nitroacetate in homogeneous conditions. In fact, reactions performed in protic solvents with a base such as triethylamine afforded mixtures of diastereoisomers where the cis isomer is the main component. Table II summarizes some results concerning reactions of ethyl nitroacetate with, respectively, 2-bromohexadecanal (8) in heterogeneous and homogeneous conditions.

Our synthetic approach to 5-substituted 2-isoxazolin-4-ols needs now to be completed by effecting the deoxygenation of the parent 2-oxides. Scheme I shows this conversion for compound **16**. The 2-isoxazolin-4-ol **23** is a potential intermediate for the synthesis of phytosphingosine,[17] the backbone component of plant sphingolipids[18,19] as its D-(+)-erythro isomer. We carried out this reaction successfully on the *tert*-butyldimethylsilyl ether **21**[20] by heating at 100 °C in trimethyl phosphite[21] followed by easy removal of the protective group with fluoride anion.[22]

In summary, a new and general procedure for the stereoselective construction of 4-hydroxylated 2-isoxazolines from readily available starting materials has been developed. The sequence is amenable to prepare several 2-deoxy-2-amino-3,4-dihydroxyalkane derivatives **2** of current interest. Furthermore, the established connection of diastereoisomeric ratios of cis and trans isomers of compound **5** to the reaction conditions allows a good control of the stereochemistry in a predictable way and augurs well for its synthetic utility.

Mechanistic studies to suggest a detailed picture of the function of alumina as solid support, the dependence of heteregeneous and homogeneous conditions on the diastereoisomeric ratio, and further applications of this route to natural product synthesis form the focus of our current endeavors and will be reported in due course.

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Supplementary Material Available: Detailed procedures and characterization data (correct elemental analyses, IR, ^{1}H NMR and ^{13}C NMR spectra) for compounds **6–23** (5 pages). Ordering information is given on any current masthead page.

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Homolytic and Heterolytic N–H Bond Strengths

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Summary: $E_{1/2}$ values for the reversible cyclic voltammetric (CV) oxidations of the nitranions derived from iminostilbene, phenoxazine, and phenothiazine, obtained at 1000 V/s scan rates, are in remarkable agreement with irreversible CV anodic peak potentials obtained at 0.1 V/s scan rates and therefore suggest that homolytic N–H bond dissociation energies based on the irreversible data do not suffer from large errors associated with electrochemical irreversibilities. Acidity and 10 000 V/s redox data for iminostilbene and its respective anion and radical, when compared to similar data for 9-phenylxanthene and its respective anion and radical, suggest that the N–H bond in iminostilbene is about 22 kcal/mol stronger, in a heterolytic cation/hydride forming sense, than the 9C–H bond in 9-phenylxanthene.

In efforts to gain new insight into the heterolytic and/or homolytic strengths of selected chemical bonds present in various organic and inorganic molecules, chemists have utilized thermochemical cycles comprised of solution-phase proton and electron transfer data.[1] An advantage of evaluating bond strengths in this way is that many of the data that result from the thermochemical cycles are often difficult to obtain using other techniques.

The dimethyl sulfoxide (DMSO) equilibrium acidity scale has proven to yield reliable data concerning the energetics of proton transfer to and from organic acids and anions.[2] Thermochemical cycles that incorporate DMSO acidity data have been shown to yield new facts concerning (a) heterolytic strengths of specific bonds in various neutral organic molecules[1a,3] and (b) homolytic strengths of various H–A bonds, where A is carbon,[1c,4] nitrogen,[5,6] oxygen, or sulfur.[7] For a given acid H–A, it has been demonstrated that the absolute DMSO acidity constant for H–A, combined with the irreversible oxidation potential for A^- (as shown in eq 1 where all parameters are in kcal/mol), yields

$$\Delta BDE(H\text{–}A) = \Delta pK_a(H\text{–}A) + \Delta E_{ox}(A^-) \quad (1)$$

