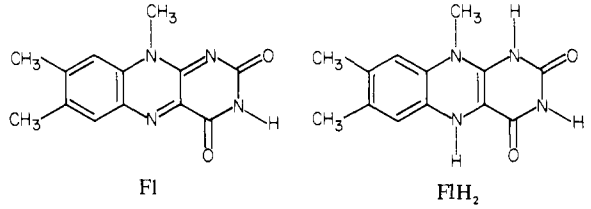
O_2 (Figure 1d). This has been confirmed by cyclic voltammetry, electronic spectroscopy, and ESR (17 lines, $g = 2.00$).[25]

N',N''-Dihydrolumiflavin (FlH_2) has been synthesized elec-



Fl FlH_2

trolytically in a manner analogous to that of the hydrophenazines. Combining 1 equiv of FlH_2 with $O_2^{-}\cdot$ in a sealed cell causes the FlH_2 to be oxidized cleanly to lumiflavin (Fl). Figure 2 illustrates the electronic spectra of (a) Fl, (b) $Fl^{-}\cdot$, (c) FlH_2, and (d) the combination of FlH_2 with $O_2^{-}\cdot$. Note that the electronic spectrum of the FlH_2–$O_2^{-}\cdot$ reaction (Figure 2d) is qualitatively and quantitatively almost the same as that of Fl (Figure 2a). Moreover, the cyclic voltammetry of the product solution closely resembles that of Fl and is ESR silent at room temperature.

N-Benzyl-4,4-dihydronicotinamide (BNH) has been synthesized by established methods.[26,27] The reaction of BNH with $O_2^{-}\cdot$ is slower than that of the reduced phenazines and flavins and requires 4–6 min for completion at millimolar concentrations; the reduced phenazines and flavins react instantaneously. The reaction stoichiometry is 1:1 and the product solution exhibits electrochemistry and spectroscopy which is similar to that for BNH. However, there are distinct differences[28] and no evidence for O_2 or $O_2^{-}\cdot$. The electrochemistry and spectroscopy of BN^{+} is completely different from that of BNH or the product(s) of the $O_2^{-}\cdot$–BNH reaction. Hence, a direct hydride transfer to $O_2^{-}\cdot$ is ruled out. These results confirm that $O_2^{-}\cdot$ reacts with BNH to yield new species, probably derivatives of an unstable primary product such as BN·.

Analogously, the reaction of NH_2OH in basic DMF with $O_2^{-}\cdot$ is complex. Adding 1 equiv of NH_2OH to a sealed cell of $O_2^{-}\cdot$ destroys all of the $O_2^{-}\cdot$, produces no O_2, and yields a bronze-colored solution for 5–10 min before it becomes colorless.[29] Preliminary results also indicate that hydrazine (N_2H_4) is oxidized by $O_2^{-}\cdot$ with an approximate 1:1 stoichiometry (actually 3 N_2H_4 per 4 $O_2^{-}\cdot$ if N_2 and OH^{-} are assumed to be the only products). Additional studies are in progress to elucidate what appears to be a complicated mechanistic pathway.

The results confirm that the two hydrogen atoms of H_2Phen and FlH_2 are oxidized by $O_2^{-}\cdot$ to give Phen and Fl, respectively

$$H_2Phen + O_2^{-}\cdot \rightarrow Phen + \cdot OH + OH^{-} \quad (4)$$

$$FlH_2 + O_2^{-}\cdot \rightarrow Fl + \cdot OH + OH^{-} \quad (5)$$

The single readily oxidizable hydrogen atom of CH_3PhenH is oxidized by $O_2^{-}\cdot$ to yield $CH_3Phen\cdot$

$$CH_3PhenH + O_2^{-}\cdot \rightarrow CH_3Phen\cdot + HO_2^{-} \quad (6)$$

The reactions of $O_2^{-}\cdot$ with BNH and NH_2OH are complicated. We propose that $O_2^{-}\cdot$ oxidizes BNH by a one-hydrogen-atom process[31]

$$BNH + O_2^{-}\cdot \rightleftarrows BN\cdot + HO_2^{-} \quad (7)$$

For NH_2OH, a plausible mechanism for the primary process is a three-hydrogen-atom transfer

$$NH_2OH + O_2^{-}\cdot \rightarrow NO + H_2O + OH^{-} \quad (8)$$

followed by further chemical reactions, such as the combination of NO with solvent or $O_2^{-}\cdot$.[30,32]

