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Electron Transfer between Superoxide Ion and an α,β-Unsaturated Ketone

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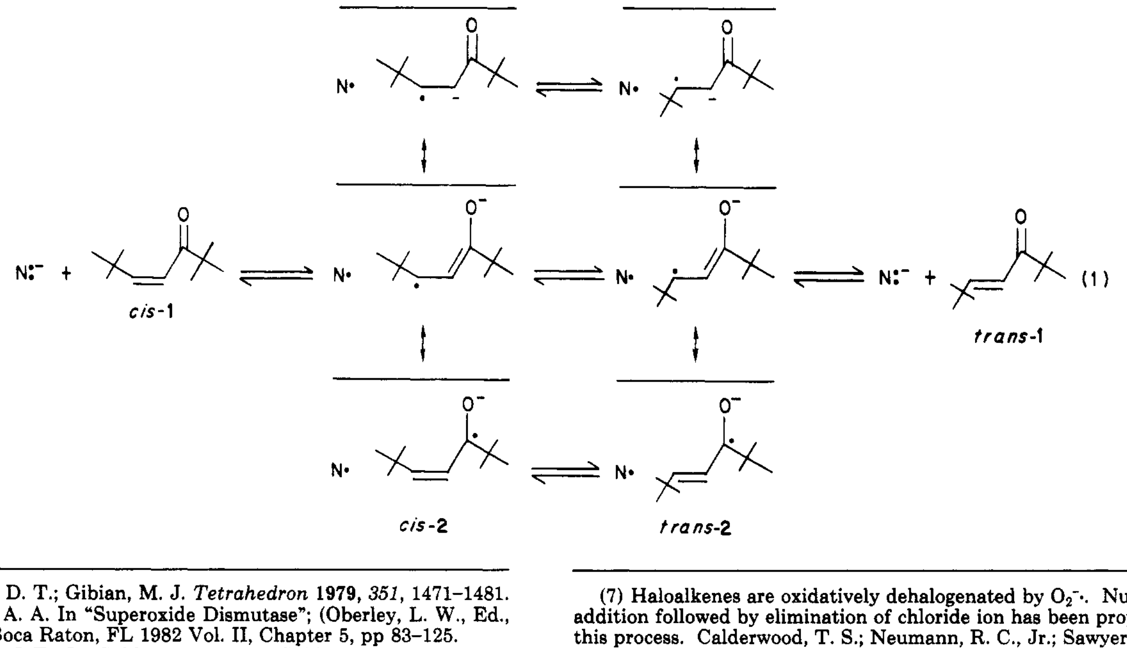
Superoxide ion in aprotic solvent is an extraordinarily reactive nucleophile;[1,2] in this report we address the notion that an important contribution to this effect may be considerable electron-transfer character in the transition state for substitution. On the basis of its low thermodynamic basicity ($pK_a \sim 4.5$), $O_2^-\cdot$ would be expected to be a relatively weak nucleophile. Even when the enhanced apparent basicity, $pK_a(\text{appx}) \sim 22$ (due to rapid disproportionation of $O_2^-\cdot$ with $HO_2\cdot$, its conjugate acid) is used in an extrapolation from a normal Brønsted relation for HO^- or RO^-, the actual reactivity of $O_2^-\cdot$ is much higher than predicted. The α effect, when an electronegative atom neighbors the attacking atom, is indeed one property contributing to the enhanced nucleophilicity, since peroxide ions exhibit this effect toward both sp^2 ($\sim 10^3$-fold) and sp^3 ($\sim$50-fold) substrates.[3,4] The increased rates for $O_2^-\cdot$, however, are considerably more than those manifest for RO_2^- ions. That displacement or addition reactions of $O_2^-\cdot$ might have a higher electron-transfer character than those of most nucleophiles is made attractive by the stability of nascent O_2 in the transition state and has been suggested earlier.[5,6]

