to shift the resonances of ^{23}Na and ^{39}K,[25-31] proved to be an efficient shift reagent for ^{7}Li as well.

A typical experiment was performed as follows. Large unilamellar egg phosphatidylcholine vesicles (LUV)[32] were loaded with NaCl, LiCl, or a mixture of the two. The external medium was changed to KCl by dialysis. In the presence of the shift reagent, the residual extravesicular signals of ^{23}Na or ^{7}Li shifted to higher field. Following the addition of L^-, the transport of Li^+ and Na^+ was clearly seen by the simultaneous decrease in intravesicular signals and increase in extravesicular ones (Figure 1). The unfacilitated transport of Na^+ and Li^+ was negligible in the timescale of the experiment. The fact that the shift between the intra- and extravesicular signals remained constant throughout the experiment indicated that the $Dy(TPP)_2^{7-}$ shift reagent did not penetrate the vesicles. In order to eliminate the possibility that the changes in signal intensities were the result of rupture of the vesicles caused by L^-, we followed the inward transport of ^{7}Li. The observed increase of the intravesicular ^{7}Li signal indicated that we were observing a genuine transport (Figure 2).

The time course of the process measured by the integrated areas in each experiment was phenomenologically fitted to an exponential function giving an apparent rate constant, k. The values of k calculated from the intravesicular signal intensities and those calculated from the extravesicular signals, for each experiment, were the same within the experimental error. The apparent rate constant was found to be proportional to the concentration of the carrier L^-. For example, in an experiment with vesicles loaded with 150 mM NaCl the k values for the transport of Na^+ were 3.2, 6.2, 8.7, 13.8, 17.9, and 26.7 $\times 10^{-3}$ min^{-1} for L^- concentrations 0.091, 0.182, 0.30, 0.40, 0.60, and 0.80 mM, respectively, giving $k/[L^-] = 33 \pm 3$ M^{-1} min^{-1}. In similar experiments with vesicles loaded with 150 mM LiCl, the k values for the transport of Li^+ were 2.6, 4.2, and 38.6 $\times 10^{-3}$ min^{-1} for L^- concentration of 0.01, 0.025, and 0.2 mM, respectively, giving $k/[L^-] = 208 \pm 50$ M^{-1} min^{-1}. These results are consistent with a 1:1 ligand to metal complex as the active species in the transport. Preliminary results indicated that the rate of transport of Li^+ is inversely proportional to Li^+ concentration and increases with H^+ concentration, pointing at LiL-HL exchange as a possible mechanism for the facilitated transport of Li^+. The selectivity in the rates of transport in favor of Li^+ over Na^+ was further demonstrated by competition experiments using vesicles loaded with mixtures of NaCl and LiCl. For vesicles loaded with 75 mM NaCl and 75 mM LiCl, the ratio of the rates of transport of Li^+ and Na^+ was 22 ± 6. In vesicles loaded with 110 mM NaCl and 40 mM LiCl, this ratio was about 40. The relative Li^+/Na^+ selectivity may further increase at lower $[Li^+]/[Na^+]$ ratios, as the rate of Li^+ transport is inversly proportional to the Li^+ concentration, while that of Na^+ is less sensitive to the $[Li^+]/[Na^+]$ ratio. The selectivity of L^- in favor of the Li^+ ions by a factor greater than 40 compares favorably with other Li^+ ionophores.[5-12]

The efficiency of L^- as a carrier compared to a known ionophore was determined by measuring the values of the apparent rate constants for the transport of Li^+ and Na^+ induced by monensin.[33] For vesicles loaded with 75 mM LiCl and 75 mM NaCl, the values $k/[\text{ionophore}]$ obtained for monensin were 1.4 $\times 10^3$ and 2.6 $\times 10^4$ M^{-1} min^{-1} for Li^+ and Na^+, respectively. For comparison, $k/[\text{ionophore}]$ values for L^- were 750 and 27 M^{-1} min^{-1} for the same two cations under identical conditions. It is hoped that chemical modification of the ligand will yield other ionophores with improved properties.