In summary, the reduction of $O_2^{-}\cdot$ by nonprotic reducing substrates is controlled by the number of readily oxidizable hydrogen atoms per substrate molecule. Conversion of such hydrogen atoms to protons provides the means to stabilize the reduction products of $O_2^{-}\cdot$ (O_2^{2-}, $\cdot O^{-}$, annd O^{2-}). Hence, $O_2^{-}\cdot$ is a selective oxidant for those substrates that are susceptible to oxidation via a hydrogen-atom transfer mechanism.

Acknowledgment. This work was supported by the National Science Foundation under Grant No. CHE-79-22040.

(25) If CH_3Phen^{+} is reduced electrochemically by one electron to $CH_3Phen\cdot$, the electrochemistry and spectroscopy are nearly identical with that of the equimolar combination of $O_2^{-}\cdot$ and CH_3PhenH. The cyclic voltammetry indicates that minor side products are formed; however, the dominant species is $CH_3Phen\cdot$. That $CH_3PhenH^{+}\cdot$ is not produced is verified by electrochemically reducing CH_3Phen^{+} by one electron in the presence of 1 equiv of HCl; the voltammetry and spectroscopy of $CH_3PhenH^{+}\cdot$ are distinctly different from that of $CH_3Phen\cdot$.

(26) Karrer, P.; Stare, F. J. *Helv. Chim. Acta* **1937**, *20*, 418.

(27) Mauzerall, D.; Westheimer, F. H. *J. Am. Chem. Soc.* **1955**, *77*, 2261.

(28) BNH in DMF has an irreversible oxidation wave at $E_{p_a} = +0.70$ V vs. SCE for an initial anodic scan, which results in three irreversible reduction waves at $E_{p_c} = -0.30$, -0.75, and -1.03 V vs. SCE on the reverse scan; it has no reduction waves for an initial cathodic scan. BNH in DMF also has an absorption band at 346 nm (ϵ 6270 M^{-1} cm^{-1}). The product solution of the $O_2^{-}\cdot$ reaction in DMF has four oxidation waves at $E_{p_a} = -0.10$, $+0.25$, $+0.59$, and $+0.87$ V vs. SCE, which result in only one reduction wave at $E_{p_c} = -1.03$ V on the reverse scan; for an initial cathodic scan reduction waves are not observed. The electronic spectrum of the product solution from the combination of BNH and $O_2^{-}\cdot$ illustrates that the 346-nm band of BNH shifts to 355 nm (ϵ 7190 M^{-1} cm^{-1}) and has two shoulders at 310 (ϵ 3700 M^{-1} cm^{-1}) and 370 nm (ϵ 6790 M^{-1} cm^{-1}) as well as a broad band of low intensity of 470 nm (ϵ 920 M^{-1} cm^{-1}).

(29) Concurrent with the loss of the bronze color is the disappearance of a broad irreversible oxidation wave at $E_{p_a} = -0.12$ V vs. SCE. In addition, two irreversible oxidation waves at $E_{p_a} = +0.13$ and $+0.58$ V vs. SCE occur. The +0.58-V wave can be attributed to the oxidation of NO_2^{-}; however, even under anaerobic conditions the autoxidation of NH_2OH in basic media results in some NO_2^{-}. Furthermore, preliminary results indicate that $O_2^{-}\cdot$ reacts with NO to produce NO_2^{-}.[30]

(30) Roberts, J. L.; Sawyer, D. T., unpublished results (1980).

(31) Presumably, BN· dimerizes, abstracts a solvent hydrogen atom, or is epoxidized by HO_2^{-} to yield a product solution similar to the starting material, BNH.

