droxymethyl-3,4-dihydro-2*H*-pyran, which was cyclized on heating in the presence of a catalytic amount of *p*-toluenesulfonic acid in benzene to provide 6,8-dioxabicyclo[3.2.1]octane. It showed a specific rotation of $[\alpha]^{26}{}_{D}$ +111.4° (*c* 0.86 g/dL, *n*-hexane), compared with the reported value,[6] $[\alpha]_D$ −115° (*n*-hexane), of (1*S*,5*R*)-6,8-dioxabicyclo[3.2.1]octane derived from D-glucose. Therefore, the 6,8-dioxabicyclo[3.2.1]octane synthesized here possesses the opposite configuration (1*R*,5*S*), and, hence, the absolute configuration of the two asymmetric carbon atoms of **7** prepared from the same diastereomeric salt **6** is determined to be (1*R*,5*R*). The details of the preparation of (+)-(1*R*,5*S*)-6,8-dioxabicyclo[3.2.1]octane and its cationic polymerization will be published elsewhere.[7]

The oligomerization of **7** was carried out at −40 °C in four different solvents with boron trifluoride etherate as the initiator. The reaction products were analyzed by gel permeation chromatography. The results are summarized in Table I. Very interestingly, cyclic hexamer was preferentially formed in each run. In particular, the extremely high selectivity, as well as high conversion to the cyclic hexamer, observed in 1-nitropropane is surprising, in view of the fact that the cyclic hexamer is a 30-membered macrocyclic compound. Such an unusually high selectivity for the formation of the cyclic hexamer may suggest that a growing chain consisting of the configurationally identical monomeric units tends to take a conformation especially favorable for the ring closure to the cyclic hexamer. Probably the main factor contributing to the selective formation of the cyclic hexamer is its precipitation out of the solution during the reaction owing to the low solubility (1.4 g/dL of 1-nitropropane at −40 °C).

It is of interest to note here that the racemic monomer produces exclusively cyclic tetramer **3** in chloroform under the specified conditions given in Table I. Therefore, the complete absence of cyclic tetramer in chloroform in the oligomerization of the optically active monomer indicates that the cyclic tetramer **3** from the racemic monomer is not an equimolar mixture of optically active, enantiomeric cyclic tetramers, but an optically inactive compound consisting of alternating enantiomeric monomeric units.[2]

It is worthy of remark that no cyclic dimer was formed from the optically active monomer irrespective of the reaction conditions, in remarkable contrast to the oligomerization of the racemic monomer.[1,2] This is compatible with the fact that the cyclic dimer **2** from the racemic monomer consisted of a pair of different enantiomeric units as revealed by X-ray analysis.[2]

The optically active cyclic hexamer thus prepared was isolated by means of a preparative gel permeation chromatography and characterized: IR 1763 cm^{-1} ($\nu_{C=O}$); UV (CH_3CN) λ_{max} 215 nm (ϵ 720); $[\alpha]^{24}{}_{D}$ −112° (*c* 1.0 g/dL, CH_3CN); CD (CH_3CN) λ_{min} 215 nm, $[\theta]$ −2200°; ^1H NMR (CD_3CN, Me_4Si), δ 6.20 (s, 1, $OCHO$), 4.42 (d, 1, $CHCO$), and 1.76 (br, 6, $CH_2CH_2CH_2$); ^{13}C NMR (CD_3CN, Me_4Si) δ 169.97 ($C{=}O$), 92.59 ($OCHO$), 70.22 ($CHCO$), 28.70 ($OCHCH_2$), 28.56 (CH_2CHCO), and 18.13 ($CH_2CH_2CH_2$); DSC (heating rate 1.25 °C/min), began to decompose at 125 °C; molecular weight, calcd 768, found (vapor pressure osmometry, $CHCl_3$) 778; crystallized from acetonitrile solution in the form of hexagonal flat plates. Anal. $(C_6H_8O_3)_6$ C, H.