As background,[1,2] it should be noted that $O_2^-\cdot$ adds quite rapidly to carbonyl compounds, but that while esters and other carboxyl derivatives are hydrolyzed, ketones and aldehydes are regenerated by facile reversal from the tetrahedral intermediate (addition is nonproductive, and $O_2^-\cdot$ disappears no more rapidly in the presence of benzaldehyde or benzophenone than in their absence). If substrate has enolizable (acidic) protons, these are removed by $O_2^-\cdot$ acting as a base, and the carbonyl compound undergoes subsequent reactions. With sp^3 substrates (alkyl halides, tosylates), usual S_N2 patterns of reactivity are found (including relative rates vs. structure and inversion of stereochemistry); products are those of net displacement. While simple olefins are unreactive, aromatic (but not aliphatic) conjugated unsaturated ketones (chalcones) are reported to be susceptible to attack.[7,8] Of course, if organics have sufficiently low reduction potentials (e.g., nitroaromatics), electron transfer occurs to give organic anion radical and O_2.

Diagnostics for single electron transfer have been developed in investigations of organometallic reactions with various functional groups. Desiring to utilize such a probe for the superoxide substitution or displacement, we chose *cis*-2,2,6,6-tetramethylhept-4-en-3-one (**1**) as a molecule fitting the appropriate reactivity criteria and that is without acidic protons. Its utility, as described by House and by Ashby,[9] is based on the fact that *trans*-**1** is by far predominant at equilibrium if there is a route to interconvert the isomers. Such a route is via the ketyl radical anion (**2**, eq 1). The design is to examine stereochemistry of recovered starting material and product at low extents of reaction. Unfortunately, product stereochemistry is of no diagnostic value here (vide infra). An ambiguity that may sometimes be resolved is whether reaction 1 (starting material equilibration), if observed, is on the reaction path for productive reaction. These issues are considered below.

Results and Discussion

Representative trans/cis ratios plotted vs. time of reaction for several concentrations of **1** (typically 0.2 M; 77% cis, 23% trans) with various ratios of KO_2 and 18-crown-6 ether (CE) with anisole as internal standard are shown in Figure 1. Several experiments in pyridine showed much faster rates of isomerization, but quantitative analysis was more difficult than in benzene. The inset shows total **1**



cis-**1**

trans-**1**

cis-**2**

trans-**2**

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(7) Haloalkenes are oxidatively dehalogenated by $O_2^-\cdot$. Nucleophile addition followed by elimination of chloride ion has been proposed for this process. Calderwood, T. S.; Neumann, R. C., Jr.; Sawyer, D. T. *J. Am. Chem. Soc.* **1983**, *105*, 3337–3339.

(8) For chalocones and both CN- and NO_2-substituted olefins, Rosenthal and Frimer favored initial electron transfer on the basis of the lack of incorporation of label in products when $K^{18}O_2$ was used in a $^{16}O_2$ atmosphere. In some of these systems the olefin radical anion ESR spectrum was observed. Frimer, A. A.; Rosenthal, I. *Photochem. Photobiol.* **1978**, *28*, 711–719; *Tetrahedron Lett.* **1976**, 2805–2808.

