), evaporated, and recrystallized from ethanol to give 6.0 g (51%): mp 79-80 °C; NMR ($CDCl_3$) 1.46 (m, 2 H), 2.48 (m, 5 H), 4.92 (s, 1 H), 7.22-8.08 (m, 10 H). Anal. C, H.

2-Hydroxy-1-(4-methylphenyl)-2-phenyl-1-ethanone was prepared using published procedures.[20,21] Trimethylsilyl cyanide (4.96 g, 50.0 mmol) was added to 4.78 g (45.0 mmol) of benzaldehyde with stirring. After the mixture cooled, 25 mL of methylene chloride was added and the solution allowed to stir overnight. A Grignard reagent was prepared in the usual manner by combining 8.55 g (50.0 mmol) of *p*-bromotoluene, 1.34 g (55.0 mmol) of magnesium, and 75 mL of absolute ether and adding this mixture to the methylene chloride solution. The mixture was stirred for 2 h and then poured onto 500 g of ice and 20 mL of sulfuric acid. The aqueous layer was allowed to stand overnight and then filtered to collect the crystals that deposited during that time. The ether layer was evaporated and taken up with 75 mL of methanol with 1 mL of 10% aqueous HCl and was also allowed to stand overnight. The solvent was removed, and the resulting solid and the crystals above were recrystallized three times from methanol and water to afford 6.1 g (64%), mp 103-4 °C (lit. mp 109[22] °C).

2-Morpholino-2-phenyl-1-(4-methylphenyl)-1-ethanone was prepared by adding 3.0 g of the previously prepared product to 10 mL of DMF and was treated with 1.4 mL of thionyl chloride under nitrogen. The mixture was stirred for 3 h and then treated with 10 mL of water and 10 mL of methylene chloride. The methylene chloride layer was washed (3 × 10 mL) with water and dried ($MgSO_4$). Rotary evaporation afforded a clear oil (the corresponding chloride), which was used without further purification by dissolving it in 20 mL of anhydrous ether and 7 mL of morpholine and allowing it to stir overnight. Water (20 mL) was added, and the ether layer was washed three times with 20 mL of water, dried (K_2CO_3), evaporated to an oil, and subjected to high vacuum. The oil was identified as nearly pure product (3.3 g, 84%) by NMR and GC-MS spectroscopy. Additional purification by thick-layer chromatography on silica gel afforded a noncrystalline colorless oil, which was pure by NMR, HPLC, and GC-MS analysis: NMR ($CDCl_3$) 1.86 (s, 3 H), 2.30-2.50 (m, 4 H), 3.51-3.66 (m, 4 H), 4.75 (s, 1 H), 6.73-7.04 (m, 5 H), 7.42 (d, J = 6 Hz, 2 H), 7.97 (d, J = 6 Hz, 2 H).

Irradiation of 2b with 9,10-Diethoxyanthracene. A solution of **2b** (6.1×10^{-3} M) and 9,10-diethoxyanthracene (6.4×10^{-3} M) in benzene-d_6 was irradiated as described above. NMR and GC-MS analysis indicated a 55% yield of **8b** along with smaller amounts of unidentified products.

Irradiation of 2b with Tributyltin Hydride. A solution of **2b** (1.5×10^{-3} M) and tributyltin hydride (3.0×10^{-3} M) was prepared as indicated above and allowed to stand in the dark for 5 days. NMR and GC-MS analysis indicated a 49% conversion to **8b**.

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Registry No. **1**, 1217-45-4; **2a**, 127029-79-2; **2b**, 794-05-8; **3a**, 63833-44-3; **4a**, 104-87-0; **5**, 100-52-7; **6a**, 1468-28-6; **7a**, 2431-00-7; **7b**, 134-81-6; **8a**, 2001-28-7; **8b**, 451-40-1; 2-hydroxy-1-(4-methylphenyl)-2-phenyl-1-ethanone, 2431-23-4; 2-chloro-1-(4-methylphenyl)-2-phenyl-1-ethanone, 41104-54-5.

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Crystal Structures of Two Activated Cyclohexanones with Opposite Pyramidalizations of the Carbonyl Groups

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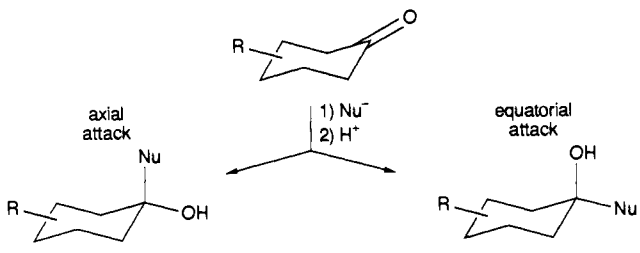
Abstract: The crystal structure analyses of the two 3,3,5,5-tetraalkylcyclohexanones **1** and **2** activated by Li^+ or $SbCl_5$ complexation show that **1** and **2** have rather different chair conformations and opposite pyramidalizations of the carbonyl group. The bicyclic ketone **1** has an exocyclic C=C double bond acting as an intramolecular nucleophile attacking the carbonyl group from the axial direction, whereas **2** is preferentially attacked by nucleophiles from the equatorial direction. In **1**, the axial α protons (but not the C_α—C_β bonds) are well aligned for hyperconjugative interactions with the carbonyl group, whereas, in **2**, both the axial C_α—H and the C_α—C_β bonds may interact with the carbonyl group. In all structures, a C=O elongation and a $C_{C=O}$—C_α shortening are observed. In addition, **2** shows a slight C_α—C_β elongation. The conformational differences between **1** and **2** are in agreement with the general conformational flexibility of cyclohexanones, as could be shown by comparison of their Cremer-Pople puckering parameters with those of cyclohexanones from the Cambridge Structural Database. The direction of the carbonyl pyramidalization is compared with that of pyramidalized sp^2 C atoms in a norbornenyl cation and discussed in terms of preferential attacks of nucleophiles, as predicted by current models of stereoselective nucleophile addition (Cieplak, Houk, Klein, Felkin).

The explanation of diastereoselective additions of nucleophiles (Nu^-) to cyclohexanones (Scheme I) was in recent years the topic of several publications, especially by Cieplak,[1] Houk,[2a-c] Klein,[2d,e]

Scheme I



Felkin,[2f,g] and Anh.[2h,i] Most arguments in the discussion of the kinetically controlled additions stem from the interpretation of product ratios[1,2] and the computation of transition states.[2,3]

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