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Table I. DMSO Solution pK_a's (25 °C) and Relative Acidity Constants (ΔpK_a) for Iminostilbene (1), Phenoxazine (2), and Phenothiazine (3), Reversible $E_{1/2}$ Values and Irreversible Anodic Peak Potentials ($E_{p,a}$ Values) for the Cyclic Voltammetric Oxidations of 1-H$^+$, 2-H$^+$, and 3-H$^+$, $\Delta E_{1/2}$ and $\Delta E_{p,a}$ Values for 1-H$^+$, 2-H$^+$, and 3-H$^+$, and Relative N–H Homolytic Bond Dissociation Energies (ΔBDE) for 1–3 Based on the $\Delta E_{1/2}$ and $\Delta E_{p,a}$ Data

substrate (*n*)	pK_a[15]	ΔpK_a,[16] kcal/mol	$E_{1/2(n-H^+)}$,[17] V	$\Delta E_{1/2}$,[18] kcal/mol	$E_{p,a(n-H^+)}$,[19] V	$\Delta E_{p,a}$,[20] kcal/mol	ΔBDE,[21] kcal/mol via $\Delta E_{1/2}$	ΔBDE,[21] kcal/mol via $\Delta E_{p,a}$
iminostilbene (1)	26.1	(0.0)	−0.28	(0.0)	−0.29 (−0.31)	(0.0)	(0.0)	(0.0)
phenoxazine (2)	21.65	−6.1	−0.24	0.9	−0.25 (−0.25)	0.9	−5.2	−5.2
phenothiazine (3)	22.7	−4.7	−0.18	2.3	−0.18 (−0.20)	2.5	−2.4	−2.2

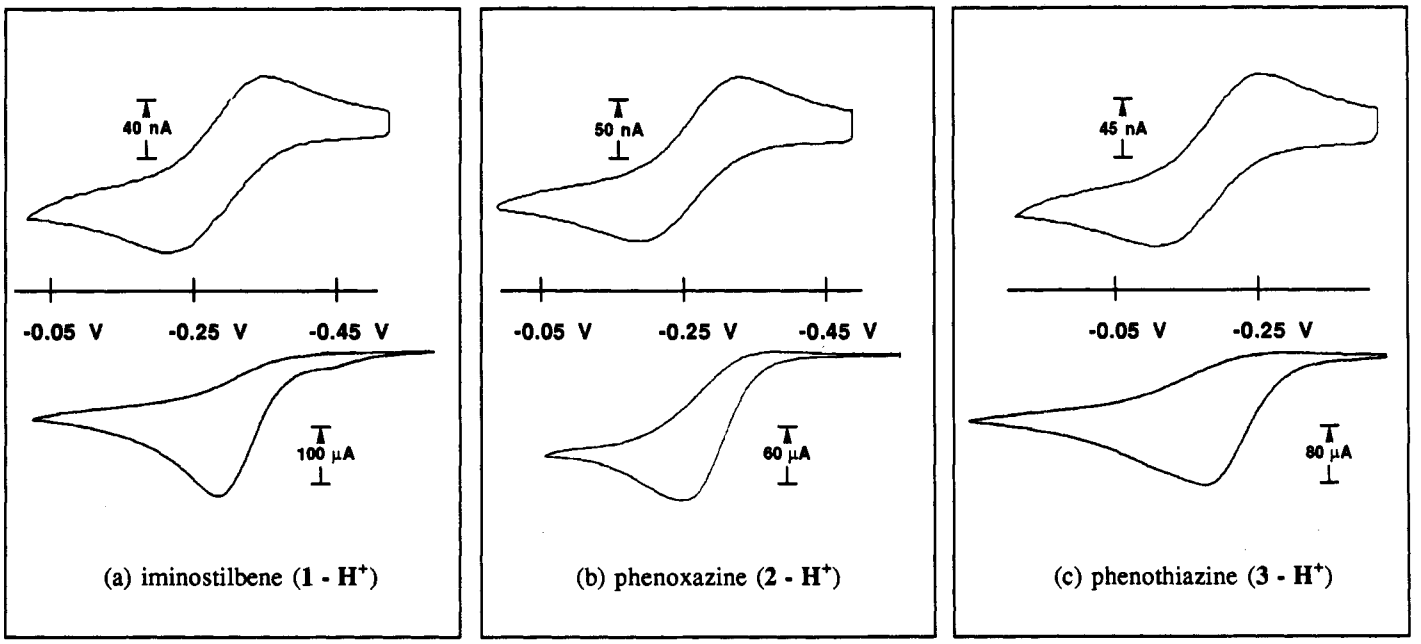
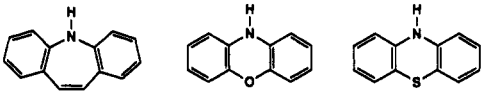


