benzylammonium permanganate oxidation of **16** in methylene chloride.[18b]

The above data suggest that the observed manganese species formed during the permanganate ion oxidation of **3a**, **3b**, **6**, and **7–15** is probably a soluble $Mn^{IV}[H_2MnO_3]$ species which slowly precipitates.[63] It also appears that the previously reported intermediates detected in the permanganate ion oxidation of **3a**, **4–6**, **16**, and (*Z*)-2-butene-1,4-diol[64] are also Mn(IV) compounds.[10]

Although the spectra of Mn(IV) from the permanganate ion oxidation of **3a**, **3b**, **6**, and the uracils show some resemblance to the spectrum of Mn(V) (Figure 5),[58,62] the oxidation state data in Table VI argue strongly against a pentavalent manganese species. However, it is not unreasonable to expect formation of a transient, undetectable hypomanganate ester (**2**) as an intermediate in these reactions. A mechanism which regards Mn(V) and Mn(VI) as short-lived intermediates (eq 3 and 4) and can

$$2MnO_4^{3-} + 2H_2O \rightarrow MnO_4^{2-} + MnO_2 + 4OH^- \quad (3)$$

$$3MnO_4^{2-} + 2H_2O \rightarrow 2MnO_4^- + MnO_2 + 4OH^- \quad (4)$$

account for the variety of products obtained from the permanganate ion oxidation of carbon–carbon double bonds is shown in Scheme I. The fate of the hypomanganate ester (**2**) and the product distribution are determined by the reaction conditions.

Acknowledgment. I express my thanks to Professor Manfred Eigen, at the Max Planck Institut für Biophysikalische Chemie, Göttingen, for his hospitality during the preparation of this manuscript.

(63) Although the composition of the soluble Mn(IV) species cannot be formulated at this time, we regard it as H_2MnO_3. Other possibilities include phosphate complexes.

(64) Son, N. T.; Jáky, M.; Simándi, L. I. *Inorg. Nucl. Chem. Lett.* **1976**, *12*, 291.

Intramolecular Catalysis of Organic Oxidation and Reduction Reactions: Rapid and Microscopically Reversible Thioether–Sulfoxide Interconversions in Dilute Acid

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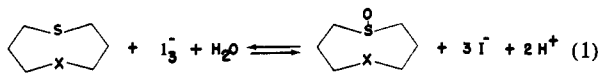
Contribution from the Department of Chemistry, University of California, Davis, California 95616. *Received August 11, 1980*

Abstract: We recently reported that the aqueous HI reduction of 1,5-dithiacyclooctane 1-oxide was accelerated by about 10^6 compared to common sulfoxides. We have now observed a rate acceleration of about the same magnitude in the reverse reaction: the I_2 oxidation of the corresponding thioether. The acceleration and insensitivity of the rate to pH and buffers are attributed to intramolecular catalysis by the transannular thioether group. Similarly, 5-methyl-1-thia-5-azacyclooctane 1-oxide and its thioether are rapidly and easily interconverted. Although different rate laws are observed in the two systems, these anchimerically assisted processes allow either the oxidation or the reduction to occur rapidly and completely in *dilute acid*. The direction of the reaction is reversed quantitatively in the same solution by a slight change of pH. These unique reversible redox systems are simple models which satisfy the criteria of speed and reversibility required by biochemical electron- and proton-transfer reactions.

We recently reported that the HI reduction of certain mesocyclic sulfoxides proceeds 10^6 times faster than the reduction of Me_2SO and attributed the acceleration to intramolecular catalysis.[1,2] We now report an acceleration of a similar magnitude in the reverse reactions: the oxidation of mesocyclic thioethers 1,5-dithiacyclooctane (A) and 5-methyl-1-thia-5-azacyclooctane (G) by aqueous I_2. *Of paramount importance is the fact that the position of the redox equilibria (eq 1) can be shifted rapidly*



(1)

A ; X = S
G ; X = NCH_3
E ; X = S
M ; X = NCH_3

and essentially quantitatively to either side by a change of less than 2 pH units. For example, under the proper conditions, the oxidation of A with I_2 at pH 3.5 is 95% complete in 2 min; the reaction can be completely reversed in the same solution in less than 5 s when the pH is lowered to 1.5. The cycle can be repeated. Further oxidation of E to 1,5-dithiacyclooctane 1,5-dioxide occurs at least 10^6 times slower than the rate of formation of E from A. This difference in rate illustrates the enormous catalytic effect of the transannular thioether group relative to a transannular sulfoxide group. The tertiary amine group is an equally effective catalyst in promoting the rapid and reversible interconversion of G and its sulfoxide M. These redox systems are unique in their speed and simplicity and in the extent of their reversibility by addition of acid or base. We are not aware of any redox reactions of organic molecules which are as rapid and which can be reversed as completely *in the same solution* by changing either the pH or the concentration of any of the reagents.

