(3d) were purchased from Ega-Chemie and used without additional purificarion.

Aziridines. Diphenyl-2,2-aziridine (1a),[15] dimethyl-2,2-aziridine (1b),[16] and phenyl-2-aziridine (1c)[17] were prepared as described in the literature.

General Procedure for Asymmetric Chlorination of Aziridines 1 to *N*-Chloroaziridines 2. A mixture of the aziridine 1 (1 mmol) and the chiral alcohol (2 mmol) was diluted with CH_2Cl_2 (2.5 mL) and treated at -60 °C with a solution of freshly prepared TBHC (1 mmol) or with NCS (1 mmol) in CH_2Cl_2 (2 mL). Chlorination of aziridine 1c was carried out with 0.5 mmol of TBHC or NCS reagent. The reaction mixture was kept for 3 h at -60 °C, and the CH_2Cl_2 solvent was then evaporated in vacuo. Optically active *N*-chloroaziridines 2 were recovered (80-90% yield) free from traces of the optically active solvent (NMR, TLC and GLC analysis) by rapid distillation at low temperature and pressure (for aziridine 2b) or by column chromatography on silica gel with *n*-hexane-ether (9:1) as the eluant [for aziridines 2a, (*E*)-2c, and (*Z*)-2d]. *N*-Chloroaziridines (2) obtained in this way release 1 molar equiv of iodine from an acetic acid solution of potassium iodide. NMR properties of these compounds are reported in Table III. In all cases, chiral trifluoromethylcarbinols (3) have been recovered quantitatively and without loss of optical activity.

1-Chloro-2,2-diphenylaziridine (2a). This compound is a relatively stable crystalline solid. Noteworthy is the fact that fractional crystallization of partially optically active 2a, as can be obtained by chlorination of 1a with TBHC in the presence of the cyclohexyl-substituted 3a, 1-naphthyl-substituted 3c, or 9-anthryl-substituted 3d carbinols (Table I), affords the highly optically pure derivative. For istance, crystallization of 2a having $[\alpha]_D$ -95.6° (*c* 3.1 $CHCl_3$) from ethyl ether-petroleum ether (bp 40-60 °C) solution gave a sample which shows the following: mp 26-30 °C; $[\alpha]_D$ -283.7° (*c* 2.8 $CHCl_3$).

1-Chloro-2,2-dimethylaziridine (2b). This compound has been recovered as clear colorless liquid by distillation of the reaction mixtures at low temperature (-5 °C) and pressure (15 mm).

1-Chloro-2-phenylaziridines (*E*)-2c and (*Z*)-2d. Clean separation of the (*E*)-2c major component, of the slow moving (*Z*)-2d diastereoisomer, and of unreacted partially optically active 1c aziridine could be achieved by column chromatography, and the compounds have not been subjected to additional purification. Diastereoisomeric 1-chloro-2-phenylaziridines 2c and 2d are clear colorless liquids which show the following mass spectra data (40 eV): *m/e* 155 (M^+, ^{37}Cl), 153 (M^+, ^{35}Cl), 118, 103, 91, 77, 65, 51. NMR spectra and epimerization studies agree upon the *E* and *Z* configurational assignment for the 2c and 2d *N*-chloroaziridines, respectively.[7]

Acknowledgment. We thank Centro Strumenti Università di Modena for the NMR measurements and the CNR, Rome, for financial support. In addition, we thank Professor W. H. Pirkle, University of Illinois, Urbana, IL, for helpful discussion.

Registry No. 1a, 25564-63-0; 1b, 2658-24-4; (±)-1c, 55297-79-5; (*R*)-(-)-1c, 18142-08-0; (*S*)-(+)-2a, 39830-44-9; (*R*)-(-)-2a, 79258-01-8; (*R*)-(+)-2b, 28112-60-9; (*S*)-(-)-2b, 83664-41-9; (1*S*,2*S*)-(+)-2c, 86014-25-7; (1*R*,2*R*)-(-)-2c, 86014-26-8; (1*S*,2*R*)-(+)-2d, 86014-27-9; (1*R*,2*S*)-(-)-2d, 86014-28-0; (*R*)-(+)-3a, 68128-21-2; (*S*)-(+)-3b, 340-06-7; (*R*)-(-)-3c, 22038-90-0; (*S*)-(+)-3d, 60646-30-2; (*R*)-(-)-3d, 53531-34-3; TBHC, 507-40-4; NCS, 128-09-6.

