Optically Active Difunctionalized Dioxocyclam Macrocycles: Ligands for Nickel-Catalyzed Oxidation of Alkenes

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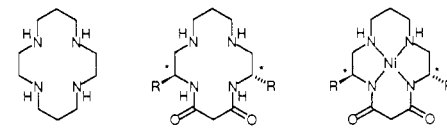
A general synthetic route has been applied to the synthesis of optically active difunctionalized dioxocyclam macrocycles, (3*S*,9*S*)-3,9-dialkyl-1,4,8,11-tetraazacyclotetradecane-5,7-diones, and their chiral tetraamine precursors. Macrocycles **2a–c** derived from phenylalanine, leucine, and valine, respectively, have been prepared and converted to their corresponding Ni^{II} complexes. These complexes as well as the Ni^{II} complex of the parent macrocycle, **2d**, were found to catalyze the oxidation of alkenes to epoxides and aldehydes with NaOCl as the terminal oxidant under phase-transfer conditions. The ability of the various disubstituted complexes to act as catalysts is correlated to their relative CH_2Cl_2 solubilities.

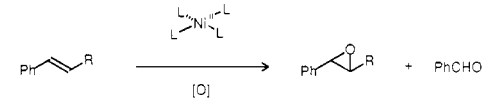
Polyazamacrocycles comprise a class of complexones complimentary to macrocyclic polyethers in cation-binding ability. While crown ethers show binding selectivity among the alkali and alkaline earth metal cations, their nitrogen analogues act as ligands for most of the transition-metal elements in di- or trivalent oxidation states.[1] The 14-membered ring system, cyclam[2] (**I**), and its derivatives have been studied extensively for their ability to form kinetically and thermodynamically stable complexes with Co^{2+}, Ni^{2+}, Cu^{2+}, and other metal ions and for their ability to stabilize high oxidation states of these metals.[3,4] More recently the amide-containing analogue dioxocyclam (**2d**) has been developed by Kimura[5] and others.[6] The macrocyclic oxo polyamines are structurally intermediate between the saturated polyamines and oligopeptides. They display complexation to a limited number of metals ions in which coordination occurs to a deprotonated ligand such as H_{-2}**2**. For Ni^{II}, complexation with H_{-2}**2** yields a diamagnetic complex (**3**), while **1**·Ni^{2+} is a mixture of both high-spin and low-spin complexes.[7] Incorporation of functionalized side chains into a macrocyclic polyamide[8,9] or oxo polyamine structure may further modify its coordination geometry, ring conformation, and redox properties.



1 **2** **3**

a: R = CH_2Ph
b: R = $CH_2CH(CH_3)_2$
c: R = $CH(CH_3)_2$
d: R = H

Certain square-planar complexes of Ni^{II}, including those of the ligands cyclam and salen, have recently been shown to act as catalysts for oxygen atom transfer to alkenes.[10-13] Epoxides are the usual product in these reactions; however, products of H atom abstraction, rearrangement, and C=C bond cleavage are also observed. Relatively strong oxidants, such as iodosylbenzene or hypochlorite are required for alkene oxidation to occur. Here, we report the synthesis and study of a new class of dioxocyclam macrocycles whose Ni^{II} complexes efficiently catalyze alkene oxidation when OCl^- is used as the terminal oxidant. Our motiva-



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(2) Abbreviations used: cyclam, 1,4,8,11-tetraazacyclotetradecane; dioxocyclam, 1,4,8,11-tetraazacyclotetradecane-5,7-dione; salen, *N,N'*-ethylenebis(salicylideneamine).

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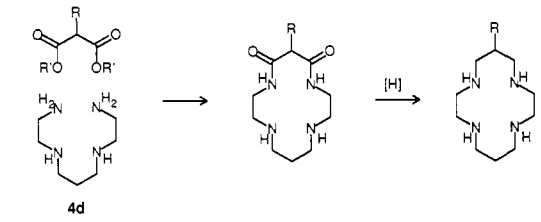
tions for this work were 2-fold: to develop a general synthetic route to optically active difunctionalized dioxocyclams derived from amino acids and to investigate the potential of their nickel complexes as oxidation catalysts. Each of the dioxocyclams and nickel complexes possesses C_2 symmetry—each face of the macrocycle is equivalent. Access to new optically active ligands of this type may ultimately have applications in catalysis of asymmetric oxidation.

Results and Discussion

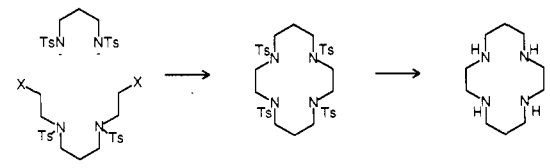
Synthesis of Disubstituted Dioxocyclams. The synthesis of the parent dioxocyclam, **2d**, was first reported by Tabushi et al.[14] who cyclized tetraamine **4d** with diethyl malonate to produce the macrocycle in 30% yield. This approach has been used in a number of cases for the syntheses of dioxocyclams and, upon reduction, cyclams.[14] Macrocyclization yields in polyamine synthesis are usually higher with the Richman–Atkins method;[15] however, the Tabushi reaction has the advantages that alkylated malonates may be used to readily incorporate side chains, that tetraamine precursors are used directly without N-protection, and that both dioxocyclams and cyclams may be synthesized.