Figure 1. Reversible (1000 V/s; nA currents) and irreversible (0.1 V/s; μA currents) CV oxidations for the nitranions derived from iminostilbene (1-H$^+$), phenoxazine (2-H$^+$), and phenothiazine (3-H$^+$).

relative homolytic bond strength data for H–A that agree nicely with the (enthalpic) gas-phase homolytic bond dissociation energies (BDE) for H–A. It has also been shown that the addition of a constant (ca. 56 kcal/mol) to the acidity and redox data enables comparison of the solution-phase homolytic BDEs with analogous gas-phase BDEs.[7] Thus, the linking of proton and electron transfer data enables evaluation of the stabilities of the radicals A$^\bullet$ in the same way that pK_a data enable evaluation of the stabilities of the anionic species A$^-$.

While interpretations of gas-phase BDEs are often hampered by uncertainties as large as 2–3 kcal/mol,[8] the solution-phase BDEs obtained via the published cycles also suffer from uncertainties of a similar or greater magnitude. Whereas DMSO pK_a data are generally thought to be accurate to the nearest 0.1 pK_a unit,[2] estimates of the uncertainties involved in the oxidations of the organic anions are problematic due to the irreversible nature of the redox processes. Nevertheless, relative and "absolute" BDE data obtained via incorporation of irreversible redox data into thermochemical cycles are in remarkable agreement with published gas-phase BDE data.[6-8]

We have constructed a microcomputer-controlled microelectrode-based fast scanning cyclic voltammetry (FSCV) apparatus similar to that described by Wightman.[9] Our FSCV device is capable of scan rates as high as 30 000 V/s and has been utilized in the anodic oxidations of several carbanions[10] and nitranions. In this Communication, we report on the anodic oxidations of the anions derived from the neutral nitrogen acids iminostilbene (1), phenoxazine (2), and phenothiazine (3) and compare the



1 2 3

reversible $E_{1/2}$ values that result from the 1000 V/s data with previously reported (0.1 V/s) irreversible $E_{p,a}$ values (where p,a refers to the potential at the *p*eak *a*nodic current; $E_{ox} = E_{p,a}$) for the same species. The main conclusion that can be drawn from these data is that the reversible 1000 V/s $E_{1/2}$ values for 1-H$^+$, 2-H$^+$, and 3-H$^+$ (i.e., the conjugate bases derived from 1–3, respectively) are within 30 mV of published irreversible 0.1 V/s $E_{p,a}$ values reported for the same species[5] and within 10 mV of 0.1 V/s data obtained in our laboratory.

Acidity data for iminostilbene (1), phenoxazine (2), and phenothiazine (3), and three sets of redox data for 1-H$^+$, 2-H$^+$, and 3-H$^+$, are listed in Table I. Inspection of the $E_{1/2}$ and $E_{p,a}$ values for 1-H$^+$, 2-H$^+$, and 3-H$^+$, respectively, reveals that the 1000 V/s derived $E_{1/2}$ values are nearly equal to the published $E_{p,a}$ values,[5] as well as to $E_{p,a}$ values obtained in our laboratories. The $E_{p,a}$ values were obtained using conventional electrodes at scan rates of 0.1 V/s.