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Difunctionalized Trans-2,5-Disubstituted Pyrrolidine (Azethoxyl) Nitroxide Spin-Labels

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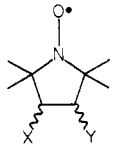
The synthesis of two short-chain trans-2,5-difunctionalized azethoxyl nitroxide spin-labels, dinitrile 12 and dicarboxylic acid 14, is described. The trans stereochemistry of 12 and 14 was established by conversion of 12 to a diastereomeric mixture of *N*-hydroxy esters 13, which was analyzed by NMR spectroscopy.

Functionalized, stable nitroxide free radicals[1] enjoy wide application as spin-labels for the study of biological and other macromolecular assemblies by electron spin resonance (ESR) spectroscopy.[2] Most of the available spin-labels bear only one functional group, although recently, several 3,4-difunctionalized 2,2,5,5-tetramethylpyrrolidinyl-1-oxy nitroxides 1 have been described.[3,4]



1

Difunctional nitroxides are important as potential cross-linking agents because they have the possibility of attachment to a macromolecule at two sites. The motion of such a nitroxide would consequently be largely confined to that of the macromolecule, an advantage in applications involving the relatively new saturation transfer electron paramagnetic resonance (STEPR) methodology for studying molecular motion in the correlation time range $10^{-7} < \tau < 10^{-3}$ s.[5]

Azethoxyl nitroxides 2, originally introduced by us[6,7] as minimum steric perturbation spin-labels for lipid systems,

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(2) Berliner, L. J., Ed. "Spin Labeling: Theory and Applications"; Academic Press: New York; 1976, Vol. I; 1979, Vol. II.
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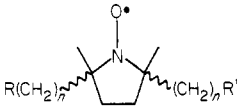
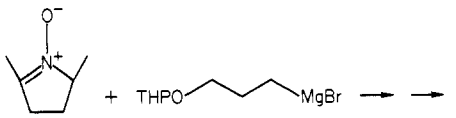
are pyrrolidinyl-1-oxy nitroxides bearing side chains at the 2- and 5-positions. This substitution pattern differs from



2, pure cis and pure trans; R = H; R′ = functional group
3, cis and trans mixture; R = R′ = functional group

most of the other available spin-labels[1] and has important consequences in spin-labeling studies owing to the canted nature of the nitroxide *z* axis[8] (largest splitting) with respect to the long molecular axis in trans azethoxyl nitroxide spin-labeled molecules.[7] The only reported examples of difunctionalized azethoxyl nitroxides are the cis and trans mixtures of long-chain azethoxyl nitroxides **3** described by Tse-Tang et al.[9] Herein, we describe the synthesis of the two short-chain trans-2,5-difunctionalized azethoxyl nitroxides dinitrile **12** and dicarboxylic acid **14** and their trans-enriched precursors. The accompanying paper[10]



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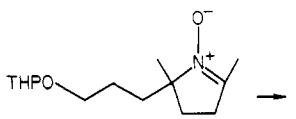

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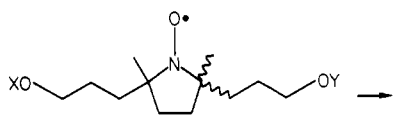
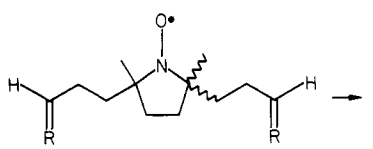
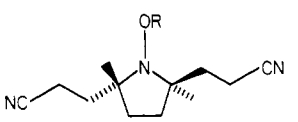


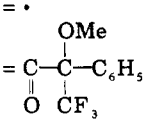
7, X = Y = THP
8, X = THP; Y = H
9, X = Y = H



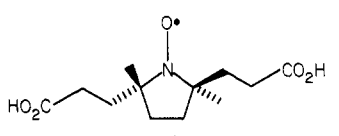
10, R = O
11, R = N⁓OH



12, R = •



13, R = C(=O)C(OMe)(CF$_3$)C$_6$H$_5$



14

describes an application of **14** for the preparation of the first example of a nitroxide cryptand.