A. Tabushi Method:



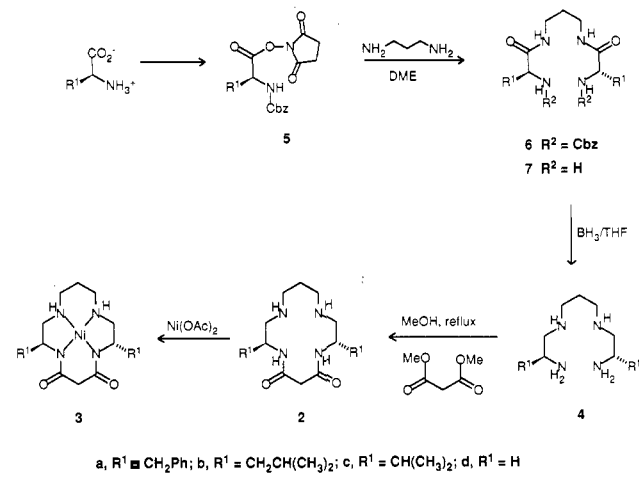
4d

B. Richman-Atkins Method:



In the present study, preparation of the substituted tetraamines **4a–c** in high yield allowed the formation of dioxocyclam macrocycles by reaction with dimethyl malonate. The overall synthetic plan is outlined in Scheme I beginning with an α-amino acid. General procedures have proved applicable toward the preparation of macrocycles derived from phenylalanine, leucine, and valine and should be successful for any α-amino acid if side-chain functional groups are suitably protected. In the general scheme, amino acids were first N-protected with the carbobenzyloxy group (Cbz) followed by activation of the carboxylic acid by conversion to an *N*-hydroxysuccinimide ester (**5a–c**). Compounds **5a–c** were chosen as starting materials because of their ease of crystallization and stability toward racemization. Subsequent condensation with 0.5 equiv of 1,3-diaminopropane produced diamides **6a–c** in >80% yields. The Cbz protecting groups were then removed by catalytic hydrogenolysis, and the diamides **7a–c** were reduced with borane/THF to give tetraamines **4a–c**. This route produced **4a–c** in overall yields of 62%, 54%, and 37%, respectively, from phenylalanine, leucine, and valine. Each step in the synthesis led to crystallization

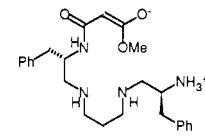
Scheme I



a, R^1 = CH_2Ph; b, R^1 = $CH_2CH(CH_3)_2$; c, R^1 = $CH(CH_3)_2$; d, R^1 = H

products with no chromatography required; thus, the tetraamines are accessible in large quantities through this route. These new chiral tetraamines[16] may themselves show interesting properties as metal-chelating agents[17] and will be the subject of further study.

Macrocyclization of equimolar amounts of a tetraamine (**4a–c**) with dimethyl malonate was carried out in refluxing MeOH for 5 days. Yields of purified dioxocyclam macrocycles were substantially lower than those previously reported, typically 8–12%. Attempts to improve the yields by working with more reactive acylating agents (malonyl dichloride), at high pressure (8–9 kbar, 50 °C, 24 h) or under high dilution conditions were all unsuccessful. In addition, tetraamine **4a** was converted to a cyclic aminal (30% aqueous HCHO) in an attempt to protect the secondary amines from reaction with dimethyl malonate.[18] In this case, however, the aminal provided little improvement in macrocyclization step and no improvement in the overall yield. The major product of the reaction of **4a** with dimethyl malonate appears to be an open-chain monoamide, e.g. **8a**. Ring closure to yield the desired macrocycle may be impeded by diminished reactivity of a zwitterionic form or by unfavorable conformational restrictions.



8a

NMR spectroscopy of the macrocycles **2a–c** indicated that no epimerization occurred at the stereogenic carbons. For example, the ^{13}C NMR spectrum of **2a** clearly showed only six aliphatic carbons between 0 and 60 ppm as expected for C_2-symmetric, diastereomerically pure material. Single-point epimerization would have generated a mixture of diastereomers and a correspondingly complex spectrum. Since this synthetic pathway appears to have preserved the 3*S*,9*S* stereocenters, it is valuable as a general route to the optically active tetraamines (**4**), the dioxocyclams (**2**), and, upon reduction, the cyclam family (**1**).

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Table I. UV-Vis and IR Spectroscopic Data for Ni^{II} Complexes

complex	λ_{max}(d-d),[a] nm	ϵ, M^{-1} cm^{-1}	$\nu_{(C=O)}$,[b] cm^{-1}
3a	450	68	1560
3b	438	44	1558
3c	442	62	1569
3d	460	100	1556

[a] In H_2O solution. [b] KBr pellet.

Table II. Percent Product Yields from Oxidation of *trans*-β-Methylstyrene with NaOCl Catalyzed by Ni^{II} Complexes[a,b]

catalyst	recovered starting material, %	epoxide, %	benzaldehyde, %
3a	0	51	23
3b	49	26	9
3c	96	1	2
3d	87	2	6

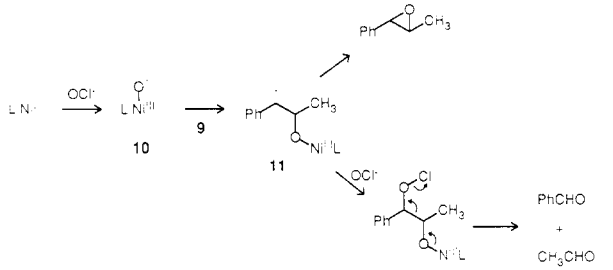
[a] Yields based on initial alkene concentration. Remainder of product is largely sodium benzoate. [b] Reaction conditions: 1.7 mmol of alkene, 0.04 mmol of Ni^{II} catalyst, 0.08 mmol of $PhCH_2NMe_3^+Br^-$(PTC) in 5 mL of CH_2Cl_2 + 10 mL of 0.77 M NaOCl, room temperature.