Experimental Section

Materials and Solvents. 1,5-Dithiacyclooctane (A) and 5-methyl-1-thia-5-azacyclooctane (G) and their sulfoxides were synthesized as described elsewhere.[1,3]

Solutions of buffer were prepared with use of analytical reagent grade salts. The pH values of the buffers and of the $HClO_4$ solutions were checked before the reaction. The solutions were diluted with conductivity water which had been boiled and cooled under N_2.

Spectrophotometric Kinetic Measurements. Equal volumes of separate solutions of the sulfide in water and the buffered triiodide solutions were thermostated and simultaneously injected into a thermostated 1-cm

(1) Doi, J. T.; Musker, W. K. *J. Am. Chem. Soc.* **1978**, *100*, 3533.

(2) Musker, W. K.; Hirschon, A. S.; Doi, J. T. *J. Am. Chem. Soc.* **1978**, *100*, 7754.

(3) Leonard, N. J.; Yethon, A. E. *Tetrahedron Lett.* **1965**, *48*, 4259. Yethon, A. E., Ph.D. Thesis, University of Illinois, Urbana, IL, 1968.

(4) Roush, P. B.; Musker, W. K. *J. Org. Chem.* **1978**, *43*, 4295.

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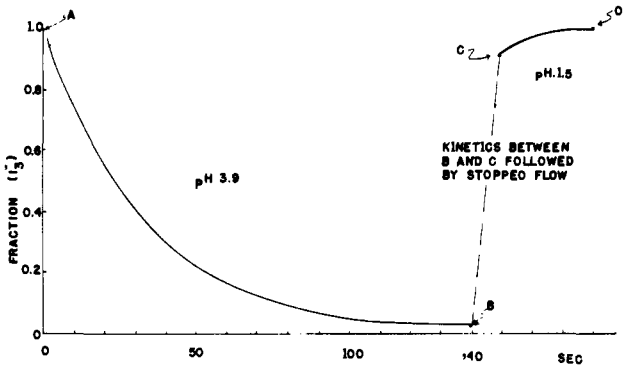


Figure 1. Extent of the reversible oxidation of 1,5-dithiacyclooctane (A). Plot of fraction $[I_3^-]$ observed spectrophotometrically vs. time at 26.0 °C. [A] = 0.415×10^{-3} M, [KI] = 0.5 M, and $[I_3^-]_0 = 5.3 \times 10^{-5}$ M. The decay of $[I_3^-]$ from A to B represents the oxidation of A at pH 3.9; k = 0.0290 s^{-1}. At point B, the pH was lowered to 1.5 by injection of additional $HClO_4$. Curve C–D represents the development of I_3^- in the acidified solution. The actual kinetics obtained by stopped-flow technique have been reported.[1]

Table I

Oxidation of 1,5-Dithiacyclooctane (A)
(26.0 °C, 0.50 M KI, $[I_3^-]_0 = (3\text{–}5) \times 10^{-5}$ M)

10^4[A], M	pH	buffer	k, M^{-1} s^{-1} [a]
4.15	6.0	0.0125 M phosphate	125 ± 3
2.96	6.0	0.0125 M phosphate	134 ± 3
2.07	6.0	0.0125 M phosphate	146 ± 3
1.19	6.0	0.0125 M phosphate	121 ± 2
4.15	3.9	none, $HClO_4$	62 ± 6
3.53	4.5	none, $HClO_4$	64 ± 10

Reduction of 1,5-Dithiacyclooctane 1-Oxide (E) (26.0 °C)

10^2[$HClO_4$], M	[salt], M	10^2k, s^{-1}
1.93	[KI] = 0.50	3.5 ± 0.8
5.0	[NaI] = 0.30	52 ± 3[b]
0.732	[NaI] = 0.30	0.61 + 0.03[b]
2[c]	[NaI] = 0.50[c]	ca. 6 (calcd)[c]

[a] Error determined from replicate runs. Additional data are in Figures 1-3. [b] Reference 1. [c] Extrapolated from data in ref 1.

quartz cell in the Cary 17 spectrophotometer. The I_3^- absorbance at 353 nm was recorded during the course of the reaction. Pseudo-first-order rate constants were calculated by least-squares plot of ln $[I_3^-]$ vs. time with the use of 6–12 points. The logarithmic relationship means that $d[I_3^-]/dt \propto [I_3^-]$, which is used in the calculation of pseudo-first-order rate constants. However, since $[I_3^-]/[I^-][I_2] = 723$ at 25 °C,[5] $d[I_3^-]/dt \propto [I^-][I_2](723)$. The latter equation is used in expressing the rate law. Since the rates of oxidation were first order in sulfide in the range $(0.4\text{–}1.2) \times 10^{-3}$ M, second-order rate constants were calculated by dividing the pseudo-first-order rate constants by the sulfide concentrations.

Reaction Products. The products of the oxidation reactions were extracted into CH_2Cl_2 from a solution which had been concentrated by freeze-drying and saturated with K_2CO_3. These sulfoxides were identified by comparison of their NMR spectra with those of known samples.[3,4] The oxidation of A yielded only E, and the oxidation of G yielded only M.