Results and Discussion

Our synthetic route parallels that of our original monofunctionalized azethoxyl nitroxide synthesis.[6] Dimethyl nitrone **4**[11] was treated with the tetrahydropyranyl (THP) ether Grignard reagent **5**,[12] and the intermediate *N*-hydroxy compound was then oxidized by $Cu(OAc)_2$–NH_4OH–air[6] to give the new nitrone **6**. This was allowed to react with Grignard reagent **5** and then oxidized with air, affording the bis(tetrahydropyranyl ether) nitroxide **7**, likely as a mixture of cis and trans isomers. It was anticipated, however, that the trans isomer would predominate because approach of the Grignard reagent to **6** should take place preferentially on the less hindered face, i.e., trans to the bulky hydroxypropyl THP ether substituent.

A variety of mild, acidic hydrolysis conditions were investigated with **7**, all of which afforded a mixture (easily separable, fortunately) of starting **7**, mono THP ether **8**, and diol **9**. The hydrolysis step proceeded optimally in MeOH containing *p*-toluenesulfonic acid at 25 °C for several hours, affording nitroxide diol **9** in 47% yield. More vigorous acidic conditions applied to **7** led to partial or complete destruction of the acid-sensitive nitroxyl group.

Preliminary attempts to oxidize **9** directly to the desired diacid **14** utilized pyridinium dichromate in dimethylformamide (DMF), a reagent combination especially effective for the oxidation of acid-sensitive alcohols to carboxylic acids under mild conditions.[13] In our hands, however, only a trace of **14** was obtained, accompanied by a mixture of nonparamagnetic products in which the nitroxide group had been destroyed. Nitroxide decomposition was also observed in attempts to prepare nitroxide dialdehyde **10** from **9** using pyridinium dichromate in CH_2Cl_2.[13]

Success was achieved with a multistep procedure that avoided a high-valent metal oxide as the oxidizing agent. Thus, diol **9** could be oxidized in 69% yield to dialdehyde **10** by using the oxalyl chloride–Et_3N–CH_2Cl_2 methodology of Swern.[14] Nitroxide **10** may well find application in spin-labeling studies as a difunctional azethoxyl nitroxide capable of attachment to biomolecules via reductive amination procedures, for example.

After a series of unsuccessful attempts to oxidize **10** to diacid **14** using, for example, $Ag(NH_3)_2OH$ in MeOH, Ag_2O in NaOH–EtOH–H_2O,[15] AgO–THF–H_2O,[16] or pyridinium dichromate in DMF,[13] dialdehyde **10** was converted into the dioxime **11**. Treatment of **11** with Me_2SO–oxalyl chloride–Et_3N[17] led to the crystalline trans dinitrile **12** in 63% overall yield. None of the cis isomer could be isolated at this stage, suggesting that the precursors to *12* likely were highly enriched in the trans isomer.