Ni^{II} Complexes. The neutral ligands **2a–d** were converted to Ni^{II} complexes by warming with 1 equiv of Ni(OAc)$_2$ in MeOH. The ligands were doubly deprotonated in this process, releasing 2 equiv of HOAc. The yellow-orange complexes **3a–d** are diamagnetic. All display maximum absorbences near 450 nm in their electronic spectra and carbonyl stretching frequencies of about 1560 cm^{-1}, representing a 80-cm^{-1} shift to lower frequency upon deprotonation of the amide (see Table I). Complexes of Co^{II},[19] Cu^{II},[20] and Pt^{II},[21] with the parent ligand **2d** have also been reported.

Oxidation Studies. In order to explore new chemistry of the nickel dioxocyclams, we tested the reaction of an alkene with various oxidants in the presence of complexes **3a–d**. Since iodosylbenzene is known to epoxidize alkenes in the presence of certain Ni^{II} complexes, the first studies were carried out with PhIO as terminal oxidant, *trans*-β-methylstyrene (**9**) as substrate, and **3a** as catalyst. Unfortunately, the low solubility of **3a** in CH_3CN prevented the study of reaction conditions strictly analogous to those previously used with 1·Ni^{2+}-catalyzed epoxidation.[12] However, Koola and Kochi also reported catalysis of olefin oxidation by 1·Ni^{2+} in CH_2Cl_2.[10] In a related experiment, epoxidation was attempted with 0.52 mmol of **9**, 0.07 mmol of PhIO, and 0.3 mmol of **3a** in CH_2Cl_2. After 18 h at room temperature, no alkene oxidation could be detected and only a trace of PhIO was reduced to PhI.

Sodium hypochlorite used under phase-transfer conditions in the presence of a transition-metal catalyst has been developed extensively in the case of manganese porphyrins for the oxidation of hydrocarbons.[22] We recently showed that nickel salen complexes also act as catalysts with this oxidant.[11] With use of similar reaction conditions, the catalytic activities of nickel complexes **3a–d** were tested. Standard reaction conditions involved treatment of 0.34 M *trans*-β-methylstyrene in CH_2Cl_2 with 4.5 equiv of 0.77 M NaOCl (pH 12–13) in the presence of 12.5 mol % nickel catalyst and 5 mol % $PhCH_2NMe_3^+Br^-$ (phase-transfer catalyst). Reactions were carried out at room temperature and monitored by GC. The yields of oxidation products obtained are listed in Table II.

Scheme II



The most efficient catalysis occurred in the presence of **3a** derived from phenylalanine. After 6.5 h, all of the alkene was consumed, and two types of reaction products were formed. About half of the methylstyrene was converted to the corresponding epoxide; the other half underwent C=C bond cleavage to produce benzaldehyde and, presumably, acetaldehyde, which was not detected under the conditions of analysis. Since benzaldehyde is slowly oxidized by basic hypochlorite to water-soluble benzoate, analysis of the CH_2Cl_2 layer provided reliable data only for the determination of disappearance of starting material and appearance of epoxide. Relative amounts of PhCHO and $PhCO_2H$ were variable.

The leucine-derived complex **3b** showed only moderate activity as an oxidation catalyst, while the valine and glycine analogues (**3c,d**) showed very low conversion of alkene. The catalytic activity of these four complexes can be correlated to their CH_2Cl_2 solubilities. Both **3a** and **3b** are readily soluble in CH_2Cl_2 while **3c** and **3d** are only sparingly soluble. Extraction experiments with equal volumes of CH_2Cl_2 and H_2O showed that between 17 and 35% of **3a** remained in the CH_2Cl_2 layer; CH_2Cl_2 solutions of complexes **3b–d** were extracted >95% into an equal volume of H_2O. Visual inspection during oxidation reactions revealed that the yellow complexes **3a** and **3b** were present in the CH_2Cl_2 layer while **3c** and **3d** were immediately extracted into the aqueous phase and, in the absence of substrate, were slowly bleached by NaOCl over a period of 24 h.

Since the largest amount of epoxide product was generated from the reaction catalyzed by **3a**, this reaction was analyzed for enantiofacial selectivity. The *trans*-β-methylstyrene oxide product was observed by ^1H NMR spectroscopy in the presence of varying amounts of the chiral shift reagent, Eu(hfc)$_3$. No asymmetric induction had occurred. This result is perhaps not surprising in light of the small steric size of the benzyl side chains of **3a** and the placement of only one such group per face of the nickel complex. Unfortunately, the valine derivative, **3c**, produced insufficient quantities of epoxide to analyze since it would be predicted to have a greater influence on stereoselection in the reaction.

The structure of the active oxidant generated from the reaction of a nickel complex **3** with OCl^- is unknown. During each of the reactions of **3a–d**, a fine black precipitate of nickel peroxide (approximate formula, $NiO(OH)_2$[23]) was

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formed and persisted for varying periods of the reaction course. From previous work,[11] it is clear that nickel peroxide is not an epoxidizing agent and is merely a byproduct of relatively facile dissociation of Ni^{II} from the macrocyclic ligand and reaction with OCl^-. In addition, control studies have shown that simple nickel salts such as $Ni(OAc)_2$ are inactive as oxidation catalysts with either PhIO or NaOCl and that no epoxidation occurs in the absence of a catalyst.[10,11] Thus, the requirement for the dioxocyclam ligand is established. Furthermore, only appropriately substituted dioxocyclams that lend sufficient CH_2Cl_2 solubility to the complex will promote the epoxidation reaction.