Results

1,5-Dithiacyclooctane (A). Data for the oxidation of A are reported in Table I and shown in Figures 1–3. The constancy of the values obtained in Table I with use of different concentrations of A demonstrates that the oxidation is first order in [A].

The dependence of the rate of oxidation on iodide is complex. At low iodide concentration, 0.2–0.4 M, the order appears to be $[I^-]^{-2}$, but as $[I^-]$ increases the apparent order increases and approaches $[I^-]^{-3}$. In Figure 2 the normalized second-order rate constants, k $(M^{-1}\ s^{-1})/b$, are plotted against iodide concentration.

(5) Gensch, K.-H.; Higuchi, T. *J. Pharm. Sci.* **1967**, *56*, 177.

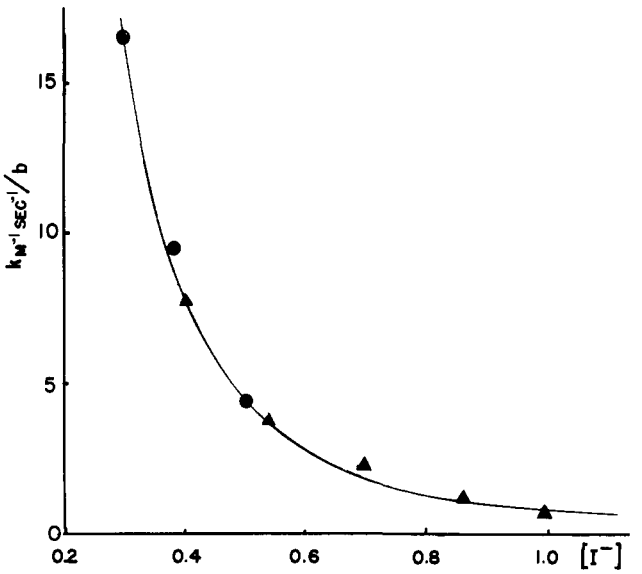


Figure 2. Iodide dependence of the rate of the I_2 oxidation of 1,5-dithiacyclooctane (A) at 26.0 °C in 0.0125 M phosphate buffer with pH 6.0: (●) [A] = 3.53×10^{-4} M, $[I_3^-]_0 = (2\text{–}5) \times 10^{-5}$ M, [KI] + [KCl] = 0.50 M; b = 32; (▲) [A] = 5.44×10^{-4} M, $[I_3^-]_0 = (2\text{–}5) \times 10^{-5}$ M, [KI] + [KCl] = 1.0 M; b = 40. The curve was generated by using the function $[I^-]^{-2}([I^-] + 0.4)^{-1}$.

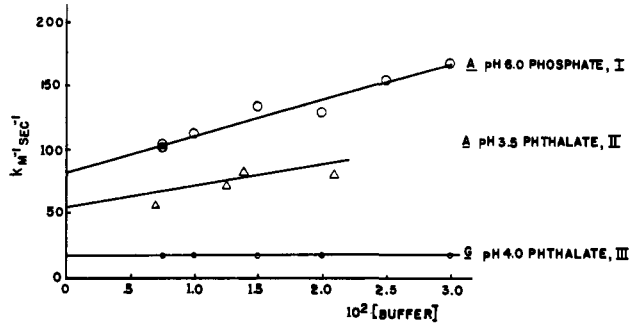


Figure 3. Effect of buffer concentration on second-order rate constants when A or G is oxidized by aqueous iodine at 26.0 °C with $[I_3^-]_0 = (2\text{–}4) \times 10^{-5}$ M. Conditions: for I, 3.53×10^{-4} M A, 0.50 M KI, pH 6.0 phosphate; for II, 6.55×10^{-4} M A, 0.50 M KI, pH 3.5 phthalate; for III, 3.64×10^{-4} M G, 0.37 M KI, 0.125 M KCl, pH 4.0 phthalate.

The normalization factors differ by 25% for the two different ionic strengths used in the data collection. The theoretical curve is drawn as the solid line in Figure 2 where the function $[I^-]^{-2}([I^-] + 0.4)^{-1}$ is plotted against the iodide concentration. The function was selected because the $([I^-] + 0.4)$ term would cause the dependence on iodide concentration to change in the region of 0.4 M I^-. Both sets of data are consistent with the theoretical curve. Thus, the rate law is $-d[I_3^-]/dt = -d[A]/dt = k_{Ox}' \cdot [A][I_3^-][I^-]^{-2}([I^-] + 0.4)^{-1} = k_{Ox}[A][I_2][I^-]^{-1}([I^-] + 0.4)^{-1}$.

