and ruthenium[21] couples, respectively, at 25°, pH 7, and $I = 0.10$. These yield a calculated rate constant for our reaction of (3–6) $\times 10^4$ M^{-1} sec^{-1}, in remarkable agreement with the observed value. It seems likely that our reaction would proceed 20–30 times more slowly were it not for the potential difference.

Presumably outer-sphere reductants even milder than $Ru(NH_3)_6^{2+}$ reduce cyt c^{III} with second-order rate constants[22,23] comparable to ours. The physiological reductant of cyt c^{III}, cyt c_1^{II}, also reacts very rapidly in solution, 3.3×10^6 M^{-1} sec^{-1} at 10°,[24] while being only a slightly stronger reductant than cyt c^{II} [24] and substantially weaker than $Ru(NH_3)_6^{2+}$. Our demonstration that an unambiguously outer-sphere reduction of cyt c^{III} can occur with first-order rate constants approximating those observed physiologically and our mechanistic arguments based on energetics provide support for associating the reactivity of cyt c^{III} with a mechanism involving outer-sphere electron transfer to the exposed edge of the heme ring,[2,3,10] collaborated physiologically with stereospecific electrostatic interactions between proteins[10] (consistent with the temperature dependence of the cyt c_1^{II}–cyt c^{III} rate reported[24] above 10°).

Finally we note the similarity of our acid-dependent term to that observed above pH 4.4 in the Cr(II)–cyt c^{III} reaction.[6a] While this path almost certainly involves reduction of protonated cyt c^{III} in both cases, it is difficult to accept the protonated sites as being the same since we have not observed the complex behavior reported below pH 4.4.[6a] This behavior was rationalized by a scheme in which one of the extraplanar iron ligands is protonated prior to reduction.[6a] Since this is presumably the initial step in the unfolding of the protein,[25] it conceivably might provide an inner-sphere reductant such as Cr(II) with a more facile path than an outer-sphere reductant. A rather speculative alternative for the site of protonation in our case is Thr 78. This idea is based on the suggestion that the physiological reduction of cyt c^{III} might be facilitated on protonation of this residue by a suitably positioned acidic function on the reductase.[10] If, in fact, the reductase protonates a cytochrome residue prior to reduction, it seems feasible that sufficiently acidic solutions could act similarly.

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Ralph X. Ewall, Larry E. Bennett*
Department of Chemistry, San Diego State University
San Diego, California 92115
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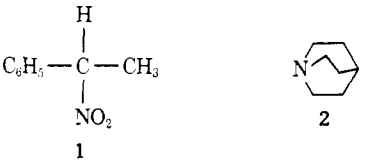
Unusual Catalytic Activity of Thiophenoxide Ions

Sir:

We have discovered a catalytic effect of thiophenoxide ion pairs which may have considerable importance in helping to understand the mechanisms of certain important enzyme-catalyzed reactions. By way of background we have been studying the racemization of 1-nitro-1-phenylethane (**1**) in propionitrile as catalyzed by



1 2

amines and by mixtures of amines and acids. There are, of course, extensive and important studies by Cram, by Streitwieser, and by others of catalysis by strong bases in a variety of nonaqueous solvents.[1-3] But there have been relatively few studies of catalysis by weak acids or bases in aprotic solvents, and this field certainly merits further work.[1,4-13]

At 25° typical rate constants for catalysis of racemization of **1** are 4.06×10^{-3} for triethylamine, 18.7×10^{-3} for *N*-methylpyrrolidine, and 192×10^{-3} for quinuclidine (**2**), all M^{-1} sec^{-1}. Mixtures of amines with 2,4-dinitrophenol show uv–visible absorption curves similar to those of tetraethylammonium 2,4-dinitrophenoxide and thus they contain hydrogen bonded ion pairs,[14,15] the acid–base reaction being virtually quantitative. Rates of racemization are predictable on two simple hypotheses: (1) with an excess of amine present the 2,4-dinitrophenol is converted quantitatively to ion pairs, and (2) the only catalytic species present is remaining free amine, the dinitrophenoxide ion pairs being catalytically inactive. Separate tests with tetraethylammonium 2,4-dinitrophenoxide showed this also to be inactive.

Contrasting results were obtained with the acid thiophenol, addition of which gave strong rate acceleration. We have not yet obtained a precise value for the equilibrium constant for the reaction between thiophenol and quinuclidine, but the approximate value is 25 M^{-1}. The catalytic constant for the ion pair is then about 2.6

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$$Q + C_6H_5SH = QH^+SC_6H_5^-$$

M^{-1} sec^{-1}, or some 10 times the value for quinuclidine, our best amine catalyst. Tetraethylammonium thiophenoxide has a catalytic constant of 4.2 M^{-1} sec^{-1} toward **1** and is also a potent catalyst for racemization of 1,2-diphenyl-1-propanone, $k = 1.6 \times 10^{-3}$ M^{-1} sec^{-1} at 25°. With amines this reaction has to be studied at temperatures above 100° to get a reasonable rate.