Complexation of the optically active cyclic hexamer with a variety of thiocyanates has been studied qualitatively in acetonitrile-d_3 by means of ^1H and ^{13}C NMR spectroscopy. Preliminary experiments have shown that the cyclic hexamer shows a specific affinity toward barium thiocyanate. Quantitative evaluation of the complexing ability of the newly prepared, optically active macrolide toward metallic ions, together with the X-ray analysis of its crystalline structure, is currently in progress.

Acknowledgment. Financial support from the Ministry of Education (Grant-in-Aid for Scientific Research No. 355392) and from Yamada Science Foundation is gratefully acknowledged.

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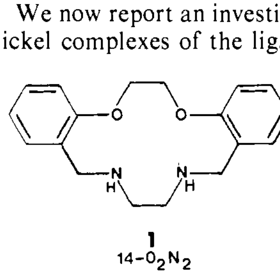
Macrocyclic Ring-Size Control of Kinetic Lability. Kinetics of Dissociation of a Range of Nickel(II) Complexes of O_2N_2-Donor Macrocycles in Acid

Sir:

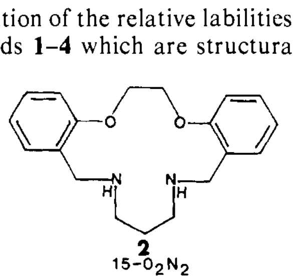
The use of macrocyclic ligands of the polyether crown or cryptand class to selectively complex alkali and alkaline earth metal ions has been well documented[1,2] and kinetic aspects of such complexation are also receiving considerable attention[1,3] since such data are of fundamental significance to aspects of metal-ion transportation in biological systems.[4]

The interaction of macrocycles containing four nitrogen donors with transition metal ions has also been studied in considerable detail.[5,6] Such studies have been largely directed toward elucidation of the nature of the macrocyclic effect—the enhanced kinetic and thermodynamic stabilities of macrocyclic ligand complexes when compared with their open-chain ligand analogues.[7] However, because of extreme kinetic inertness and associated high formation constants, comparative studies of kinetic and thermodynamic stabilities of the complexes of an extended series of N_4-donor ligands varying only in macrocyclic ring size have proved difficult.[8] In addition, the study of the effects of alteration of macrocyclic ring size on the kinetics of dissociation of nickel complexes of saturated N_4-donor macrocycles are complicated by stereochemical and spin-state changes along the series.[6]

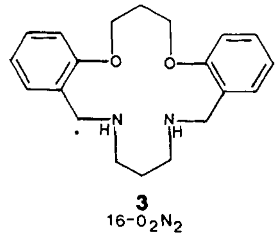
We now report an investigation of the relative labilities of nickel complexes of the ligands **1–4** which are structurally



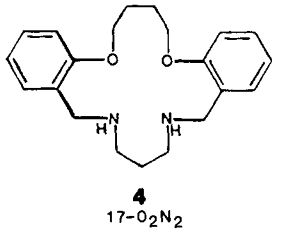
1
14-O_2N_2



2
15-O_2N_2



3
16-O_2N_2



4
17-O_2N_2

0002-7863/79/1501-4014$01.00/0

Table I. Kinetic Data for Dissociation of the Complexes in 1 M HCl at 25 °C

	complex			
	$Ni(14\text{-}O_2N_2)Cl_2$[a]	$Ni(15\text{-}O_2N_2)Cl_2$	$Ni(16\text{-}O_2N_2)Cl_2$	$Ni(17\text{-}O_2N_2)Cl_2$
k_{obsd}, s^{-1}	8.8×10^{-1}	3.4×10^{-3}	6.3×10^{-4}	
	8.7×10^{-1}	3.5×10^{-3}	6.6×10^{-4}	>0.5[b]
	8.9×10^{-1}	3.6×10^{-3}	6.5×10^{-4}	
	8.7×10^{-1}	3.3×10^{-3}	6.2×10^{-4}	
	8.8×10^{-1}			
	8.8×10^{-1}			
mean k_{obsd}, s^{-1} [c]	$(8.8 \pm 0.4) \times 10^{-1}$	$(3.5 \pm 0.3) \times 10^{-3}$	$(6.4 \pm 0.4) \times 10^{-4}$	>0.5
$\Delta H^{\ddagger}$, kJ mol^{-1} [c,d]	45 ± 2	68 ± 2	97 ± 2	
$\Delta S^{\ddagger}$, J deg^{-1} mol^{-1} [d]	−95 ± 4	−63 ± 8	52 ± 6	