A suggested mechanism is depicted in Scheme II and is based on similarities of this reaction to that catalyzed by Ni^{II} salen.[11] Square-planar ligation with strong donor ligands (salen, cyclam, and dioxocyclam) is known to stabilize the Ni^{II} oxidation state.[24] Structure **10** is a likely candidate for the reactive oxidant formed with **3** and OCl^-.[25] If **10** has considerable radical character at oxygen, its addition to an alkene would proceed in a stepwise fashion to first generate the benzylic radical **11**. Compound **11** could then be the branch point in the mechanism at which either reductive elimination of **3** to yield epoxide or further reaction with OCl^- might occur. The latter pathway would give rise to C=C bond cleavage products. Although the mechanism is speculative at this point, it is consistent with the observed reactivities of nickel complexes and the reaction products obtained. Future studies will attempt to characterize the reactive intermediates more definitively.

Conclusions

A synthetic scheme has been developed by which optically active linear tetraamines, macrocyclic dioxocyclams, and saturated cyclams can be prepared from an amino acid precursor. The tetraamines are available in very high yields. Despite rather low yields in macrocyclization, relatively large quantities of the C_2-symmetric Ni^{II} complexes can be prepared. These complexes join a limited number of other square-planar Ni^{II} compounds, including salen and, to a lesser extent, cyclam complexes, that are capable of catalysis of alkene oxidation with OCl^-, a convenient and inexpensive oxidant. The inability of Ni^{II}–tetraphenylporphyrin or simple Ni^{2+} salts to effect this chemistry suggests that special stabilization of a higher oxidation state of nickel is a prerequisite for catalysis. In this regard, it will be important to investigate systems that allow for subtle ligand modification in order to best determine the redox, solubility, and steric requirements for catalysis.

Experimental Section

General Methods. Commercial reagents were used as obtained without further purification. Solvents were generally purified and dried by standard methods before use.[26] Domestic bleach was used for NaOCl solutions and was titrated before use. Melting points were determined using a Thomas-Hoover apparatus (<225 °C) or a Mel-Temp apparatus (>225 °C) and are uncorrected. ^1H NMR spectra were recorded at 300 MHz on a General Electric QE-300 spectrometer with chemical shifts reported in parts per million relative to internal tetramethylsilane unless otherwise noted. ^{13}C NMR spectra were recorded at 75.4 MHz on the same instrument with $CDCl_3$ as internal standard. IR spectra were recorded as KBr pellets on a Perkin-Elmer 1600 series FT spectrophotometer. Low-resolution mass spectra were recorded on a Hewlett-Packard 5980A GC/MS system. High-resolution and positive FAB mass spectra were recorded on a Kratos MS80RFA system. Optical rotations were measured on a Perkin-Elmer 241 polarimeter in a 10-cm cell. Electronic spectra were recorded in H_2O on a Hewlett-Packard 8452-A spectrophotometer. Oxidation product analysis was performed on a Hewlett-Packard 5890A gas chromatograph. Column chromatography was performed on silica gel (Baker 40–140 mesh). Analytical thin-layer chromatography was conducted on Macherey-Nagel plastic precoated silica (0.20 mm) with fluorescent indicator. Elemental analysis was performed by Desert Analytics, Inc. All reactions were routinely carried out under an inert atmosphere of nitrogen.

General Procedure for *N*-(Carbobenzyloxy)-L-amino Acid *N*-Hydroxysuccinimide Esters (5a–c). L-α-Amino acids were converted to their Cbz analogues by using literature procedures.[27] These products were then treated with *N*-hydroxysuccinimide by known procedures to produce compounds **5a–c**.[28]

***N,N'*-Bis(*N*-(carbobenzyloxy)-L-phenylalanyl)-1,3-diaminopropane (6a).** Compound **5a** (2.52 g, 6.40 mmol) was dissolved in anhydrous dimethoxyethane (100 mL) and cooled to 0 °C in an ice bath, and 1,3-diaminopropane (0.27 mL, 3.20 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature for 18 h. The white precipitate that formed was collected by vacuum filtration, and the solid material was washed with small portions of cold H_2O followed by cold MeOH. The final product was stored in a vacuum desiccator containing P_2O_5: yield 1.98 g (98%); mp 226–227 °C; ^1H NMR (Me_2SO-d_6) δ 1.41 (m, 2 H), 2.7–3.1 (br m, 8 H), 4.20 (m, 2 H, asymmetric methine), 4.92 (s, 4 H), 7.1–7.4 (m, 20 H, aromatic), 7.50 (d, 2 H, amide NH), 7.99 (br s, 2 H, carbamate NH); ^{13}C NMR (Me_2SO-d_6) δ 29.3, 36.5, 37.9, 56.6 (asymmetric carbon), 65.5, 126.5, 127.9, 128.1, 128.3, 128.5, 129.4, 137.3, 156.1 (urethane C=O), 171.5 (amide C=O); IR (KBr) 3295, 1690, 1649, 1540 cm^{-1}. Anal. Calcd for $C_{37}H_{40}N_4O_6$: C, 69.79; H, 6.33; N, 8.79. Found: C, 69.81; H, 6.29; N, 8.81.