(32) Although Elstner and Heupel[33] conclude that formation of $O_2^{-}\cdot$ in aqueous media in the presence of NH_2OH yields NO_2^{-} by a primary one-hydrogen-atom transfer to $O_2^{-}\cdot$, the autoxidation of NH_2OH to NO_2^{-} in basic aqueous media is rapid. Thus, the role of $O_2^{-}\cdot$ under aqueous aerobic conditions may be as a Brønsted base rather than an oxidant.[20,34]

(33) Elstner, E. F.; Heupel, A. *Anal. Biochem.* **1976**, *70*, 616.

(34) Sawyer, D. T.; Gibian, M. J. *Tetrahedron* **1979**, *35*, 1471.

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Free Radical and Electron-Transfer Mechanisms for Tertiary Amine Oxidation

Sir:

We recently reported that the photooxidation of nonsymmetrical tertiary amines, e.g., R_2NR', by the singlet state of *trans*-stilbene in acetonitrile solution can result in the formation of two stilbene–amine adducts via the mechanism shown in Scheme I for ethyldimethylamine (**1**, R = CH_3).[1]

These reactions display moderate to high selectivity for formation of the adduct which results from oxidation of the less substituted alkyl group (a > b). Selective oxidation is attributed to a stereoelectronic effect on the deprotonation of an intermediate amine cation radical (aminium radical) and has been reported for chemical[2] and electrochemical[3] as well as photochemical[4] reactions. All of these oxidation reactions are believed to produce an α-amino radical by a sequential electron-transfer, proton-transfer mechanism rather than a one-step hydrogen-atom-transfer mechanism (Scheme I).

(1) Lewis, F. D.; Ho, T.-T. *J. Am. Chem. Soc.* **1980**, *102*, 1751.

(2) Lindsay Smith, J. R.; Mead, L. A. V. *J. Chem. Soc., Perkin Trans. 2* **1973**, 206.

(3) Lindsay Smith, J. R.; Masheder, D. *J. Chem. Soc., Perkin Trans. 2* **1976**, 47.

(4) (a) Lewis, F. D.; Ho, T.-I. *J. Am. Chem. Soc.* **1977**, *99*, 7991. (b) Lewis, F. D. *Acc. Chem. Res.* **1979**, *12*, 152.

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Scheme I

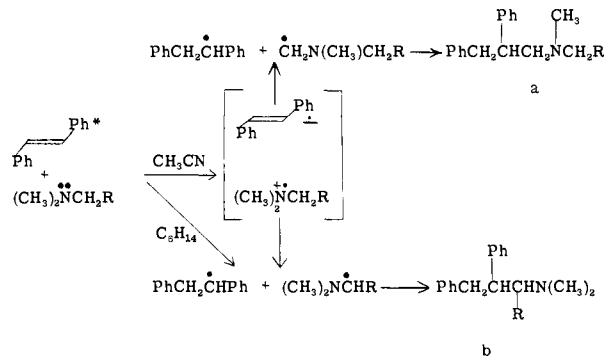

Table I. Quantum Yields and Reactivity of Tertiary Amines with Singlet *trans*-Stilbene[a]

	$(CH_3)_2NCH_2R$		hexane		acetonitrile	
	a	b				
no.	R =		k_q(rel)	$\Phi_b \times 10^2$	$\Phi_b \times 10^2$	$\Phi_a \times 10^2$
1	$-CH_3$		1.0	<0.1	0.20	2.6
2	-Ph		0.83	<0.1	1.2	4.0
3	$-CH=CH_2$		0.65	0.76	0.27	2.1
4	$-CO_2Et$		0.63	1.1	1.0	2.0
5	$-C\equiv CH$[b]		0.29	1.8		

[a] All data obtained on degassed solutions irradiated at 313 nm. [b] Strongly absorbing product formed in acetonitrile.