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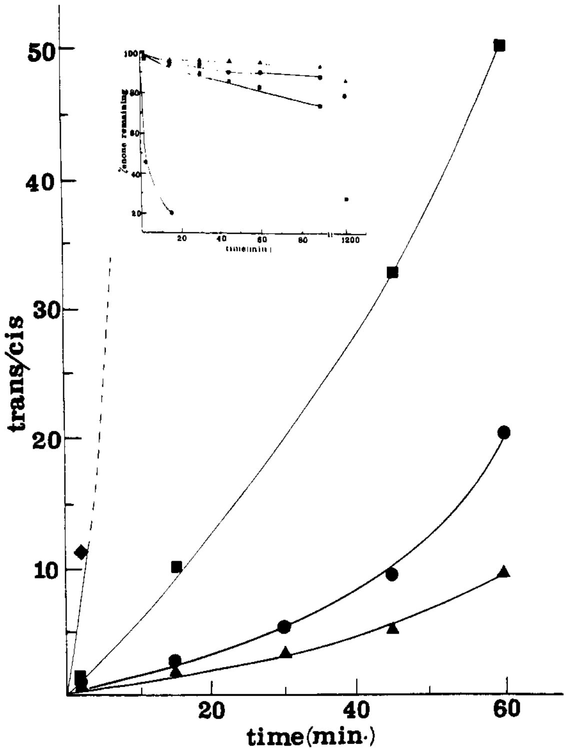
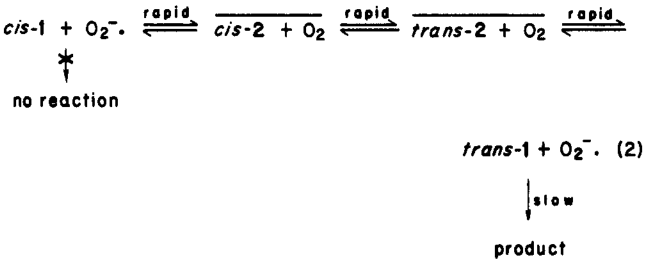


Figure 1. Ratio of *trans*- to *cis*-1 as a function of time for different conditions. All runs in benzene. ▲, ●, ■ are 0.10 mL containing 21.9 μmol of *cis*-1 (0.22 M) and 6.43, 22.7, and 22.7 μmol of CE with 35.2, 25.3, and 43.6 μmol of KO_2 added last, respectively. ◆ is 0.047 mL with 4.8 μmol of *cis*-1 (0.10 M) with 35.9 μmol of CE and 196 μmol of KO_2. The reagent ratios (olefin/CE/KO_2) are thus 1/0.3/1.6 (▲), 1/1/1.2 (●), 1/1/2 (■), and 1/7.5/40 (◆). Inset: same symbols, total 1 remaining (vs. internal standard anisole) as a function of time.

recovery vs. time. At the three lower KO_2/CE concentrations, greater than 80% (90% for the two lowest) of total 1 (largely isomerized) is still present in 60 min. For the high values of KO_2 and CE both isomerization and loss of starting material are rapid, but isomerization is still clearly faster.

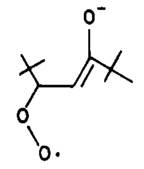
At approximately equimolar quantities of all reagents rapid conversion (minutes) of *cis*- to *trans*-olefin occurs, followed by a much slower (hours to days) loss of total enone 1. The isomerization process is dependent both on the amount of KO_2 and the amount of CE.[10] At the higher ratios of KO_2/CE to olefin (40/7.5/1) isomerization is essentially quantitative within ~1 min. In all runs (even that with KO_2/CE/1 = 1.6/0.3/1.0), isomerization was almost complete within an hour, and at early times all 1 was accounted for as starting material. In a number of experiments further amounts of KO_2 (and/or CE) were added after an hour (varying degrees of loss of 1), leading to more rapid destruction of *trans*-1. Reacted solutions showed no pivalic acid or 3,3-dimethylpyruvic acid, the products analogous to those ultimately obtained from chalcones.

We envision the process occurring as in eq 2. In this scheme, superoxide rapidly and reversibly electron

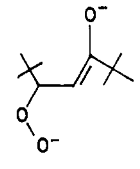


transfers to olefin to produce the ketyl radical anion (2) in a cage with O_2. This sets up a cis–trans isomerization, followed by slow loss of trans. It is not clear whether intermediates 2 are on the path for ultimate product development or not.[11]

The rate of isomerization makes it unlikely that the intermediate responsible for isomerization (which is formed so rapidly and reversibly) is an actual adduct such as 3,