***N,N'*-Bis(*N*-(carbobenzyloxy)-L-leucyl)-1,3-diaminopropane (6b).** In a procedure similar to that described above for the synthesis of **6a**, **5b** (11.60 g, 0.032 mol) was treated with 1,3-diaminopropane (1.19 g, 0.016 mol) to yield a white solid, which was recrystallized from methanol to produce fine white crystals: yield 8.01 g (88%); mp 177–178 °C; ^1H NMR (Me_2SO-d_6) δ 0.82 (dd, 12 H), 1.42 (m, 6 H), 1.58 (m, 2 H), 3.01 (m, 4 H), 3.95 (m, 2 H, asymmetric methine), 4.99 (s, 4 H), 7.31–7.39 (m, 12 H, aromatic and urethane NH), 7.88 (t, 2 H, amide NH); ^{13}C NMR (Me_2SO-d_6) δ 21.5, 22.9, 24.2, 29.2, 33.3, 36.1, 40.8, 53.2 (asymmetric carbon), 65.4, 127.0, 127.7, 127.8, 137.0, 155.9 (urethane C=O), 172.2 (amide C=O); IR (KBr) 3294, 2956, 1690, 1640, 1538 cm^{-1}. Anal. Calcd for $C_{31}H_{44}N_4O_6$: C, 65.49; H, 7.75; N, 9.86. Found: C, 65.41; H, 8.08; N, 9.99.

***N,N'*-Bis(*N*-(carbobenzyloxy)-L-valyl)-1,3-diaminopropane (6c).** In a procedure similar to that described for **6a**, **5c** (16.51 g, 0.047 mol) was treated with 1,3-diaminopropane (1.74 g, 0.024 mol) to yield **6c** as a white solid recrystallized from 2-propanol: yield 10.62 g (83%); mp 211–212 °C; ^1H NMR (Me_2SO-d_6) δ 0.85 (dd, 12 H), 1.45 (m, 2 H), 1.90 (m, 2 H), 2.98 (m, 4 H), 3.70 (t, 2 H, asymmetric methine), 4.98 (s, 4 H), 7.15 (d, 2 H, carbamate NH), 7.25 (m, 10 H, aromatic), 7.83 (t, 2 H, amide NH); ^{13}C NMR (Me_2SO-d_6) δ 17.7, 18.7, 28.6, 29.7, 35.7, 59.9, 64.9, 127.1, 127.2, 127.8, 136.6, 155.6 (urethane C=O), 170.6 (amide C=O); IR (KBr) 3294, 2956, 1690, 1645 cm^{-1}. Anal. Calcd for $C_{29}H_{40}N_4O_6 \cdot 0.5H_2O$: C, 63.39; H, 7.47; N, 10.20. Found: C, 63.42; H, 7.58; N, 10.45.

***N,N'*-Bis(phenylalanyl)-1,3-diaminopropane (7a).** Compound **6a** (3.00 g, 4.72 mmol) was suspended in 200 mL of MeOH. 5% Pd on activated carbon (0.35 g) was added, and the mixture was degassed (by successive evacuation and venting to hydrogen) and treated with H_2 (40 psi) for 15 h. The resulting solution was

(24) For a recent review, see: Lappin, A. G.; McAuley, A. In *Advances in Inorganic Chemistry*; Sykes, A. G., Ed.; Academic: San Diego, 1988; Vol. 32, pp 241–295.

(25) Other possible structures include a variant with Cl^- still partially or fully bonded to oxygen, LNi–O···Cl, and simply ClO• generated from an electron-transfer reaction.

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filtered through Celite, washed several times with MeOH, and concentrated to give a clear colorless oil. Trituration with diethyl ether resulted in the formation of a white solid: yield 1.67 g (96%); ^{1}H NMR (Me_2SO-d_6) δ 1.40 (m, 2 H), 2.46–2.90 (m, 8 H), 3.29 (t, 2 H, asymmetric methine), 7.10–7.22 (m, 10 H, aromatic), 7.81 (t, 2 H, amide); ^{13}C NMR (Me_2SO-d_6) δ 29.2, 35.7, 41.2, 56.3, 126.0, 128.0, 129.24, 138.72, 174.25 (amide C=O).

***N,N'*-Bis(leucyl)-1,3-diaminopropane (7b).** In a procedure similar to that described for **7a**, compound **6b** (3.07 g, 5.40 mmol) was subjected to hydrogenolysis to produce a slightly yellow semisolid: yield 1.60 g (98.6%); ^{1}H NMR ($CDCl_3$) δ 0.70 (dd, 12 H), 1.01 (m, 2 H), 1.45 (br m, 6 H), 1.49 (br s, 4 H, exchangeable with D_2O), 2.89 (m, 4 H), 3.01 (m, 2 H, asymmetric methine), 7.60 (br t, 2 H, amide NH); ^{13}C NMR ($CDCl_3$) δ 21.0, 21.2, 21.8, 29.4, 35.4, 43.0, 53.3 (asymmetric carbon), 175.8 (amide C=O).

***N,N'*-Bis(valyl)-1,3-diaminopropane (7c).** In a procedure analogous to that described for the preparation of **7a**, compound **6c** (2.97 g, 5.50 mmol) was subjected to hydrogenolysis to produce **7c** as a clear colorless oil: yield 1.46 g (98%); ^{1}H NMR ($CDCl_3$) δ 0.98 (dd, 12 H), 1.51 (br s, 4 H, exchanges with D_2O), 1.65 (m, 2 H), 2.25 (m, 2 H), 3.24 (d, 2 H, asymmetric methine), 3.33 (m, 4 H), 7.75 (br t, 2 H, amide NH); ^{13}C NMR ($CDCl_3$) δ 15.5, 18.8, 28.9, 30.3, 34.9, 59.6 (asymmetric carbon), 174.3 (amide C=O).