[a] Corresponding values for the analogous complex containing the 14-membered macrocycle in which the $-CH_2-CH_2-$ bridge between the nitrogen donors of $14\text{-}O_2N_2$ has been replaced by a $-CH_2-CH(CH_3)-$ bridge are k_{obsd}, s^{-1}, $(1.4 \pm 0.1) \times 10^{-1}$; $\Delta H^{\ddagger}$, 49 ± 2; $\Delta S^{\ddagger}$, −96 ± 6. [b] Value obtained in 50% (v/v) dimethyl sulfoxide and also in 90% methanol; because of low solubility it was not possible to obtain the corresponding value in water. [c] Errors are an estimate of the total uncertainty involved in the measurements. [d] Activation parameters were derived from measurement of k_{obsd} over a range of temperatures (accurate to ±0.1 °C). Each of the following rate constants (k_{obsd}, s^{-1}) is the mean of between two and eight individual determinations. $Ni(14\text{-}O_2N_2)Cl_2$: 2.9×10^{-1} (10.0 °C), 5.2×10^{-1} (17.3 °C), 8.8×10^{-1} (25.0 °C), 1.3 (30.7 °C), 1.8 (36.0 °C), 2.3 (41.4 °C). $Ni(15\text{-}O_2N_2)Cl_2$: 1.4×10^{-3} (15.4 °C), 2.0×10^{-3} (20.0 °C), 3.6×10^{-3} (25.0 °C), 5.9×10^{-3} (30.4 °C), 9.1×10^{-3} (34.6 °C), 14.2×10^{-3} (40.1 °C). $Ni(16\text{-}O_2N_2)Cl_2$: 1.8×10^{-4} (15.8 °C), 3.3×10^{-4} (20.3 °C), 6.4×10^{-4} (25.0 °C), 12.3×10^{-4} (30.4 °C), 23.0×10^{-4} (35.2 °C), 49.0×10^{-4} (41.3 °C), 88.0×10^{-4} (50.8 °C). Although the data are limited, the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values show compensating trends along the series.

intermediate between the two categories of macrocyclic ligand mentioned above. Since they contain two ether oxygens (weak donors), these ligands yield only high-spin octahedral nickel complexes which are of lower kinetic and thermodynamic stabilities than related complexes of N_4-donor macrocycles. These nickel complexes are thus ideal for a comparative study of the relationship between macrocyclic ring size and kinetic lability. Such a study is now reported.

Complexes of ligands **1**–**4** of type $Ni(macrocycle)Cl_2$ have been described previously[9] and, from physical measurements, the complexes were assigned pseudooctahedral structures; X-ray structural investigations of the complexes of **2**[10] and **3**[11] confirm that these have six-coordinate trans-dichloro geometries. Stock solutions of the analytically pure complexes were used for the dissociation studies. In a typical experiment an aqueous solution of the complex (10^{-2}–10^{-3} M) was mixed with an equal volume of hydrochloric acid (2 M) and the rate of dissociation followed spectrophotometrically (using the stopped-flow technique when necessary). For each complex, the dissociation was followed at the wavelength of the ${}^3A_{2g} \rightarrow {}^3T_{1g}$ transition (600–650 nm) and, in each case, the spectrum at the end of the reaction was identical with that of $NiCl_2$ in excess acid. The observed dissociation rate constants were found to be independent of the concentration of complex present. No acid dependence of the rate was detected over the range studied (0.05–1.0 M) and hence the acid merely acts as a scavenger for the free ligand once it dissociates from the nickel.