The reversible (1000 V/s) and irreversible (0.1 V/s) CV traces for the anodic oxidations of 1-H$^+$, 2-H$^+$, and 3-H$^+$ are shown in Figure 1a–c. Examination of Figure 1 reveals that the 1000 V/s data are fully reversible. The $E_{1/2}$ values obtained from these experiments are thermodynamically valid and can therefore be incorporated into the thermochemical cycle depicted in eq 1 with confidence. Insertion

(8) McMillen, D. F.; Golden, D. M. *Ann. Rev. Phys. Chem.* **1982**, *33*, 493–532.
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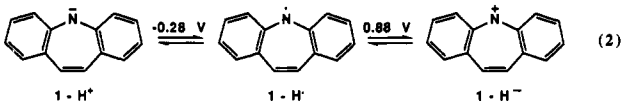
of the appropriate data from Table I into eq 1 enables comparison of the homolytic strengths (in a free energy sense) of the N-H bonds contained within 1, 2, and 3. Since the absolute pK_a's for 1, 2, and 3 are accurate to the nearest 0.1 pK_a unit (±0.14 kcal/mol), and the $E_{1/2}$ values for the oxidations of 1-H$^+$, 2-H$^+$, and 3-H$^+$ are reproducible to less than 0.010 V (±0.23 kcal/mol), the uncertainties in the ΔBDE values are ≤1 kcal/mol. Furthermore, comparison of the ΔBDE data based on either the reversible $E_{1/2}$ values or the irreversible $E_{p,a}$ values indicates that neglible errors are associated with the use of irreversible oxidation potentials for the delocalized nitranions 1-H$^+$, 2-H$^+$, and 3-H$^+$.[11] While not necessarily indicative of a general trend, these data suggest that small errors are associated with the incorporation of irreversible oxidation potentials into eq 1, at least for the oxidations of delocalized nitranions 1-H$^+$, 2-H$^+$, and 3-H$^+$.

Finally, the voltammogram that results from the 10 000 V/s oxidation of the nitranion derived from iminostilbene (1-H$^+$) is interesting in that reversible couples are observed at $E_{1/2}$ values of −0.28 and 0.88 V. The redox couples centered around −0.28 and 0.88 V are due to the processes depicted in eq 2. Reversible anion/radical ($E_{1/2}$ = −0.84



(2)

V) and radical/cation ($E_{1/2}$ = 0.38 V) redox couples are also observed for 9-phenylxanthene (pK_a = 27.9[2]). *Comparison* of the heterolytic strengths (in a cation/hydride forming sense) of the N-H bond in iminostilbene (1) and 9C-H bond in 9-phenylxanthene is facilitated by eq 3 (as

$$\Delta BDE_{het}(H\text{-}A) = \Delta pK_a(H\text{-}A) + \Delta E_{ox}(A^-) + \Delta E_{ox}(A^\cdot) \quad (3)$$

in eq 1, all parameters in kcal/mol), where $\Delta E_{ox}(A^\cdot)$ refers to the difference in the oxidation potentials of the *radicals* derived from iminostilbene and 9-phenylxanthene.[12]

Insertion of the appropriate acidity and redox data for 9-phenylxanthene and iminostilbene into eq 3 indicate that the N-H bond in iminostilbene is ca. 22 kcal/mol stronger than the C-H bond in 9-phenylxanthene, when comparing the heterolytic strengths of these bonds in a "nitrenium-" and "carbocation"-forming sense.[13] We are not aware of published data that enable comparisons of C-H and N-H bond strengths in hydride/cation-forming reactions. Nevertheless, a difference of this magnitude is sensible in light of (a) the known stability of the 9-phenylxanthenium cation (pK_{R^+} = 1.1[3]) and (b) the likely instability of the cation derived from iminostilbene (1-H$^-$), due to the greater electronegativity of nitrogen (compared to carbon) as well as the nitrenium character of 1-H$^-$.[14] Our investigations of the heterolytic and homolytic strengths of chemical bonds are continuing.

Acknowledgment. The financial support of the United States Department of Energy (Office of Basic Energy Science) is gratefully acknowledged.

(11) Similar agreement between irreversible $E_{p,a}$ values and reversible $E_{1/2}$ values has been observed when oxidizing 9-arylxanthenide carbanions. Rudy Gostowski, unpublished results.