(2*S*,10*S*)-2,10-Dibenzyl-1,4,8,11-tetraazaundecane Tetrahydrochloride (4a·4HCl). A 1 M BH_3/THF solution (67 mL, 0.067 mol) was added dropwise over a 1-h period to a cooled (0 °C) solution of **7a** (4.1 g, 11.1 mmol) in anhydrous THF (100 mL). After addition was complete, the solution was allowed to warm to room temperature for 1 h followed by heating to reflux for an additional 18 h. The resulting solution was cooled, and the excess diborane was quenched by the dropwise addition of a 10% H_2O/THF solution. The solvent was removed in vacuo, and 6 M HCl (100 mL) was added to the residue and heated to reflux for 1 h. After cooling, the solution was concentrated to a white semisolid. A 4 M NaOH solution (40 mL) was added, and the solution was extracted four times with 100-mL portions of $CHCl_3$. The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated to give a yellow oil, which was subsequently dissolved in absolute EtOH (75 mL), and HCl gas was passed through the solution. The resulting white precipitate that formed was collected by vacuum filtration and washed with cold EtOH: yield 5.3 g (83%); mp 243–245 °C dec; ^{1}H NMR (D_2O) δ 2.20 (m, 2 H), 3.00–3.24 (m, 8 H), 3.43 (m, 4 H), 4.00 (t, 2 H, asymmetric methine), 7.22–7.51 (m, 10 H, aromatic); ^{13}C NMR (D_2O) δ 19.3, 33.1, 42.1, 45.9, 46.7 (asymmetric carbon), 124.9, 126.1, 126.2, 130.5; IR (KBr) 3447, 2922, 1578, 1507, 1451 cm; $[\alpha]^{27}_D$ −9.9° (c = 1, H_2O). Anal. Calcd for $C_{21}H_{36}N_4Cl_4$: C, 51.85; H, 7.41; N, 11.52. Found: C, 51.55; H, 7.36; N, 11.50.

(2*S*,10*S*)-2,10-Diisobutyl-1,4,8,11-tetraazaundecane Tetrahydrochloride (4b·4HCl). In a procedure similar to that described above, compound **7b** (1.44 g, 5.30 mmol) was treated with 6 equiv of BH_3/THF. After the normal workup, the tetrahydrochloride salt of **4b** was isolated as a white powder: yield 2.08 g (93%); mp 288–290 °C; IR (KBr) 3420, 2940, 1550, 1500, 1451 cm^{-1}. Anal. Calcd for $C_{15}H_{40}N_4Cl_4·H_2O$: C, 41.28; H, 9.63; N, 12.84. Found: C, 41.26; H, 9.73; N, 12.63. The free tetraamine could also be isolated as a white solid (mp 50–51 °C) by extraction of a basic solution with $CHCl_3$: ^{1}H NMR ($CDCl_3$, free amine) δ 0.70 (dd, 12 H), 0.99 (t, 4 H), 1.35 (br s, 6 H, exchangeable with D_2O), 1.50 (m, 4 H), 2.10–2.60 (m, 8 H), 2.68 (m, 2 H, asymmetric methine); ^{13}C NMR ($CDCl_3$, free amine) δ 21.8, 23.2, 24.4, 30.0, 45.5, 48.3, 48.4 (asymmetric carbon), 56.9; $[\alpha]^{23}_D$ +17.3° (c = 6.2, $CHCl_3$).

(2*S*,10*S*)-2,10-Diisopropyl-1,4,8,11-tetraazaundecane Tetrahydrochloride (4c·4HCl). In a procedure similar to that described above, compound **7c** (1.40 g, 5.14 mmol) was treated with 6 equiv of BH_3/THF. The normal workup produced the tetrahydrochloride salt of **4c** as a white solid: yield 1.50 g (75%); mp >260 °C; ^{1}H NMR (D_2O) δ 1.00 (dd, 12 H), 2.02 (m, 2 H), 2.30 (m, 2 H), 3.20 (m, 2 H, asymmetric methine), 3.55 (m, 8 H); ^{13}C NMR (D_2O) δ 21.8, 22.5, 27.9, 34.3, 50.8, 52.9, 59.3; IR (KBr) 3435, 2942, 1555, 1450 cm^{-1}; $[\alpha]^{23}_D$ +12.5° (c = 1.1, H_2O). Anal. Calcd for $C_{13}H_{36}N_4Cl_4$: C, 40.00; H, 9.23; N, 14.36. Found: C, 39.80; H, 9.30; N, 14.04.

(3*S*,9*S*)-3,9-Dibenzyl-1,4,8,11-tetraazacyclotetradecane-5,7-dione (2a). Compound **4a** (1.02 g, 2.90 mmol) and dimethyl malonate (0.47 g, 2.90 mmol) were heated at reflux in anhydrous MeOH (100 mL) for 5 days. After cooling, the reaction mixture was concentrated to a yellow oil, which was then triturated with diethyl ether, resulting in the formation of an off-white solid. Further purification of the solid material by column chromatography on silica gel (15% MeOH/$CHCl_3$) led to the isolation of **2a** as a white solid: yield 70.8 mg (8%); mp 235–237 °C dec; TLC (silica, 100:10:1 $CHCl_3$, MeOH, NH_3) R_f 0.30; ^{1}H NMR ($CDCl_3$) δ 1.61 (m, 2 H), 2.04 (br s, 2 H, amine NH, exchangeable with D_2O), 2.42–2.82 (m, 12 H), 3.18 (s, 2 H, $COCH_2CO$), 4.39 (m, 2 H, asymmetric methine), 7.10 (d, 2 H, amide NH), 7.18–7.38 (m, 10 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 28.9, 39.6, 46.1, 49.7, 50.1, 53.7, 126.5, 128.4, 129.1, 137.8, 167.7; IR (KBr) 3280, 3050, 2950, 2900, 1645, 1530 cm^{-1}; $[\alpha]^{23}_D$ +16.3° (c = 4.6, EtOH); HRMS m/e calcd for $C_{24}H_{32}N_4O_2$ 408.2518 (M^+), found 408.2518.