The trans stereochemistry of **12** was established as follows.[6] Because the trans isomer **12** must be produced as a racemic mixture whereas the cis is a meso form, attachment of the former to a chiral molecule will give a

(8) Following the usual convention for a planar nitroxide, the *x* axis is defined by the N—O bond. The *z* axis passes through the N atom parallel to the p-orbital.
(9) Tse-Tang, M. W.; Gaffney, B. J.; Kelly, R. E. *Heterocycles* **1981**, *15*, 965–974.
(10) Keana, J. F. W.; Cuomo, J.; Lex, L.; Seyedrezai, S. E. *J. Org. Chem.* following paper in this issue.
(11) Elsworth, J. F.; Lamchen, M. *J. S. Afr. Chem. Inst.* **1971**, *24*, 196–204; *Chem. Abstr.* **1971**, *75*, 151083d, Keana, J. F. W., ref 1b, p 157.
(12) Preliminary experiments utilized $BrMgCH_2CH_2\overline{CHO(CH_2)_2O}$. Yields, however, were low, and acid-catalyzed hydrolysis of the acetal function in a subsequent step proved to be difficult.
(13) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399–402.
(14) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651–1660. Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.
(15) Shamma, M.; Rodriguez, H. R. *Tetrahedron* **1968**, *24*, 6583–6589.
(16) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616–5617.
(17) Ho, T. L.; Wong, C. M. *Synth. Commun.* **1975**, *5*, 423–425.

mixture of two diastereomers while the cis would afford a single stereoisomer. Therefore, dinitrile **12** was hydrogenated catalytically to the *N*-hydroxy intermediate, which was then esterified with Mosher's reagent,[18] affording ester **13**. That **13** was a mixture of two diastereomers was shown by the appearance of the methoxy groups as two singlets (δ 3.47 and 3.53) in the 360-MHz ^1H NMR spectrum. The trans assignment was confirmed by the observation of two singlets (5.902 and 6.112 ppm downfield from CF_3CO_2H) for the trifluoromethyl groups in the 339.7-MHz ^{19}F NMR spectrum. We note in passing that nitriles are the usual precursors to the versatile imidate series of acylating agents. Thus dinitrile **12** may well enjoy applications in spin-labeling through such methodology.

The synthesis of nitroxide diacid **14** was achieved by hydrolysis of dinitrile **12** in refluxing aqueous sodium hydroxide for 44 h. Neutralization followed by recrystallization gave pure *trans*-**14** in 73% yield. In certain applications, chiral spin-labels are required in order to avoid diastereotopic interactions between a racemic label such as **14** and a chiral substrate.[19] The carboxyl groups of **14** should permit its ready resolution into the two enantiomeric forms for such studies.

Experimental Section[20]

***cis*- and *trans*-2,5-Dimethyl-2,5-bis(3-(tetrahydropyranyloxy)propyl)pyrrolidinyl-1-oxy (7).** To a stirred mixture of 10.5 g (0.43 mol) of dry Mg turnings in 180 mL of dry tetrahydrofuran (THF) at 0 °C was added 1 mL of 1,2-dibromoethane. After 20 min, 20 mL (26 g, 0.115 mol) of 3-bromopropan-1-yl tetrahydropyranyl ether (prepared from 3-bromopropanol by the procedure of Miyashita et al.,[21] bp 65 °C (0.01 mm)) in 70 mL of THF was added dropwise over 1.5 h at 0 °C. The mixture containing **5** was stirred at 0 °C for 1 h and then added to a stirred solution of 10 mL (10 g, 0.088 mmol) of 3,4-dihydro-2,5-dimethyl-2*H*-pyrrole 1-oxide (**4**)[11] in 100 mL of THF by means of a canula. The heat of reaction was sufficient to warm the initially cool solution to 25 °C. After a 1-h stir at 25 °C, the dark solution was treated with 6.13 g of NH_4Cl in 53 mL of water. The organic layer was separated and the aqueous layer was extracted with ether (2 × 150 mL). The combined organic layers were then concentrated, and the residue was treated with a mixture of 100 mL of MeOH, 10 mL of concentrated NH_4OH, and 2.5 g of $Cu(OAc)_2$ to give a pale yellow solution. A stream of O_2 was bubbled through the yellow solution until it became dark blue (5–10 min). This was concentrated and the residue was treated with $CHCl_3$ (50 mL), dried ($MgSO_4$), and filtered through a short plug of activity I neutral alumina. Concentration of the filtrate afforded quite pure (by NMR) 3,4-dihydro-2,5-dimethyl-2-(3-(tetrahydropyranyloxy)propyl)-2*H*-pyrrole 1-oxide (**6**) contaminated with some hydroxypropyl THP ether (removed by prolonged exposure to high vacuum) and the Wurtz coupled product, 1,6-bis(tetrahydropyranyloxy)hexane.