As reported earlier,[1] the rate law for reduction of E in the range of 0.15–0.30 M NaI is $-d[E]/dt = k_{Red}[E][H^+]^2$. These rates were extremely fast, but because of the second-order dependence on acid concentration, the rates could be measured in dilute acid $(2.0 \times 10^{-1}\text{–}5.0 \times 10^{-3}$ M $HClO_4)$. The combined rate laws allow a determination of the steps leading to the activated complex from both sides of the reversible reaction. At a given pH, the effect of buffer concentration on the oxidation rates is small and is shown in Figure 3 for both phosphate and phthalate buffers. If rate constants for oxidation are extrapolated to 0 M buffer, the extrapolated rate constants are 61–68% of the rate measured at 0.0125 M buffer. Thus, the extrapolated values of buffered runs in Figure 3 are 52 and 80 M^{-1} s^{-1}. These values bracket the values of 62 and 64 M^{-1} s^{-1} found in unbuffered $HClO_4$ and are reported in Table I. The insensitivity of the oxidation of A to buffer is one of major kinetic differences between the behavior of the mesocyclic dithioether and simple acyclic monothioethers. For

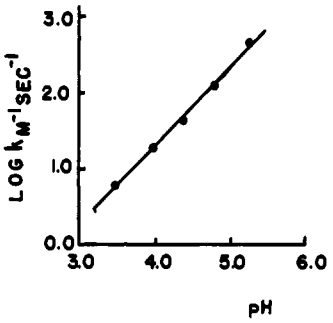


Figure 4. Plot of log k (M^{-1} s^{-1}) against pH for the oxidation of G·HBF_4 (3.64×10^{-4} M) by iodine in solutions containing 0.375 M KI, 0.125 M KCl, and 0.0125 M phthalate buffer; $[I_3^-]_0 = (2\text{–}4) \times 10^{-5}$ M; slope = 1.01; coefficient of correlation = 0.992.

example, in the I_2 oxidation of tetrahydrothiophene,[6] the rate is ca. 1 M^{-1} s^{-1} at 0.0125 M phthalate and, when the data are extrapolated to 0 M buffer, the rate would be 0.

The effect of pH on the rate of oxidation is also small. As seen in Figure 3, a change in pH from 3.5 to 6.0 causes the rate to change only by a factor of 1.5. In contrast, the I_2 oxidation of methionine[5] and of tetrahydrothiophene[6] (either with or without buffer) shows rate changes of about 100 over the pH range 4.0–6.0. The relative rates of oxidation, extrapolated to 1 M KI, are, for A:methionine:tetrahydrothiophene (no buffer) at pH 6, 20:0.6:2 $\times 10^{-6}$; and at pH 4, 16:0.01:3 $\times 10^{-8}$.

Throughout this study our results and conclusions were compared with those previously reported for methionine.[5] The main reason for making this comparison is that the I_2 oxidation of methionine and the HI reduction of dehydromethionine are well-studied two-electron processes. The reactions are similar in that an internal nucleophile is intimately involved in the oxidation of methionine, A, and G, and specific buffer effects are minimal. The main difference occurs only after the electron-transfer step because dehydromethionine is relatively stable to a hydrolytic ring-opening reaction.

The effects of both buffer and pH on the anchimerically assisted I_2 oxidation of A in dilute acid appear to be perturbations of much smaller magnitude than those found in other systems. Thus, intramolecular catalysis is the dominant feature in the oxidation of A.

The NMR of the isolated product E is consistent with an authentic sample of 1,5-dithiacyclooctane 1-oxide. To further confirm that the product of the fast reaction is E and not some unexpected intermediate, it was necessary to perform the following kinetic experiment: In 10^{-3} M $HClO_4$, A was oxidized with an equivalent amount of iodine. The acid concentration of this solution was raised to 0.0193 M, and the rate of I_3^- regeneration was followed. The rate constant was calculated by using a standard relationship with allowance for the back-reaction which is still significant at this acidity. As seen in Table I the value (3.5 ± 0.8) $\times 10^{-2}$ s^{-1} compares favorably with the value of ca. 6×10^{-2} s^{-1} calculated from the data on the HI reduction of E reported earlier.[1]

The extent of the reversibility of the reaction is demonstrated in Figure 1, which shows a plot of the fraction $[I_3^-]$ observed spectrophotometrically vs. time. The decay of $[I_3^-]$ from A to B represents the oxidation of 1,5-dithiacyclooctane at pH 3.9. At point B, when only 4% of the I_3^- remains, the pH of the solution was lowered to 1.5 by injection of additional dilute $HClO_4$. Points between C and D represent the last 10% of the reduction of 1,5-dithiacyclooctane 1-oxide. The actual kinetics for the entire reduction reaction were obtainable only by stopped-flow techniques and were reported.[1]