(3*S*,9*S*)-3,9-Diisobutyl-1,4,8,11-tetraazacyclotetradecane-5,7-dione (2b). Via the general procedure outlined above, compound **4b** (0.69 g, 2.5 mmol) was allowed to react with dimethyl malonate for 5 days, cooled, and concentrated to a yellow oil. The product was purified by column chromatography on silica gel (20% MeOH/$CHCl_3$) and recrystallized from hexane to give a white crystalline material: yield 102 mg (12%); mp 215–216 °C; TLC (silica, 100:10:1 $CHCl_3$–MeOH–NH_3) R_f 0.22; ^{1}H NMR ($CDCl_3$) δ 0.85 (dd, 12 H), 1.20 (m, 4 H), 1.60 (m, 4 H), 2.01 (br s, 2 H, amine NH, exchangeable with D_2O), 2.50–2.80 (m, 8 H), 3.20 (s, 2 H, $COCH_2CO$), 4.20 (m, 2 H, asymmetric methine), 6.65 (d, 2 H, amide NH); ^{13}C NMR ($CDCl_3$) δ 22.1, 23.1, 24.9, 28.5, 42.5, 46.2, 47.5 (asymmetric carbon), 50.1, 55.1, 167.6 (amide C=O); $[\alpha]^{23}_D$ +20.6° (c = 6.8, MeOH); IR (KBr) 3326, 2956, 2923, 1636, 1542, 1473 cm^{-1}; MS (EI) m/e 340 (M^+), 297 (M − CONH). Anal. Calcd for $C_{18}H_{36}N_4O_2·0.5H_2O$: C, 61.89; H, 10.60; N, 16.05. Found: C, 61.86; H, 10.71; N, 15.71. HRMS m/e calcd 340.2830 (M^+), found 340.2836.

(3*S*,9*S*)-3,9-Diisopropyl-1,4,8,11-tetraazacyclotetradecane-5,7-dione (2c). In a procedure analogous to that described for **2a**, compound **4c** (1.36 g, 5.57 mmol) and dimethyl malonate (0.74 g, 5.57 mmol) were allowed to react at reflux for 5 days and concentrated to a yellow oil. The oil was purified by silica gel column chromatography (20% MeOH/$CHCl_3$), and the white solid obtained was recrystallized from a large volume of hexane to give fine white crystals of **2c**: yield 130 mg (7.5%); mp 233–234 °C dec; TLC (silica, 100:10:1 $CHCl_3$–MeOH–NH_3) R_f 0.31; ^{1}H NMR ($CDCl_3$) δ 0.97 (dd, 12 H), 1.65 (br m, 6 H), 2.45–2.85 (m, 8 H), 3.23 (s, 2 H, $COCH_2CO$), 3.92 (m, 2 H, asymmetric methine), 6.62 (d, 2 H, amide NH); ^{13}C NMR ($CDCl_3$) δ 18.5, 19.5, 28.9, 31, 46.2, 49.9, 52.4, 54.4, 167.9 (amide C=O); IR (KBr) 3280, 2940, 2920, 1640, 1560, 1470; $[\alpha]^{23}_D$ +38.2° (c = 5, MeOH); HRMS m/e calcd for $C_{16}H_{32}N_4O_2$ (M^+) 312.2518, found 312.2525. Anal. Calcd for $C_{16}H_{32}N_4O_2$: C, 61.50; H, 10.32; N, 17.93. Found: C, 60.94; H, 10.27; N, 17.26.

[(3*S*,9*S*)-3,9-Dibenzyl-1,4,8,11-tetraazacyclotetradecane-5,7-dione]nickel(II) (3a). Compound **2a** (54.8 mg, 0.132 mmol) and $Ni(OAc)_2·4H_2O$ (24.7 mg, 0.099 mmol) were dissolved in 10 mL of MeOH. The pale green color of $Ni(OAc)_2$ was replaced by a yellow color upon warming. The solution was concentrated to give a yellow oil, which was redissolved in EtOH. Addition of ether resulted in the formation of a yellow precipitate: yield 42 mg (69%); IR (KBr) 1560 cm^{-1} (C=O); λ_{max} (d-d) = 450 nm (ϵ = 68); FABMS m/e 465 (M + 1).

[(3*S*,9*S*)-3,9-Diisobutyl-1,4,8,11-tetraazacyclotetradecane-5,7-dione]nickel(II) (3b). Via the general procedure given for **3a**, compound **2b** (39.8 mg, 0.117 mmol) was treated with $Ni(OAc)_2$ (30 mg, 0.12 mmol) to give the yellow complex **3b**: yield 32 mg (70%); IR (KBr) 1558 cm^{-1} (C=O); λ_{max} (d-d) 438 nm (ϵ = 44); FABMS m/e 397 (M + 1).