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Epoxidation of Olefins by Iodosylbenzene Catalyzed by Binuclear Copper(II) Complexes

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The enzyme tyrosinase catalyzes the oxygenation of phenolic derivatives by dioxygen to give catechols. The active site of the enyzme consists of a binuclear cuprous center which binds O_2 to give a peroxo-bridged dicupric center analogous to that found in oxyhemocyanin.[1] Recent studies by Karlin and co-workers on reactions of binuclear cuprous complexes with dioxygen have been dramatically successful both in mimicking the enzymatic reaction by causing the hydroxylation of an aromatic group in the ligand by dioxygen[2] and in synthesizing analogues of the peroxo-bridged binuclear cupric species.[3] However, these synthetic binuclear copper systems have not been reported to catalyze the oxygenation of externally added substrates by dioxygen or by other sources of oxygen atoms.

We have reported our observations that simple metal salts, including those of copper, are capable of catalyzing the epoxidation of olefins by iodosylbenzene in acetonitrile.[4,5] In the case of cupric nitrate, we observed a marked catalyst concentration effect and our preliminary evidence indicated that iodosylbenzene complexes were formed in a ratio of one OIPh per two cupric ions.[4] This result prompted us to investigate binuclear cupric complexes as potential catalysts for our system. We report here that **1** and **2**, binuclear cupric complexes of ligands synthesized by Karlin and co-workers,[2,6] and **3**, a binuclear cupric complex synthesized by Lippard and co-workers,[7] catalyze the epoxidation of olefins by iodosylbenzene. The mononuclear analogue of **1**,[8] i.e. **4**, is not an effective catalyst under the same reaction conditions, and **1-3** are also considerably better catalysts than cupric triflate (**5**).

Complexes **1** and **2** were prepared and isolated by reacting the ligands with cupric triflate in acetonitrile. Complex **3** was prepared in solution by reaction of the ligand with cupric triflate in methanol. In a typical oxygenation experiment, 0.040 g (0.18 mmol) of iodosylbenzene was added all at once to a solution of

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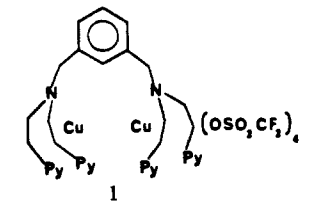

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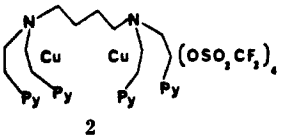

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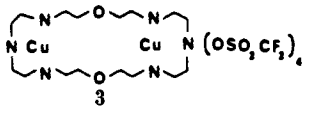

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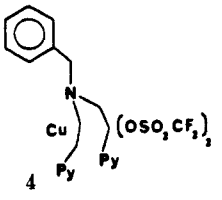

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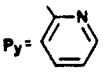


$Cu(OSO_2CF_3)_2$

5

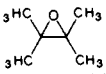
olefin (20 mM) and catalyst (2 mM) in 5 mL of dry, deaerated acetonitrile. The reaction mixture was stirred at room temperature under argon and 100-μL aliquots were periodically removed and diluted with methanol for analysis by GC/MS or HPLC. Several internal olefins gave the corresponding epoxides as products, but the terminal olefins 1-hexene and 1-octene gave no epoxide products. The reactivities of the stilbenes followed the same pattern as was observed for the reactions catalyzed by the metal ion salts.[4,5] That is, (*E*)-stilbene was found to be more reactive than (*Z*)-stilbene and the products in both cases were the trans oxides and benzaldehyde. Results are summarized in Table I.

Comparisons of the relative efficiencies of **1–5** as catalysts for the epoxidation of cyclohexene were also carried out (see Table II for conditions and results). Significantly lower yields were obtained when the reactions were carried out in air, and different product distributions with much lower yields were seen in the presence of 2–5% H_2O. When the mononuclear cupric complex **4** was substituted for **1** in the reaction of cyclohexene, almost no reaction was observed. When a copper-deficient version of **1** was used,[9] small amounts of epoxide and 2-cyclohexen-1-one were formed. Thus the binuclear nature of **1–3** appears to play an important role in their reactivities as catalysts for this reaction. In this regard, it is important to note that cupric triflate, which we had previously found to be an active catalyst when used at 20–40 mM concentrations,[4] gave only small amounts of epoxide when used under the present conditions (2 mM copper).