5-Methyl-1-thia-5-azacyclooctane. The rate of oxidation of G was too fast too be determined at pH >5.3 by conventional means. When $[G]_0$ was varied, the rate was directly proportional to $[G]_0$ as shown in Table II. The dependence of the rate on $[H^+]$ as shown in Figure 3 reflects an inverse first-order dependence on acid concentration. The data at pH 4.0 as given in Figure 5 indicate a dependence on $1/[I^-]^{0.8}$. Noninteger orders in halide are not uncommon in aqueous oxidations.[6,8] The concentration of phthalate buffer does not affect the rate. The rates of oxidation of G at pH 4.0 in phthalate buffer were invariant with changing buffer concentration as shown by the horizontal line in Figure 3. Additionally, the rates of oxidation are the same in pH 3.5 phthalate as in $HClO_4$, as shown by runs 3 and 4, Table II. From these experiments

$$d[I_3^-]/dt = -k[G{\cdot}H^+][I^-]^{-1}[H^+]^{-1}[I_3^-] = d[G]/dt$$

but

$$[G{\cdot}H^+][H^+]^{-1} = [G]/K_a$$

where K_a = dissociation constant for acid G·H^+ and, as explained earlier, $[I^-]^{-1}[I_3^-] \propto [I_2]$.

The rate law is then

$$-d[G]/dt = k_{Ox}'[G][I_2]$$

Table II. Oxidation of 5-Methyl-1-thia-5-azacyclooctane (G)[a] (26.0 °C, 0.12 M KI, pH 3.5, $[I_3^-]_0 = (2\text{–}5) \times 10^{-5}$ M)

10^4[G], M	buffer	[buffer], M	k^b
0.55	phthalate	0.0125	15.5 ± 0.7
0.79	phthalate	0.0125	15.2 ± 0.2
1.10	phthalate	0.0125	16 ± 1
0.55	$HClO_4$	none	20 ± 1

[a] Additional data are summarized in Figures 3-6. [b] k given in terms of M^{-1} s^{-1}. Error determined from replicate runs.

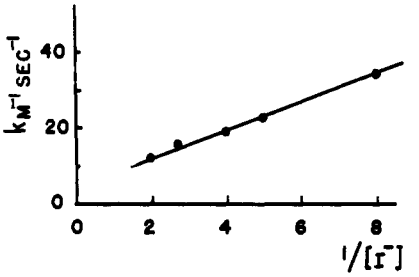


Figure 5. Plot of k (M^{-1} s^{-1}) against $1/[KI]$ for the oxidation of G·HBF_4 (3.64×10^{-4} M) with I_2; $[I_3^-]_0 = (2\text{–}4) \times 10^{-5}$ M. The pH was maintained at 4.0 with use of 0.0125 M phthalate buffer and at constant ionic strength with use of [KI] + [KCl] = 0.50 M.

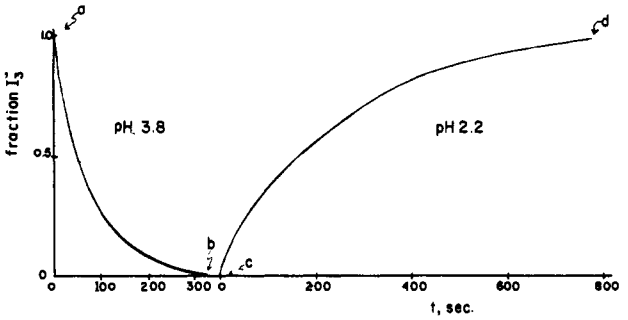


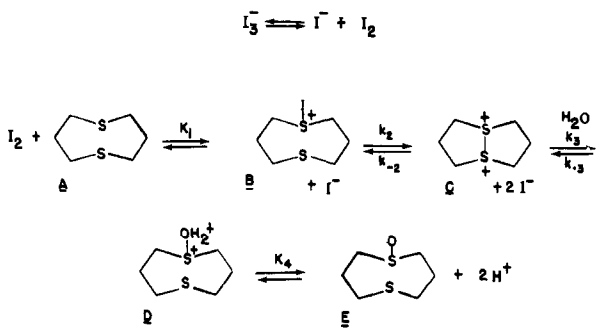
Figure 6. Extent of the reversible oxidation of 5-methyl-1-thia-5-azacyclooctane (G). Plot of fraction $[I_3^-]$ observed spectrophotometrically vs. time at 26.0 °C. $[G]_0 = 0.36 \times 10^{-3}$ M, $[I_3^-]_0 = 3.0 \times 10^{-5}$ M, and $[I^-] = 0.12$ M. The decay of $[I_3^-]$ from A to B represents oxidation of G at pH 3.8, and the development of $[I_3^-]$ from C to D represents reduction of M at pH 2.2.

(6) (a) Higuchi, T.; Gensch, K.-H. *J. Am. Chem. Soc.* **1966**, *88*, 3874. (b) Higuchi, T.; Gensch, K.-H. *Ibid.* **1966**, *88*, 5486.

(7) (a) Miotti, G.; Modena, G.; Sedea, L. *J. Chem. Soc. B* **1970**, 802. (b) Landini, D.; Modena, G.; Montanari, F.; Scorrano, G. *J. Am. Chem. Soc.* **1970**, *92*, 7168.