[(3*S*,9*S*)-3,9-Diisopropyl-1,4,8,11-tetraazacyclotetradecane-5,7-dione]nickel(II) (3c). Via the general procedure described for **3c**, compound **2c** (32 mg, 0.102 mmol) was treated with $Ni(OAc)_2$ (25 mg, 0.100 mmol) to give **3c** as a yellow solid: yield 33 mg (88%); IR (KBr) 1569 cm^{-1} (C=O); λ_{max} (d-d) = 442 nm (ϵ = 62); FABMS m/e 369 (M + 1).

General Procedure for Oxidation Studies. In a typical experiment 1.7 mmol of *trans*-β-methylstyrene, 0.04 mmol of the appropriate Ni^{II} catalyst (**3a–d**), and 0.08 mmol of $PhCH_2NMe_3^+$ Br^- (phase-transfer catalyst) were dissolved in 5 mL of CH_2Cl_2 and stirred vigorously with 10 mL of 0.77M aqueous NaOCl (pH

12–13). Aliquots of the organic layer were periodically removed, passed through a short column of neutral alumina, and analyzed for oxidation products by gas chromatography using a 5% phenyl methyl silicone capillary column (10 m × 0.53 mm) with PhBr as an internal standard.

Determination of the Optical Purity of *trans*-β-Methylstyrene Oxide. A sample of *trans*-β-methylstyrene oxide (2–3 mg) obtained from the oxidation above with dissolved in $CDCl_3$ (0.3 mL), and solid portions of shift reagent tris[3-[(heptafluoropropyl)hydroxymethylene]-*d*-camphorato]europium(III) were added incrementally until a desired separation of the methyl, α-, and/or β-proton signals in the ^1H NMR spectrum of the epoxide was obtained. Integration of the fully separated enantiomeric peaks was used to determine the enantiomeric purity of the epoxide. Each experiment showed essentially equal intensities of all enantiomeric pairs of protons.

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Registry No. **2a**, 119274-66-7; **2b**, 119296-11-6; **2c**, 119274-67-8; **3a**, 119296-12-7; **3b**, 119274-68-9; **3c**, 119274-69-0; **3d**, 78737-53-8; **4a**, 94405-01-3; **4a**·4HCl, 119274-70-3; **4b**, 119274-71-4; **4b**·4HCl, 119274-72-5; **4c**, 94405-03-5; **4c**·4HCl, 119274-73-6; **5a**, 3397-32-8; **5b**, 3397-35-1; **5c**, 3496-11-5; **6a**, 83852-28-2; **6b**, 119274-74-7; **6c**, 119274-75-8; **7a**, 83852-29-3; **7b**, 119274-76-9; **7c**, 110465-49-1; PhCHO, 100-52-7; 1,3-diaminopropane, 109-76-2; dimethyl malonate, 108-59-8; *trans*-β-methylstyrene, 873-66-5; *trans*-β-methylstyrene oxide, 23355-97-7.

Rational Design of Templates for Intramolecular O,N-Acyl Transfer via Medium-Sized Cyclic Intermediates Derived from L-Cysteine. Definition of an Experimental Maximum in Effective Molarity through the Study of "Tunable" Templates

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Rate constants and effective molarities for intramolecular O,N-acyl transfer have been measured for a series of unsymmetrical disulfides derived from cysteine and having the general structure H-Cys(S-XY-OAc)-OMe, for which XY is a rigid molecular spacing element that maintains a fixed OS distance lying in the range of 4.5–6.5 Å. A synthetic route is described to 4-hydroxy-6-mercaptodibenzothiophene, involving lithiation of 4-methoxydibenzothiophene followed by reaction with elemental sulfur and positional isomer separation. A maximum effective molarity (EM) value of 5 M is seen for the 4,6-disubstituted dibenzofuran function (OS = 5.45 Å) while EM values of less than 0.1 M are seen for 4,6-disubstituted phenoxathiin and 4,6-disubstituted dibenzothiophene functions (OS = 3.90 and 6.30 Å, respectively). Distance calculations and estimates of strain energy based on torsional and van der Waals terms are used to show that this result is consistent with a cyclic transition state containing one conformation of the cysteine framework. Energy minimization calculations were carried out by using a novel null-vector procedure for finding allowed torsional motions. They imply that the transition state for O,N-acyl transfer is strained by ca. 6 kcal/mol in the dibenzofuran case.

In earlier reports[1,2] we have described progress toward a new methodology for the chemical ligation of medium-sized polypeptides. A central issue throughout this work has been the rational design of a spacing element or template that can permit intramolecular O,N-acyl transfer across the cysteine disulfide function of **1**. After synthesis and study of 10 distinct molecular frameworks, we have attained effective molarity (EM) values of 5–10 M for templates derived from 4,6-difunctionalized dibenzofurans.

Developing a new type of practical acylation chemistry has led us to consider a variety of fundamental problems connected with entropy-induced rate acceleration.[4,5] In this paper we present a detailed analysis of our results to date on the optimization of size and shape of spacers that facilitate the reaction **1** → **2** → **3** as well as new results that define an experimental maximum in EM as a function of spacer length. A simple energy minimization analysis is used to interpret these results and to predict a maximum EM value that might be obtained by using an optimal template belonging to this structural series.

Underlying Issues. Effective molarity can be estimated when an intramolecular reaction involving a reactive pair of atoms can be successfully modeled by an intermolecular reaction in which the pair of reactive groups appear in separate molecules. Formally, EM is the ratio of first- and second-order rate constants for these reactions and is equal to the concentration of the external nucleophile that must be added to the intramolecular reaction mixture to permit inter- and intramolecular processes to proceed at equal rates. More than 15 years ago in a paper concerned with the role of entropy in enzymatic catalysis, Page and Jencks[4] related the EM values that can be observed for intramolecular reactions that generate small,

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