The observed first-order rate constants are listed in Table I. There is a dependence of dissociation rate on macrocyclic ring size: the rate shows a progressive decrease as the macrocyclic ring size increases from 14- to 16-membered followed by a sharp increase for the complex of the 17-membered ring. The occurrence of a minimum rate at the 16-membered ring complex is a clear illustration of macrocyclic ring-size control of kinetic lability and follows a similar pattern to the thermodynamic stabilities (measured in 95% methanol) which peak at the 16-membered ring complex.[12] A previous study[13] involving copper complexes of a series of S_4-donor macrocycles has also demonstrated a correlation between dissociation rates and thermodynamic stabilities for particular complexes; in this study ring size was shown to strongly influence the respective dissociation rates whereas formation rates showed only a weak dependence. Further, limited kinetic data for two high-spin nickel complexes of saturated N_4 macrocycles suggest that the complex of the macrocycle of best fit will show the slowest dissociation rate.[6] This also appears to be the situation for the present complexes. Hole-size considerations[14] also suggest that the 16-membered macrocycle provides the fit of lowest strain for the nickel ion, although the optimum hole size may lie somewhere between those of the 15- and 16-membered rings.

Preliminary experiments indicate very different dissociation rates for complexes with a given macrocycle of the present type but incorporating transition metal ions other than nickel. This kinetic discriminating ability shows promise for development of efficient separation techniques for metal ions of the transition series. Further studies in this area are proceeding.

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(14) It has been demonstrated (see Bullock, J. I.; Ladd, M. F. C.; Povey, D. C. *J. Chem. Soc., Dalton Trans.* **1977,** 2243) that aryl–alkyl ethers coordinated to copper regularly result in Cu–O distances which are longer than the sum of the published respective covalent radii. A survey of published data for nickel–ether oxygen bond distances indicates that a similar tendency also occurs for octahedral nickel where a mean (eight distances) of 2.15 Å was obtained vs. 2.05 Å for the sum of the published covalent radii for nickel and oxygen (see Pauling, L. "The Nature of the Chemical Bond", 3rd ed.; Cornell University Press: Ithaca, New York, 1960). Taking a mean value

of 2.10 Å as being typical of neutral sp^3-hybridized nitrogen atoms in macrocyclic high-spin nickel complexes (see ref 7 and 11), then an optimum hole size of ~4.25 Å is predicted for nickel(II). This is larger than that of 4.13 Å determined by X-ray for free 15-O_2N_2 in a flat conformation (McPartlin, M.; Tasker, P. A.; Trotter, J., unpublished results) and supports the postulate that the hole size of 16-O_2N_2 is the one of best fit for the present series of ligands.

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Photooxygenations in Aqueous Solution with a Hydrophilic Polymer-Immobilized Photosensitizer

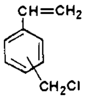
Sir:

In 1973 the synthesis and use of the first example of a heterogeneous sensitizer for singlet oxygen formation in organic solvents was reported.[1] This polymer-immobilized reagent, Ⓟ-Rose Bengal, consists of a photosensitizing dye, Rose Bengal, covalently bound to an insoluble poly(styrene–divinylbenzene) matrix. Photooxygenations employing this heterogeneous sensitizer, in place of a soluble dye, have been reported to be synthetically convenient and mechanistically less complicated.[2] Ⓟ-Rose Bengal has proved particularly useful in the isolation of unstable primary photooxygenation products such as 1,2-dioxetanes.[3]

Heterogeneous sensitizers permit the design of experiments not possible with soluble dyes. An example is Foote's recent three-phase test for the intermediacy of singlet oxygen in photooxidation.[4] Use of a polymer-bound substrate and Ⓟ-Rose Bengal allowed for more definitive conclusions than possible with Kautsky's early experiments.[5] Ⓟ-Rose Bengal has also been used in a similar way to show that photodynamic inactivation of *E. Coli* requires diffusion of singlet oxygen into the cell.[6] In addition to these unique features, heterogeneous sensitizers have a number of practical advantages over soluble sensitizers. These include (1) increased photostability of the dye on the polymer; (2) decreased secondary interaction of the photosensitizer with substrates or products; (3) utility in solvents in which the free dye is insoluble; (4) reuse of the sensitizer; (5) removal by simple filtration or sedimentation. The last feature implies, for example, that a continuous photooxidation process should be feasible, and that photooxygenations may be followed spectroscopically in regions normally masked by dye absorption.