(8) When a sulfide also contains a protonated tertiary amine or quaternary ammonium salt functionality, the iodide dependence is consistently a few tenths of a unit lower than integral: Doi, J. T.; deLeeuw, D. L., unpublished results.

Scheme I. Reversible Oxidation and Reduction of 1,5-Dithiacyclooctane



This is complementary with the rate law for the reduction of M which is

$$-d[M]/dt = k_{Red}[M][H^+]^2[I^-]^2$$

The oxidation of G by I_2 at pH 3.8 and the reduction of M in the same solution at pH 2.2 were observed. These data are shown in Figure 6. The first-order rate constant for the reduction of M was 6.5×10^{-3} s^{-1} at pH 2.6, which is about twice as fast as that calculated from the data we reported earlier (in pH 2.65, NaI–$NaClO_4$ solutions). This variation should not cause any particular problem. The reaction is sensitive to both $[H^+]^2$ and $[I^-]^2$, and small variations in the value of either of these concentrations cause a significant change in the apparent value of k. The reaction was observed between <1 and >99% completion in both directions (Figure 6). This required 21 min. Examination of the rate law leads to the conclusion that the use of a wider pH range would shorten the time for oxidation and reduction.

Discussion

1,5-Dithiacyclooctane. The data in Figure 2 indicate that the rate of oxidation of A by I_2 is proportional to $[I^-]^{-1}([I^-] + 0.4)^{-1}$. This dependence on iodide concentration is compatible with the mechanism proposed in Scheme I using a steady-state approximation[1] in which the dication C is a steady-state intermediate.

$$\frac{d[A]}{dt} = -\frac{[A][I_2]}{[I^-]}K_1k_2k_3\frac{1}{[I^-]k_{-2} + k_3}$$

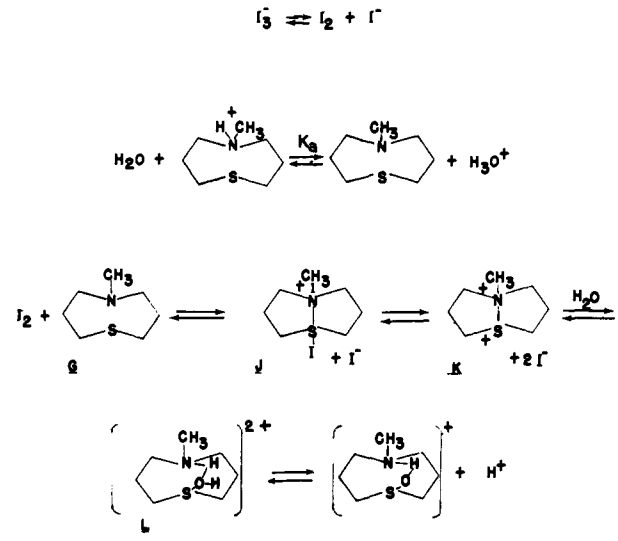
The $[I^-]$ dependence of the reaction indicates that the ratio of $k_{-2}/k_3 = 2.5 \pm 0.6$. This is compatible with the rate law for the reduction of E.[1]

$$\frac{d[A]}{dt} = [E][H^+]^2\frac{K_4k_{-3}[I^-]k_{-2}}{[I^-]k_{-2} + k_3}$$

The mechanism which best describes the complete reversible redox reaction is shown in Scheme I. It should be noted that the reduction kinetics were previously used to define steps 3 and 4 since they preceded the rate-determining step of the reduction. However, steps 1 and 2 were speculative since they occurred after the rate-determining step. The kinetics of the oxidation reaction are interpreted in terms of these steps. The order of the oxidation in iodide is most simply interpreted in terms of an establishment of an equilibrium between A and B followed by the rate-determining formation of C. Reversibility is easily achieved by intercepting the intermediate dication either by water (k_3) at the higher pH to give E or by iodide (k_{-2}) at the lower pH to give A. Intermediates B and D are written without a formal bond between the two sulfur atoms since we have no experimental evidence which suggests that such a bond is present. Nevertheless we believe that a strong intramolecular interaction is present in both B and D which, in the limit, gives rise to S–S bonded sulfurane intermediates.[9]

5-Methyl-1-thia-5-azacyclooctane. Scheme II outlines a series of steps which is compatible with the unusual rate law observed for this system. The rate law for the oxidation, $-d[G]/dt = k_{Ox}'[G][I_2]$, indicates that a reaction involving the free amine G and I_2 is rate determining, and intermediate J is the product of the rate-determining step. The remaining steps in Scheme II had been proposed[2] to explain the acceleration and kinetics for the HI reduction of M in which iodide attack on J appears to be rate determining. This experimental evidence which confirms that the same step is rate determining in both the forward and backward directions is important since evidence of this type has rarely been reported in an organic redox reaction.