The crude nitrone **6** was dissolved in 100 mL of THF and treated with Grignard reagent **5** (same quantity as above). A pasty precipitate formed initially and dissolved by the end of the addition. After a 1-h stir at 25 °C, the dark brown reaction mixture was worked up as described above. The residue was dissolved in 100 mL of MeOH and treated with 10 mL of concentrated NH_4OH and 2 g of $Cu(OAc)_2$, giving a pale yellow solution, which became green upon treatment with a stream of O_2. The dark green solution was concentrated and the residue was triturated with hexane–ether (4:1). The extract was dried ($MgSO_4$) and concentrated, and the residue was flash chromatographed over silica gel. Elution with hexane–ether (3:2) gave a yellow fraction, which amounted to 2.1 g (6%) of nitroxide **7** as a viscous oil: ESR ($CHCl_3$) 3 lines, a_N = 14.6 G (~1 spin per molecule). Anal. Calcd for $C_{22}H_{40}NO_5$: C, 66.30; H, 10.12; N, 3.51. Found: C, 65.87; H, 9.84; N, 3.37. Yields of **7** approaching 10% overall were achieved with smaller scale runs.

***cis*- and *trans*-2,5-Dimethyl-2-(3-(tetrahydropyranyloxy)propyl)-5-(3-hydroxypropyl)pyrrolidinyl-1-oxy (8) and cis- and *trans*-2,5-Dimethyl-2,5-bis(3-hydroxypropyl)pyrrolidinyl-1-oxy (9).** A solution of 1.0 g of nitroxide **7** and 50 mg of *p*-toluenesulfonic acid in 25 mL of MeOH was stirred in the dark at 25 °C. The progress of the reaction was monitored by HPLC analysis (μ-Bondapak C_{18} reverse phase column, MeOH–H_2O, 85:15). After 7 h $NaHCO_3$ was added and the mixture was concentrated. The residue was extracted with $CHCl_3$ and then flash chromatographed over silica gel. Elution with EtOAc brought down a small quantity of starting **7** followed by 155 mg (20%) of monosubstituted THP nitroxide **8**: ESR ($CHCl_3$) 3 lines, a_N = 14.5 G; MS, *m/e* 314.234 (32) (calcd for $C_{17}H_{32}NO_4$, 314.233), 198 (14), 172 (59), 154 (65), 128 (22), 114 (41), 95 (24), 85 (100).

Continued elution gave 274 mg (47%) of nitroxide diol **9**: ESR ($CHCl_3$) 3 lines, a_N = 14.5 G; MS, *m/e* 230 (13), 172 (100), 156 (20), 154 (29). Anal. Calcd for $C_{12}H_{24}NO_3$: C, 62.58; H, 10.50; N, 6.08. Found: C, 62.63; H, 10.25; N, 6.08.

***cis*- and *trans*-2,5-Dimethyl-2,5-bis(3-oxopropyl)pyrrolidinyl-1-oxy (10).** To 10 mL of dry CH_2Cl_2 at –60 °C was added with stirring 168 μL (240 mg, 1.9 mmol) of oxalyl chloride (freshly distilled) followed by 300 μL (330 mg, 4.0 mmol) of Me_2SO. After 5 min at –60 °C, 200 mg (0.88 mmol) of diol nitroxide **9** (dried by azeotropic removal of water with benzene) in 6 mL of CH_2Cl_2 was added. After a 20-min stir at –60 °C, the cloudy mixture was treated with 1.2 mL (870 mg, 8.6 mmol) of dry Et_3N and then allowed to warm to 25 °C. This was diluted with 20 mL of CH_2Cl_2 and poured into 10 mL of water. The organic layer was washed with brine, dried (K_2CO_3), and concentrated. The residue was purified by preparative TLC (silica gel, ether), affording 136 mg (69%) of dialdehyde nitroxide **10** as a yellow oil: ESR (CH_3CN) 3 lines, a_N = 14.4 G; MS, *m/e* 227 (5), 226.145 (12) (calcd for $C_{12}H_{20}NO_3$, 226.144), 212 (13), 193 (12), 178 (15), 171 (14), 170 (100).