Although Ⓟ-Rose Bengal has been demonstrated to be useful in most organic solvents, we have found it to be a poor photosensitizer in aqueous systems. The reason for this limited effectiveness is related to the observations that the hydrophobic polymer is not wetted by water, is difficult to suspend in aqueous media, and does not swell in water. A water-compatible, covalently immobilized sensitizer would extend the utility of the method to biological media. In view of the wide interest in singlet oxygen in biochemical systems, for instance regarding its role in photodynamic action,[7] and because of its use as a tool to probe protein structure,[8] we now report the preparation of such a sensitizer, suitable for use in water.

A hydrophilic polymer was prepared by copolymerization of chloromethylstyrene (60:40 mixture of meta and para isomers) (**1**) and the monomethacrylate ester of ethylene glycol (**2**) with the bis methacrylate ester of ethylene glycol (**3**) as cross-linking agent. The resulting polymer was obtained in the form of beads (38–75 μ) and was heated with Rose Bengal in dry dimethylformamide at 60 °C for 3 days to yield the hydrophilic sensitizer, (HP)-Rose Bengal.[9] After careful extraction with several solvents to remove occluded dye,[10] the bright red beads were analyzed for bound Rose Bengal. The iodine content of 4.61% indicated that the heterogeneous sensitizer contained 0.091 mmol of Rose Bengal/g. The (HP)-Rose Bengal was found to be wetted by water and to swell by 40% in this solvent.



1

$CH_2{=}C(CH_3)CO_2CH_2CH_2OH$

2

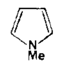
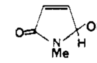
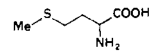
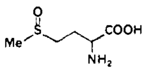
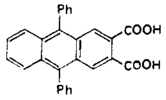
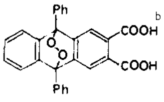
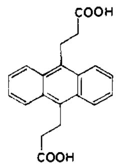
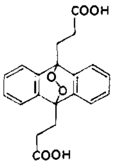
$(CH_2{=}C(CH_3)CO_2CH_2\text{-})_2$

3

The effectiveness of (HP)-Rose Bengal in sensitizing singlet oxygen formation in water is illustrated by the successful photooxygenation of a number of substrates known to react with singlet oxygen in water.[11] Typically, photooxidations were conducted with 0.01–0.1 M substrate[12] in distilled water. Sodium hydroxide or hydrochloric acid were used to adjust pH where necessary. Suspensions of 5 to 20 mg/mL of (HP)-Rose Bengal were generally used, except in large-scale reactions where as little as 0.3 mg/mL was found adequate.[13] Experiments have shown that a 1-cm depth of a stirred suspension containing 10 mg/mL of (HP)-Rose Bengal absorbs ~93% of the incident light at 550 nm. Both 500-W quartz-halogen lamps with a UV-cutoff filter and a 300-W xenon lamp coupled with a 0.25 m Jarrell-Ash monochromator were used as light sources. Recently we have found that a 400-W sodium lamp (General Electric Lucalox) is particularly suited to this sensitizer. The bulk of the emission is at wavelengths absorbed by (HP)-Rose Bengal, and the absence of a significant UV component obviates the need for filters. Further, the lamp is energy efficient, has a long lifetime, and requires little cooling.

The results of the photooxidation experiments are presented in Table I. The last entry indicates that the sensitizer is also synthetically useful in alcoholic solvents. In each case, the products of the reaction using (HP)-Rose Bengal were compared with those obtained using soluble dye. UV-visible spectroscopy of filtered reaction solutions did not show any

Table I. Photooxygenations with (HP)-Rose Bengal

substrate	solvent	product	isolated yield	ref
	H_2O, pH 7	 [a]	36%	16
	H_2O		85%	17
	H_2O, pH 9	 [b]	89%	18
	H_2O, pH 8		95%	19
PhSMe	MeOH	PhSOMe[c]	99%	20

[a] With soluble Rose Bengal, purification of this product was significantly more troublesome. [b] This product was quantitatively converted back to starting material upon heating. [c] Overoxidation to the sulfone was not observed.

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