Scheme II. Reversible Oxidation and Reduction of 5-Methyl-1-thia-5-azacyclooctane



Reversible Organic Redox Reactions. Only a few samples of reversible homogeneous organic redox reactions have been studied. The oxidation of *o*-methylthiobenzoic acid to its sulfoxide by I_2 is catalyzed by the neighboring carboxyl group.[10] The reaction can be reversed by adding HI.[11] Likewise the oxidation of methionine[5] and some of its derivatives to isothiazolidines by I_2[12,13] can also be reversed by HI.[12,13] In each of these examples, the rate in either direction is much slower than that in the mesocycles and the acid concentration must be changed by at least 10^5 to completely and rapidly reverse the reaction. The methionine–dehydromethionine interconversion is not always completely reversible.[5] If any hydrolysis of dehydromethionine occurs, reversibility is severely restricted since the reduction of methionine sulfoxide proceeds at a much slower rate than dehydromethionine.

In truly catalytic thioether–sulfoxide interconversions, the principle of microscopic reversibility must be obeyed. However, in previous studies, the catalytic path which the reaction follows on oxidation at high pH may be different from the path it follows on reduction at low pH. The large changes in pH required to reverse the reaction change the relative concentrations of both intramolecular and external catalytic species. For example, it was proposed that the reduction of 2-methylsulfinylbenzoic acid[11] is catalyzed by the undissociated carboxylic acid group whereas the oxidation of 2-methylthiobenzoic acid[10] proceeds via the carboxylate anion. In the extreme it is possible for a reduction to proceed via a noncatalyzed path at low pH if the catalytic site is masked by protonation. In these mesocyclic systems the transannular thioether and tertiary amine groups which function as catalysts are so efficient that external perturbations such as buffer species and pH are relatively unimportant.

Other classes of organic redox reactions are notoriously irreversible. For example, the stoichiometry and acid dependence of these thioether–sulfoxide interconversions are similar to the well-known hydroquinone–benzoquinone redox couple. Since the

(9) Young, P. R.; Hsieh, L.-S. *J. Am. Chem. Soc.* **1978**, *100*, 7121.

(10) Tagaki, W.; Ochiai, M.; Oae, S. *Tetrahedron Lett.* **1968**, *58*, 6131.
(11) Landini, D.; Rolla, F.; Torre, G. *Int. J. Sulfur Chem., Part A* **1972**, *2*, 43.
(12) Lambeth, D. O.; Lardy, H. A. *Biochemistry* **1969**, *8*, 3395.
(13) Lambeth, D. O.; Swank, D. W. *J. Org. Chem.* **1979**, *44*, 2632.

heterogeneous hydroquinone–benzoquinone electrode is reversible and its potential can be varied by altering the pH, we thought that homogeneous systems involving this couple might show similar behavior. However, we were unable to find any redox reaction involving this couple[14] in which reactants were converted essentially completely to products and then regenerated by changing the pH.

In one of the most thorough studies of the kinetics of the benzoquinone–hydroquinone redox system,[14d] Castro and coworkers examined the oxidation of hydroquinone by low-spin iron(III) porphyrins and the reduction of benzoquinone by low-spin iron(II) prophyrins. Redox reactions were shown to proceed in both directions, but only initial rates could be used because pseudo-order plots drifted with time. Because of the nonideal behavior, a complete kinetic analysis could not be carried out and no attempt to completely shift an equilibrium mixture could be made.

Likewise, redox indicators and dyes are other systems which come to mind when organic molecules which may undergo reversible redox reactions are being screened. However, these systems are not completely reversible as they have a tendency to undergo slow irreversible solvolytic and photolytic decomposition.

From these results on thioether–sulfoxide interconversions it is clear that suitable neighboring groups effectively catalyze both the oxidation and the reduction reaction. These intramolecular catalysts can provide an efficient, reversible low-energy path for *electron-transfer, oxide-transfer, and proton-transfer processes* in biology. There is precedent for the suggestion that a thioether–sulfoxide couple may be important in biological redox reactions.[15] It has been proposed at various times that the conversion of a thioether to a sulfoxide could provide a molecular basis of oxidative phosphorylation.[12,15,16] However, Wang pointed out that sulfoxide reduction must also be achieved in an efficient way in order for the mechanism to be valid.[17]

Our results show that a thioether–sulfoxide two-electron interconversion is kinetically feasible when an intramolecular interaction leads to a stabilized cationic thioether intermediate.[18] Various other substituents on amino acid side chains may also be capable of providing anchimeric assistance.

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(14) (a) Baxendale, J. H.; Hardy, H. R.; Sutcliffe, L. H. *Trans. Faraday Soc.* **1951**, 47, 963. (b) Yamazaki, I.; Ohnishi, T. *Biochim. Biophys. Acta* **1966**, *112*, 469. (c) Mentasti, E.; Pelizzetti, E.; Saini, G. *J. Chem. Soc., Dalton Trans.* **1973**, 2609. (d) Castro, C. E.; Hathaway, G. M.; Havlin, R. *J. Am. Chem. Soc.* **1977**, *99*, 8032. (e) Deuchert, K.; Hünig, S. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 875.