The failure of singlet stilbene to react with simple trialkyl amines in nonpolar solvents was attributed to the inability of the fluorescent singlet stilbene–amine exciplex to undergo full electron transfer.[4] We now report that several amines of structure $(CH_3)_2NCH_2R$, where R is capable of resonance stabilization of an adjacent free radical, undergo highly selective reaction with singlet stilbene via the *more* substituted α-amino radical in nonpolar solvent. Furthermore, both the orientation of stilbene–amine addition and the reaction mechanism are dependent upon solvent polarity.

Irradiation of *trans*-stilbene (0.05 M) and amines **3–5** (R = $-CH=CH_2$, $-CO_2Et$, and $-C\equiv CH$, respectively, 1.0 M) in hexane solution results in the formation of adducts of type b, but no adducts of type a (Scheme I, b/a > 10).[5] Lesser amounts of the other termination products of 1,2-diphenylethyl and α-amino radicals were also formed.[4] Quantum yields for stilbene–amine adduct formation are given in Table I along with the relative rate constants for quenching of stilbene fluorescence (k_q) by several amines in hexane solution. The values of k_q for amines **3–5** are smaller than those for **1** and other trialkylamines which fail to yield stilbene–amine adducts in hexane solution.[4] The low k_q values are in accord with the electron-withdrawing inductive effect of the R groups. Since 1.0 M amine does not completely quench singlet stilbene (66% quenching for **1**, 36% quenching for **5**), the efficiency of the addition process is somewhat higher than indicated by the quantum yields given in Table I.

Irradiation of stilbene with amines **1–4** in acetonitrile solution yields adducts of both type a and b, with a as the major adduct in all cases. Quantum yields for adduct formation in acetonitrile solution are given in Table I. The effect of solvent polarity upon the quantum yields of adduct formation from amines **3** and **4** is shown in Figure 1. The quantum yields for type a adducts increase with increasing solvent polarity, as previously observed for the formation of both type a and type b adducts of stilbene and trialkyl amines such as **1** and **2**.[4] In contrast, the yield of **3b** first decreases and then increases with increasing solvent polarity, while the yield of **4b** is essentially independent of solvent polarity. The isotope effect for addition of stilbene to the methylene carbon of $(CH_3)_2NCHDCO_2Et$ (CH vs. CD abstraction followed by radical coupling) is also solvent dependent,

(5) In the case of amine **3**, 10% of the stilbene–amine adduct was an isomer of **3b**, $PhCH_2CHPhCH_2CH=CHN(CH_3)_2$.