(12) (a) This cycle is similar to one used previously to estimate pK_{R^+} values in DME solution.[12b] (b) Breslow, R.; Mazur, S. *J. Am. Chem. Soc.* **1973**, *95*, 584-585.

(13) Comparison of the DMSO acidity data for 9-phenylxanthene and iminostilbene (pK_a = 27.9 and 26.1, respectively) reveals that the 9C-H bond in 9-phenylxanthene is 2.5 kcal/mol *stronger*, in a heterolytic anion/proton forming sense, than the N-H bond in iminostilbene, a result presumably due to the greater electronegativity of nitrogen (compared to carbon). Insertion of the appropriate redox data into eq 1 for 9-phenylxanthene and iminostilbene suggests that the 9C-H bond in 9-phenylxanthene is ca. 10 kcal/mol *weaker*, in a homolytic radical forming sense, than the N-H bond in iminostilbene.

(14) (a) Gassman, P. G. *Acc. Chem. Res.* **1970**, *3*, 26-33. (b) Gassman, P. G.; Granrud, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 1498-1499.

(15) The acidity data in Table I are taken from ref 2 and are believed to be accurate to ±0.1 pK_a unit (0.14 kcal/mol).

(16) At 25 °C, 1 pK_a unit is equal to 1.37 kcal/mol. Therefore, for a given substrate *n*, ΔpK_a (kcal/mol) = 1.37[$pK_{a(n)}$ − 26.1], where 26.1 is the pK_a for iminostilbene in DMSO solution. Negative ΔpK_a values signify that the molecule in question is a stronger acid than iminostilbene.

(17) Electrochemistry conditions: (a) scan rate = 1000 V/s; (b) supporting electrolyte, tetrabutylammonium perchlorate (1 M), nitranions present at 0.015 M concentrations; (c) Ag/AgI reference and platinum working electrodes, where the ferrocene/ferrocenium redox couple = 0.875 V; (d) the Ag/AgI data were corrected to NHE_{aq} by substracting 0.125 V.[4,7] The $E_{1/2}$ values are reproducible to less than 0.010 V (0.23 kcal/mol). Complete details concerning the microelectrode-based FSCV device will be published separately.

(18) At 25 °C, 1 V is equal to 23.06 kcal/mol. For the anion derived from a given substrate *n*, $\Delta E_{1/2}$ (kcal/mol) = 23.06[$E_{1/2(n\text{-}H^+)}$ − 0.28]; where −0.28 is the $E_{1/2}$ value for the anion derived from iminostilbene (1).

(19) $E_{p,a}$ refers to the potential at the peak anodic current for the oxidative wave. Scan rate = 0.1 V/s; conventional size (2 mm diameter) platinum disk electrode; BAS 100A analyzer. All other CV parameters identical to the FSCV conditions.[17] Values in parentheses are from ref 5 and were collected using 0.1 M tetraethylammonium tetrafluoroborate electrolyte and 0.002 M analyte.[5]

(20) For the anion derived from a given substrate *n*, $\Delta E_{p,a}$ (kcal/mol) = 23.06[$E_{1/2(n\text{-}H^+)}$ − 0.29], where −0.29 is the $E_{p,a}$ value for the anion derived from iminostilbene (1).

(21) The ΔBDE values in Table I have been determined with the aid of eq 1. Negative ΔBDE values signify that the bond in question is weaker than the analogous bond in iminostilbene.

Study of Receptor–Ligand Interactions through Receptor Labeling and Isotope-Edited NMR

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Summary: The use of isotopically labeled receptor in isotope-edited NMR experiments is used to study receptor–ligand complexes.

The interactions of proteins with small molecules are responsible for a vast array of biological phenomena, including, among others, the regulation of metabolism and intra- and intercellular communication. Protein–small molecule complexes also provide windows into the general structural, dynamical, and energetic requirements for intermolecular interaction. Thus, by studying the various properties of receptor–ligand complexes, it should be possible not only to illuminate specific biological problems but also to gain insight into the general rules governing intermolecular interaction.

One technique that has proven extremely useful in recent years for studying receptor–ligand complexes is isotope-edited nuclear magnetic resonance (NMR) spec-

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