(15) Lardy, H. A.; Ferguson, S. M. *Annu. Rev. Biochem.* **1969**, *38*, 991.

(16) Glass, R. S.; Williams, E. B., Jr.; Wilson, G. S. *Biochemistry* **1974**, *13*, 2800.

(17) Wang, J. H. *J. Bioenerg.* **1976**, *8*, 209.

(18) Because thioether cation radicals are also well-known, one-electron, oxidations may also be catalyzed. In this regard it should be noted that an S–S bonded dimethionyl cation radical has been implicated as the source of the EPR signal on oxidation of yeast cytochrome *c* oxidase by hydrogen peroxide.[19]

(19) Hoffman, B. M.; Roberts, J. E.; Brown, T. G.; Kang, C. H.; Margoliash, E. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 6132.

Synthesis and Complexation Properties of Macrocyclic Polyethers Derived from Chiral and *meso*-1,1′-Bicyclohexyl-2,2′-diols[1,2]

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Abstract: Five novel macrocyclic polyether ligand systems containing the bicyclohexyl structural unit are reported. The requisite 1,1′-bicyclohexyl-2,2′-diols were prepared by hydroboration–oxidation of bi-1-cyclohexen-1-yls. Equimolar reaction of bi-1-cyclohexen-1-yl (**4**) with borane in THF, followed by oxidation, gave two products, *d,l*- and *meso-trans,trans*-[1,1′-bicyclohexyl]-2,2′-diols (**5** and **6**, 3:1, respectively). Employment of a larger excess of borane led selectively to diol **5**, which could be obtained in optically active form by using the novel resolving agent (–)-menthoxyacetaldehyde or by asymmetric hydroboration of **4**, using monoisopinocampheylborane. Hydroboration–oxidation of (3*R*,3′*R*,5*R*,5′*R*)-tetramethylbi-1-cyclohexen-1-yl, prepared in six steps from (+)-pulegone, gave a *pseudomeso*-1,4-diol (**14a**, 51%) and a symmetrical 1,4-diol (**15a**, 21%). Hydroboration–oxidation of 3,3,3′,3′,5,5,5′,5′-octamethylbi-1-cyclohexen-1-yl, prepared in three steps from isophorone, was controlled to yield a single product, *meso*-1,4-diol **14b**. Diols **5**, **6**, **14a**, **14b**, and **15a** were converted to the *trans–transoid–trans*-2,5,8,11,14,17-hexaoxatricyclo[22.4.0.0^{18,23}]octacosanes **24a** and **24b** and the trans–cisoid–trans analogues **25a**, **25b**, and **25c** by using sodium hydride and pentaethylene glycol ditosylate. The free energies of association of these systems in $CDCl_3$ at 25 °C with Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and *t*-$BuNH_3^+$ picrates and at 0 and 25 °C with *t*-$BuNH_3^+$ thiocyanate were determined. The ion selectivity of each bicyclohexyl ligand system was similar to those of analogous binaphthyl hosts and 18-crown-6 derivatives. The average negative free energies of association ($-\Delta G°_{av}$) for Li^+, Na^+, K^+, Rb^+, Cs^+, and NH_4^+ picrates decreased in the order **25a** > **24b** > **25b** = **24a** > **25c**. In the trans–transoid–trans series methylation (**24a** → **24b**) increased $-\Delta G°_{av}$, whereas in the trans–cisoid–trans series methylation (**25a** → **25b** → **25c**) decreased $-\Delta G°_{av}$.

The design of synthetic macrocyclic ligand systems capable of selective complexation with metal and ammonium cations has been the subject of numerous investigations.[4-7] The accurate prediction of complexation properties of such systems requires detailed knowledge of the structural factors that control molecular association. The ion and enantiomer selectivities of macrocyclic

(1) This work was supported by a grant from the National Science Foundation, CHE 77-00452, and was performed in the laboratories of Professor Donald J. Cram.

(2) Some of these synthetic results were outlined in a preliminary communication. Bell, T. W. *Tetrahedron Lett.* **1980**, 3443-3446.

(3) Current address: Cornell University, Department of Chemistry, Baker Laboratory, Ithaca, N.Y. 14853.

(4) (a) Chao, Y.; Weismann, G. R.; Sogah, G. D. Y.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 4948-4958 and earlier publications in this series. (b) Cram, D. J.; Cram, J. M. *Science* **1974**, *183*, 803-809. (c) *Acc. Chem. Res.* **1978**, *11*, 8-14.

(5) Lehn, J.-M. *Acc. Chem. Res.* **1978**, *11*, 49-57. *Pure Appl. Chem.* **1978**, *50*, 871-892.

(6) Prelog, V. *Pure Appl. Chem.* **1978**, *50*, 893-904.

(7) Stoddart, J. F. *Chem. Soc. Rev.* **1979**, *8*, 85-142.

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