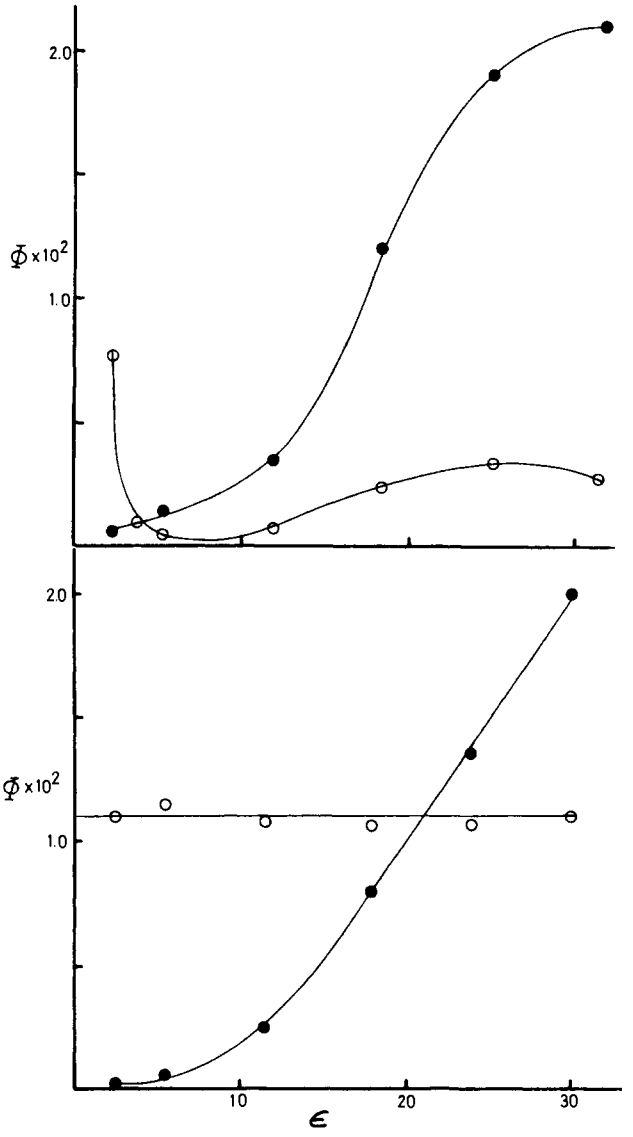

Figure 1. Quantum yields for the formation of adducts **3a** (●) and **3b** (○) (upper plot) and adducts **4a** (●) and **4b** (○) (lower plot) vs. solvent dielectric constant in hexane–ethyl acetate and ethyl acetate–acetonitrile mixed solvents.

decreasing from 2.24 in hexane to 1.53 in acetonitrile. The failure to observe formation of adducts of amine **5** in acetonitrile is due to the rapid formation of a strongly absorbing product which prevents the absorption of light by *trans*-stilbene.

The striking feature of our present results is the change from highly selective formation of type b adducts from stilbene and amines **3–5** in hexane solution to the formation of both type a and type b adducts in acetonitrile solution (Table I). While the orientation of chemical[6] and electrochemical[7] oxidation of amine **2** has been observed to be solvent dependent, selectivity of the type observed for stilbene–amine adduct formation in hexane solution has not previously been reported. The most attractive explanation of the observed solvent effect is that the extent of stilbene–amine charge transfer is small in hexane and large in acetonitrile, resulting in a change in the dominant reaction mechanism from hydrogen atom transfer to proton transfer. This explanation is in accord with the known effect of solvent polarity on the extent of charge transfer in aromatic hydrocarbon–tertiary amine exciplexes[8] and with our experimental results. A hydrogen-atom-

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transfer mechanism can account both for the highly selective formation of the more stable α-amino radical (Scheme I) and the failure of simple trialkyl amines such as **1** to yield stilbene–amine adducts in nonpolar solvents. The failure of amine **2** to yield a type b adduct in nonpolar solvent is, at first, surprising. However, nonbonded interactions between an *N*-methyl group and an ortho hydrogen of the phenyl group may prevent through-conjugation in the α-(dimethylamino)benzyl radical. Steric inhibition of resonance should be much less pronounced for the α-amino radicals from amines **3**–**5**. As we have previously reported, a proton-transfer mechanism can account for the selective formation of the less stable α-amino radical in polar solvents.[1,4] At present we cannot distinguish between hydrogen-transfer and proton-transfer mechanisms for the formation of type b adducts in moderately to highly polar solvents. The solvent dependence of the deuterium isotope effect on the formation of adduct **4b** is more consistent with a solvent-induced change in mechanism, as is the solvent dependence of the quantum yield for formation of **3b** (Figure 1).

The orientation of oxidation of amines **3**–**5** may prove to be a useful chemical diagnostic of radical vs. one-electron-transfer mechanisms for amine oxidation. For example, the triplet state of flavins (isoalloxazines) oxidizes the methylene carbon of *N*,*N*-dimethylglycine (free-radical mechanism?), whereas the flavoenzyme monoamine oxidase oxidizes the methyl carbons (electron-transfer mechanism?).[9] Further studies of selective amine oxidations are in progress in our laboratory.[10,11]

(8) Mataga, N.; Ottolenghi, M. "Molecular Association"; Academic Press: London, 1979; Vol. 2, Chapter 1.
(9) Frisell, W. R.; Chung, C. W.; Mackenzie, C. G. *J. Biol. Chem.* **1959**, *234*, 1297.
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A Model for Asymmetric Induction in the Diels–Alder Reaction

Sir:

The Diels–Alder reaction continues to stimulate much thought from a synthetic, mechanistic, and theoretical point of view. The application of this reaction to chiral synthesis has had mixed results, but some of the recent work has been highly encouraging.[1] The development of a model for enantioselectivity in such a reaction would serve to enhance the utility of this reaction in natural product synthesis. We wish to report the development of such a model and its application to the asymmetric formation of adduct **1**, a key intermediate toward several classes of important tetracycline natural products.[2,3]