Complex **1** was reacted with iodosylbenzene in acetonitrile in the absence of substrate in an attempt to identify the reactive species. One equivalent of the normally insoluble solid iodosylbenzene was found to dissolve readily in a 10 mM blue solution (λ = 630 nm) of **1**. The resulting blue solution was quickly filtered and then reacted with methanol to convert any solubilized iodosylbenzene to iodobenzene dimethoxide,[4] the concentration of which was determined by HPLC. Our results indicated that the freshly prepared solution gave 0.1–0.3 equiv of $PhI(OMe)_2$. Increasing amounts of IPh were observed as the solution was allowed to sit. These results suggest that a complex of OIPh or a related species was initially formed and that this complex decomposed to give IPh. Addition of 100 equiv of cyclohexene to a similarly prepared solution of **1** and OIPh was found to give 0.5–0.8 equiv of cyclohexene oxide per equiv of OIPh added, suggesting that the complex formed under these conditions is responsible for the observed epoxidation reaction and that it is capable of reacting with olefin to give epoxide in high yield. The monomeric analogue of **1**, i.e., **4**, was shown similarly to react with OIPh, although the dissolution of the iodosylbenzene was observed to occur much more slowly than in the case of the binuclear complexes. The resulting solution gave 0.1–0.4 equiv of $PhI(OMe)_2$ upon addition of MeOH. However, addition of cyclohexene to such a solution did not result in the production of cyclohexene oxide.

(9) The complex was prepared by adding 1 equiv of $Cu(OSO_2CF_3)_2$ to 1 equiv of ligand in CH_3CN.

Table I. Products of the Reaction of Cu Catalysts and Iodosylbenzene with Olefins in Acetonitrile[a]

Cu catalyst	substrate	product(s) detected	yield,[e] %	% substrate consumed
1			23	49[b]
		PhCHO	13[c]	
1			8	38[b]
		PhCHO	6[c]	
1			41	63[d]
1	pinene	pinene oxide	24	30[b]
1	norbornylene	norbornylene oxide (exo)	25	28[d]
1	1-hexene	no reaction[d]		
1	1-octene	no reaction[d]		
3			70	35[d]
4		no reaction[d]		

[a] In 5 mL of acetonitrile; 2 mM copper complex, 20 mM olefin, and 0.18 mmol of OIPh at 25 °C. [b] One-hour reaction. [c] Yields of benzaldehyde are calculated on the basis of two benzaldehyde molecules per stilbene. [d] Two-hour reaction. [e] Percent yields are based on the substrate consumed.

Table II. Comparison of Cyclohexene Oxidation Products of Different Copper(II) Complexes under Catalytic Conditions[a]

Cu catalyst	 mM (%)[b]	 mM(%)	 mM(%)	turnover based on epoxide
1	15.4 (19)	trace[c]	3.2 (4)	8
2	18.7 (23)	trace	2.2 (3)	9
4	1.2 (1.5)	0	0	<1
5	3.3 (4)	trace	1.3 (1.6)	1.7

[a] In 5.0 mL of acetonitrile; 2 mM copper complex, 200 mM olefin and 0.4 mmol of OIPh at 25 °C. [b] Percent yield based on OIPh added. [c] Trace (<1%).

Addition of excess OIPh to complexes **1** and **2** caused the solutions to turn green (λ = 660 nm) and solid iodoxybenzene, O_2IPh, to precipitate. In the case of complex **1**, the green solution was filtered to remove excess OIPh and O_2IPh. The resulting solution gave 2 equiv of $PhI(OMe)_2$ per equiv of **1** upon addition of MeOH (indicating that 2 equiv of OIPh had been solubilized) but yielded only trace amounts of epoxide upon addition of cyclohexene. Removal of solvent from the filtered solution gave a green solid which was demetalated following the procedure of Karlin et al.[2] The resulting brown oil was analyzed by mass spectrometry and found to give a parent ion of m/z = 556, which corresponds to the molecular weight of the starting ligand.[2] This result indicates that reaction of OIPh with **1** does not result in hydroxylation of the ligand.