3



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although we cannot absolutely rule out this possibility. If there is such an adduct from cis, it must quantitatively revert to 1 (after rotation), since at early times complete isomerization with no net loss of enone is found. In polar addition–elimination processes,[12] very reactive nucleophiles tend to give long-lived anionic intermediates (which would be an enolate in this case) with favorable equilibria for adduct formation in the first step (expected to lead to products, not revert to starting material). If 3 were to be formed, our data requires rapid reversal, or else 3 should be rapidly reduced by $O_2^{-}\cdot$ to give O_2 and 4, which would not readily revert to 1 (O_2^{2-} is very basic and would be a very poor leaving group[1]). Reactivity–stability reasoning appears to argue against 3 as the isomerizing species. Indeed, this kind of system is among those in vinyl substitution or addition–elimination for which one-electron transfer and radical anion isomerization (resulting in stereoconvergence) is suspected.[12]

Certainly the carbonyl is a major factor in the reactivity of our probe, since superoxide does not react with simple olefins. Aromatic olefins are also inert; a four-fold excess of CE and KO_2 in chlorobenzene effected neither isomerization nor net loss of *cis*-stilbene (0.5 M) in 18 h.

Attempts to observe CIDNP at 60 MHz in the enone 1 system under a variety of conditions were unsuccessful (Me_2SO or hexane as solvent, 0.3 to 0.9 M enone, and from 0.1 to 1.0 equiv of KO_2/CE). We observed the rapid cis to trans isomerization in the NMR, but no experimentally significant intensity variations.

Although these experiments do not unambiguously prove that eq 1 and 2 occur with $O_2^{-}\cdot$, they are highly suggestive of this SET process. We cannot comment on the possibility of such a process being on the reaction path for net reaction of enones (intermediates 2 partitioning primarily back to isomerized enone 1 and superoxide, but

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[10] Plots of log (trans/cis) vs. time are quite linear for the three lower ratio runs shown here. The relative slopes are in fairly good agreement with reagent ratios.

[11] Examination of available values of $E_{1/2}$ in the closest appropriate solvents for α,β-unsaturated ketones indicate that reversible electron transfer between 1 and $O_2^{-}\cdot$ is feasible (equilibrium not prohibitively far in either direction). An approximate calculation (appropriate reversible $E°$ values in the same solvent are unavailable) indicates that 1 and $O_2^{-}\cdot$ should be favored. Bowers, K. W.; Giese, R. W.; Grimshaw, J.; House, H. O.; Kolodny, N. H.; Kronberger, K.; Roe, D. K. *J. Am. Chem. Soc.* **1970**, *92*, 2783–2799. Siegerman, H. *Techn. Electroorg. Synth.* **1974**, *5*, 667–1256. Also Mandell, L.; Cooper, S. M.; Rubin, B.; Campana, C. F.; Day, R. A., Jr. *J. Org. Chem.* **1983**, *48*, 3132–3134.

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going on to products at a low rate) or whether this electron transfer is purely reversible and another slower path (direct one-step addition, e.g., via **3**) leads from trans to product. The rapid isomerization with no net loss, however, is reminiscent of the situation proposed for the lack of reactivity of aldehydes and ketones[13] and certainly helps explain the unusual reactivity of $O_2^{-}\cdot$ toward S_N2 substrates. In the present case there is no really facile path available rather than reversal to **1**, but for alkyl halides, production of peroxy radical and halide from the ET cage products could be efficiently competitive with reversal. Two recent publications presented convincing evidence for inversion of configuration at a normal 2° alkyl bromide in an electron transfer, radical process.[14] Further probes for this component should be examined in order to understand the chemical reactivity of this biochemically ubiquitous species.

Experimental Section

Materials. KO_2 (Alpha, 96.5%) is finely ground under N_2 and stored in a vacuum dessicator. 18-Crown-6 ether (Aldrich, CE) is purified as its acetonitrile complex. All solvents and anisole were fractionally distilled. Synthesis of **1**[15] ($\sim$99% trans by GC and NMR) was followed by photoisomerization and partial crystallization (−78 °C) of trans from hexane solution, leaving a mixture predominantly *cis*-**1** (typically 77% cis, 23% trans) which is then evaporated to dryness. NMR (T-60 in (Me_2SO-d_6), GC, and mp data are in accord with literature values (*trans*-**1**; δ 6.23, 6.90 (J = 9.5 Hz); *cis*-**1**, δ 5.67, 6.33 (J = 10 Hz)).