(1) David, S.; Lubineau, A.; Thieffry, A. *Tetrahedron* **1978**, *34*, 299; David, S.; Eustache, J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2230. David, S.; Eustache, J.; Lubineau, A. *Ibid.* **1979**, 1795. Korolev, A.; Mur, V. *Dokl. Akad. Nauk. S.S.S.R.* **1948**, *59*, 251; *Chem. Abstr.* **1949**, *42*, 6776+. Most work has dealt with chiral dienophiles. See Boeckman, R. K., Jr.; Naegeby, P. C.; Arthur, S. D. *J. Org. Chem.* **1980**, *45*, 754. Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908; Jurczak, J.; Tracy, M. *J. Org. Chem.* **1979**, *44*, 3347; Hashimoto, S.; Komeshima, N.; Koga, K. *Chem. Commun.* **1979**, 437; Farmer, R. F.; Hamer, J. *J. Org. Chem.* **1966**, 6359; Walborsky, H. M.; Barash, L.; Davis, T. C. *Tetrahedron* **1963**, *19*, 2333.
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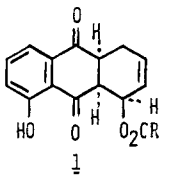
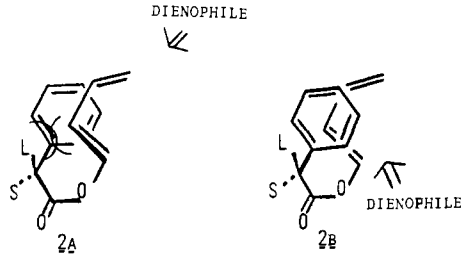


1

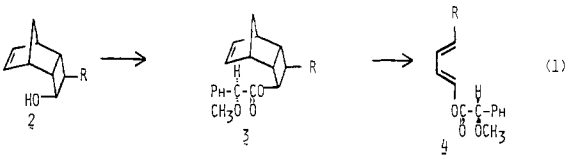
On the basis of a π-stacking model, two conformations can be envisioned for a diene such as **2**. In the folding represented by **2a**, the large group L projects toward the diene, encountering a



2A 2B

severe nonbonded interaction. Such a nonbonded interaction is between the small group S and the diene in conformer **2b**. On this basis, the latter would be favored. Effectively, the aromatic ring then serves as a steric steering group to direct the incoming dienophile to one of the two enantiotopic faces of the diene. Indeed, this simple model nicely predicts the observations.

The requisite dienes were synthesized according to eq 1.[4]

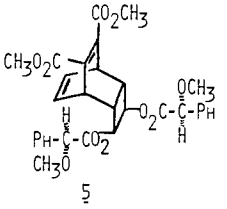


(1)

2 3 4

Esterification of **2** with (*S*)-*O*-methylmandeloyl chloride[5] or (*S*)-*O*-methylmandelic acid in the presence of dicyclohexylcarbodiimide and DMAP[6] led to the esters **3** (R = H, C_2H_5). Thermolysis liberated the dienes **4** (R = H, C_2H_5), quantitatively.

The diene **4** (R = (*S*)-*O*-methylmandeloxy) was available by the thermolysis of **5**.[7] Because of the possibility of racemization,



5

especially in the esterification step, the optical purity of diene **4** (R = H), $[\alpha]_D^{23}$ +14.4° (*c* 0.025, $CHCl_3$), was determined independently. Use of the chiral shift reagent Eu(hfbs)$_3$[8] showed no doubling of peaks whereas the racemic compound, prepared identically from racemic O-methylmandelic acid, showed two methoxy singlets of equal intensity at δ 4.09 and 4.20 with 20 mol % shift reagent. Thus, on this basis, we estimate the optical purity of **4** to be >95% and, probably, ~97% based upon the fact that the starting mandelic acid is 97% optically pure.

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