We conclude from these results that OIPh reacts with both mononuclear and binuclear cupric complexes to form OIPh complexes or related species containing hypervalent iodine, but that the species formed from the binuclear complexes are much more effective as epoxidation reagents than those formed from the mononuclear complexes. Moreover, it is clear that the intermediate formed in the reaction of OIPh with **1** is different from that generated from reaction of **1** with hydrogen peroxide[10] or from

the reaction of the analogous cuprous complex with dioxygen,[2] since the latter reactions give hydroxylation of the ligand. We are still unable at this time to distinguish between a reaction pathway in which the olefin reacts directly with an iodosylbenzene complex as opposed to one in which iodobenzene dissociates and the olefin traps a reactive high-valent oxo intermediate. However, we are able to conclude that the binuclear nature of complexes **1-3** plays an important role in determining the reactivity of the active species. Future studies will include attempts to observe and isolate intermediates in these reactions and to determine the relationship of our results to oxygenation reactions catalyzed by copper enzymes with binuclear active sites.

Acknowledgment. We are grateful to Professor Stephen J. Lippard of MIT for providing a sample of the macrocycle used in **3**. Financial support from the National Science Foundation is also gratefully acknowledged.

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Sequence-Specific Chiral Recognition of Right-Handed Double-Helical DNA by (2*S*,3*S*)- and (2*R*,3*R*)-Dihydroxybis(netropsin)succinamide

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We report a class of chiral sequence-specific DNA binding molecules[1,2] based on two netropsin analogues and the enantiomers of *dl*-tartaric acid: (2*R*,3*R*)- and (2*S*,3*S*)-dihydroxybis(netropsin)succinamide-EDTA [(*R*,*R*)- and (*S*,*S*)-**1**, respectively] (Figures 1 and 2).[3] The enantiomeric *threo*-(*R*,*R*)-**1** and -(*S*,*S*)-**1** should afford diastereomeric complexes at common binding sites on double-helical DNA (Figure 1). Attachment of EDTA to one terminus of the crescent-shaped hexamides allows use of the affinity cleaving method[4,5] to determine the differences between (*R*,*R*)-**1**·Fe^{II} and (*S*,*S*)-**1**·Fe^{II} with regard to relative binding affinities, sequence specificities, and orientations by analysis of the DNA-cleavage patterns on a ^{32}P end-labeled DNA restriction fragment using high-resolution gel electrophoresis.[6] For comparison to the enantiomers of **1**, bis(netropsin)succinamide-EDTA

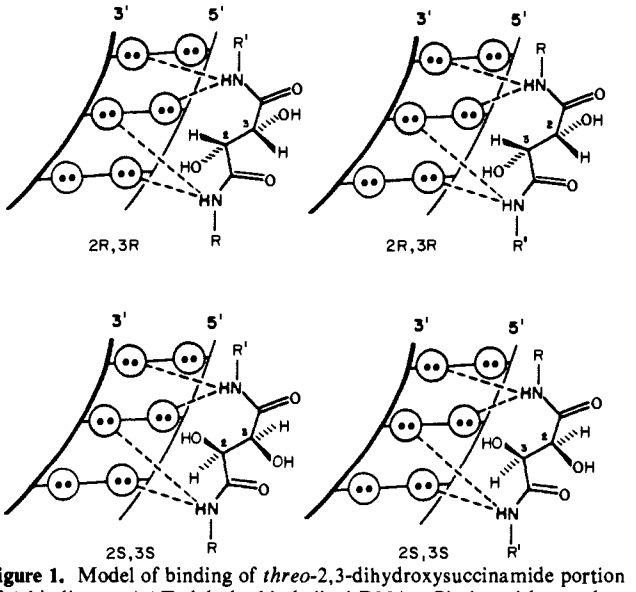

Figure 1. Model of binding of *threo*-2,3-dihydroxysuccinamide portion of **1** binding to A+T-rich double-helical DNA. Circles with two dots represent lone pairs of electrons of N3 of adenine (A) and O2 of thymine (T) at the edges of the base pairs on the floor of the minor groove of the right-handed B DNA helix. (Top) Two diastereomeric binding orientations of (*R*,*R*)-**1** on A+T-rich double-helical DNA. (Bottom) Two diastereomeric binding orientations of (*S*,*S*)-**1** on A+T-rich double-helical DNA.