Apparently, the strong catalytic effect of thiol anions toward proton removal has not been noted before. This effect may be of considerable importance in connection with several enzyme systems. For example β-aspartate ammonia lyase has been postulated to use a cysteinyl-S$^-$ group to remove the β-proton in the elimination of the groups H...NH$_3^+$, a step which previously did not have strong support.[16] It turns out that many enzymes which catalyze a reaction that formally requires removal of a proton from carbon such as aldol-type condensations and β elimination do in fact have -SH groups at the active site. Specific examples are rabbit muscle aldolase[17] and thiolase[18] where alternative roles have been suggested for the thiol group at the active site. We have no intention to suggest that a -S$^-$ group must participate in all enzymes of these classes. Since the substrate is often actually enclosed in a relatively hydrophobic region,[19] our example in propionitrile may have direct bearing on an important aspect of these mechanisms.

1-Nitro-1-phenylethane was prepared by oxidation of α-methylbenzylamine by peracetic acid[20] and purified from acetophenone by a combination of distillation and treatment with 2,4-dinitrophenylhydrazine. We obtained crystalline product in 10% yield, mp 28–31°, $[\alpha]^{25}_{546}$ −32 (*c* 4, propionitrile). The 1,2-diphenyl-1-propanone was a sample prepared by J. LeBlanc.[21,22]

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DeLos F. DeTar,* Don M. Coates
Department of Chemistry and Institute of Molecular Biophysics
The Florida State University
Tallahassee, Florida 32306
Received November 11, 1973

Circular Dichroism of Disulfides with Dihedral Angles of 0, 30, and 60° in the 400–185 nm Spectral Region[1]

Sir:

In efforts to understand the dependence of the optical activity of disulfide-containing biological molecules on the CSSC dihedral angle φ, we have measured the CD spectra of (9*S*,10*S*)(−)-*trans*-2,3-dithiadecalin (**1a**),[2,3] (4*R*,5*R*)(+)-4,5-isopropylidenedioxy-1,2-dithiane(**1b**),[2,4] (4*R*,5*R*)(+)-4,5-dihydroxy-1,2-dithiane (**1c**)[2,4] and the 4,5-*O*,*O*-diacetate of **1c** (**1d**),[5] φ ≃ 60°,[6,7] methyl 4,6-dideoxy-4,6-epidithio-α-D-galactoside (**2a**)[8] and the 2,3-*O*,*O*-diacetate of **2a** (**2b**), φ ≃ 30°,[9] and 1α,5α-epidithioandrostane-3α,17β-diol (**3**),[10] φ ≃ 0°.[10] The disulfide chirality in **1a**, **2a**, and **2b** is *M* (left-handed helix) and *P* in **1b**, **1c**, and **1d**.

Previous studies have demonstrated the blue shift (370–250 nm) of the first transition as φ is opened from 0 to 90°[11] and correlated the sign of the CD band (negative) for this transition with the disulfide chirality (*M*).[2,12] Various theoretical treatments[13] are in substantial agreement as to the nature of this transition, which is in Boyd's notation[13b] $n_a \rightarrow \sigma^*_{SS}$. While CD bands at ~240[2,3,12a] and 200 nm[3,14] have been observed for 1,2-dithianes, the chiroptical properties of the higher energy transitions remain in general little understood. Of particular interest is a CD band ($n_b \rightarrow \sigma^*_{SS}$)[13b] of opposite sign to $n_a \rightarrow \sigma^*_{SS}$ which is predicted to shift toward the red as φ is opened, becoming nearly degenerate with $n_a \rightarrow \sigma^*_{SS}$ at φ ≃ 90°.[15]

The CD spectrum of **1a** in hexane (294 (−5.5),[16] 243.5 (+5.0), 205 (−33), shortest wavelength recorded 182 (+42)) is shown in Figure 1. Better insight into the origin of optical activity in the far-uv region is provided by CD spectra of **1a** in vapor (negative bands at 216 and 206 nm, positive bands at 196 sh and 188 nm),[17] **1a** in methanol (210 sh (−18), 202 (−24)), **1c** in

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(16) Measurements were made with a Durrum/JASCO Model ORD/UV CD-5 incorporating the SS-10 modification. CD data are represented as λ_{max} ($\Delta\epsilon$) where $\Delta\epsilon = [\theta]/3300$. Shoulders are designated by sh.
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