Methods. Analysis by GC is on a 6 ft × $^1/_8$ in. Carbowax 20M (10%) column at 100 °C (225 °C for stilbene), giving good isomer separations, with anisole as internal standard. For a typical run a small vial containing deaerated benzene (or other solvent), **1** (usually 0.2 M), anisole, CE, and a Teflon-coated stirring bar is placed in an argon-containing glovebag. Preweighed KO_2 is added, and the vial is serum-capped and removed from the glovebag. A microliter syringe is used to remove small samples for immediate GC injection from the continuously stirred solution. Nmr experiments are done under argon by filling a capped tube in an argon atmosphere glovebag immediately adjacent to the spectrometer.

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Registry No. *cis*-**1**, 29569-89-9; *trans*-**1**, 20859-13-6; KO_2, 12030-88-5.

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Autoxidation of 1-(*tert*-Butylthio)-2-(*n*-propyl)isoindole

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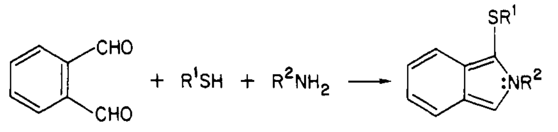

OPA

1

(1)

	R^1	R^2
a	CH_2CH_2OH	alkyl
b	alkyl	alkyl
c	$C(CH_3)_3$	$CH_2CH_2CH_3$

The fluorogenic reaction of *o*-phthalaldehyde (OPA) with primary amines in the presence of a thiol to produce intensely fluorescent 1-(alkylthio)-2-alkylisoindoles[1,2] **1** forms the basis for a sensitive analytical method specific for primary amines and primary amino acids.[3-8] These 1-thio-substituted isoindoles form a relatively new class of isoindoles for which only limited chemical information currently exists. Various alkyl (aryl) substituted isoindoles are known to be air-sensitive and undergo autoxidation,[9-14] but for the specific case of isoindoles bearing the 1-(2-hydroxyethyl)thio substituent the results of recent studies have shown that degradation occurs by nonoxidative processes that involve either intramolecular nucleophilic[1,15] or solvolytic attack[16] at C-1. It has not been determined whether these nonoxidative degradation pathways are an inherent property of 1-thio-substituted isoindoles or if they occur only with isoindoles bearing the 1-(2-hydroxyethyl)thio substituent, i.e., **1a**. Since these 1-thio-substituted isoindoles are rapidly gaining importance as analytically useful derivatives of primary amines and amino acids, the present work was undertaken to evaluate the reactivity of compounds of general structure **1b**. We now report the results of our investigation with a model compound of this class, 1-(*tert*-butylthio)-2-*n*-propylisoindole, **1c**.

When CH_3CN/H_2O (1:1, v/v) solutions of **1c** were exposed to air for 24 h, complete loss of the starting isoindole was observed by HPLC). Workup of a degraded solution followed by column chromatographic fractionation on silica gel and spectroscopic analysis (^{1}H NMR, low resolution MS, IR) resulted in the isolation and tentative identification of four degradation products as shown in Scheme II. 3-Hydroxy-2-*n*-propylphthalimidine (**2**) formed in 4% isolated yield, *N*-*n*-propylphthalimide (**3**), in 16% yield; 1,3-(di-*tert*-butylthio)-2-*n*-propylisoindole (**4**), 12% yield; and 3-(*tert*-butylthio)-2-*n*-propylphthalimidine (**5**), 35% yield. Degradation products **2** and **3** were confirmed from spectroscopic (^{1}H NMR, IR, MS) and chromatographic (TLC, silica gel; reversed-phase HPLC) comparisons to authentic samples prepared from literature procedures[9,17]

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