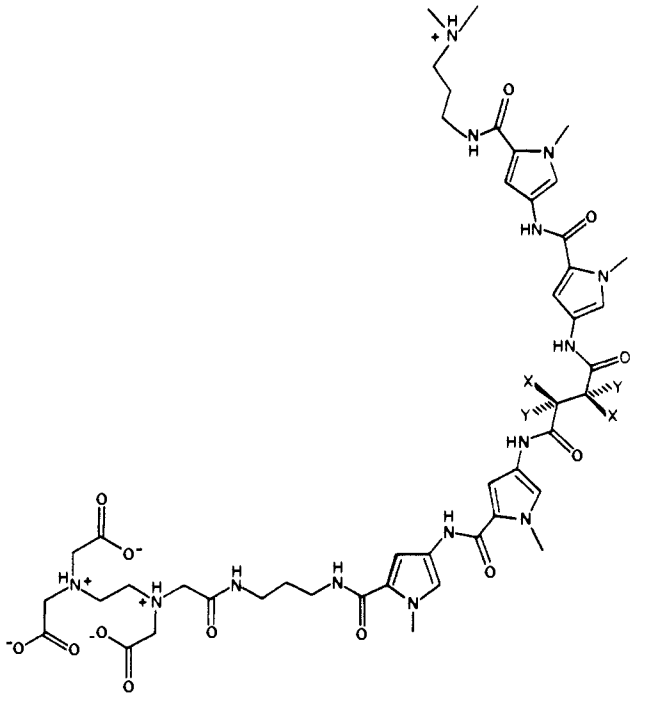

Figure 2. For (*S*,*S*)-**1**: X = OH, Y = H. For (*R*,*R*)-**1**: X = H, Y = OH. For **2**: X = H, Y = H.

(**2**) was synthesized (Figure 2).

A 517-base-pair restriction fragment from plasmid pBR322 DNA, labeled with ^{32}P on the 3' end,[4b,5] was allowed to react with a 100-fold range of concentrations of (*R*,*R*)-**1**·Fe^{II}, (*S*,*S*)-**1**·Fe^{II}, and **2**·Fe^{II} under the same conditions (5 mM dithiothreitol, 5mM NaOAc, pH 7.9, 1.5 h, 37 °C). The DNA cleavage sites were visualized on a DNA sequencing gel (Figure 3). Densitometric analysis of the bottom half of the autoradiogram reveals cleavage flanking two sites, seven-base-pairs in size, 5'-TTTTTAT-3' and 5'-TAATAAT-3', for all three molecules (Figure 4). The binding locations, site sizes, and orientation preferences for the three compounds are similar. However, the *concentrations* of (*R*,*R*)-**1**, (*S*,*S*)-**1**, and **2** required to achieve comparable cleavage efficiency at these seven-base-pair A·T-rich sites vary by *2 orders of mag-*

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(3) (*R*,*R*)-**1** was synthesized from optically pure (>99%) (2*R*,3*R*)-dihydroxysuccinic acid (L-tartaric acid) obtained from Aldrich $[\alpha]^{D}_{23}$ +15.6° (*c* 20, H_2O). (*S*,*S*)-**1** was synthesized from optically pure (99%) (2*S*,3*S*)-dihydroxysuccinic acid (D-tartaric acid) obtained from Aldrich $[\alpha]^{D}_{23}$ -15.2° (*c* 20, H_2O). The NMR, IR, UV, and mass spectral data are consistent with the structural assignments. Synthetic details will be published elsewhere.

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