***trans*-2,5-Dimethyl-2,5-bis(2-cyanoethyl)pyrrolidinyl-1-oxy (12).** To a stirred solution of 263 mg (3.78 mmol) of hydroxylamine hydrochloride in 0.6 mL of water was added a solution of 390 mg (1.72 mmol) of **10** in 6 mL of pyridine. After a 3-h stir at 25 °C, the mixture was concentrated. The residue was dissolved in $CHCl_3$ (10 mL), washed with water, dried ($MgSO_4$), and concentrated. The resulting oil was dried by azeotropic removal of water with benzene, then dissolved in 5 mL of dry CH_2Cl_2, and added to a solution of 336 μL (489 mg, 3.85 mmol) of oxalyl chloride and 600 μL (660 mg, 8.4 mmol) of Me_2SO in 25 mL of dry CH_2Cl_2 at –60 °C, which was prepared as described above for the oxidation of **9**. The resulting cloudy mixture was stirred at –60 °C for 30 min and then treated with 2.0 mL (14 mmol) of Et_3N. The mixture was allowed to warm to 25 °C and then it was diluted with 20 mL of CH_2Cl_2 and poured into 5 mL of water. The organic layer was washed with brine, dried (K_2CO_3), and concentrated. The residue was chromatographed over silica gel. Elution with $CHCl_3$–MeOH (97:3) gave crystalline **12**. Recrystallization from CH_2Cl_2–ether gave 240 mg (63%) of **12** as yellow needles: mp 107–108 °C; ESR ($CHCl_3$) 3 lines, a_N = 14.4 G; IR ($CHCl_3$) 2249 cm^{-1}. Anal. Calcd for $C_{12}H_{18}N_3O$: C, 65.43; H, 8.24; N, 19.07. Found: C, 65.34; H, 8.12; N, 18.97.

***trans*-1-[Methoxy(trifluoromethyl)phenylacetoxy]-2,5-dimethyl-2,5-bis(2-cyanoethyl)tetrahydropyrrole (13).** Following the procedure of Lee and Keana,[6] 10 mg of nitroxide **12** was converted into 8 mg (41%) of ester **13**, obtained as a colorless oil after silica gel chromatography and elution with $CHCl_3$–MeOH (9:1): IR ($CDCl_3$) 1781 cm^{-1}; NMR ($CDCl_3$) δ 1.13

(18) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.

(19) See, for example: Wetherington, J. B.; Ament, S. S.; Moncrief, J. W. *Acta Crystallogr., Sect. B*, **1974**, *B30*, 568–573. Flohr, K.; Paton, R. M.; Kaiser, E. T. *J. Am. Chem. Soc.* **1975**, *97*, 1209–1218. Hsia, J. C.; Er, S. S.; Tam, C. T.; Tinker, D. O. *J. Biol. Chem.* **1982**, *257*, 1724–1729.

(20) Melting points were obtained in a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded on a 3-200 Sargent-Welch spectrometer. NMR spectra were recorded either on a Varian XL-100 or a Nicolet 360-MHz spectrometer in $CDCl_3$ unless otherwise stated. Chemical shifts are expressed in δ units with Me_4Si as an internal standard. ESR spectra were recorded on a Varian E-3 spectrometer. Elemental analyses were determined either at the University of Oregon by Dr. R. Wielesek or at Galbraith Laboratories, Tn. All reactions were routinely run under a N_2 atmosphere. Solvents were routinely distilled.

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(s, 6), 1.58–1.94 (m, 8), 2.40 (br t, 4), 3.52 (m, 3), 7.49 (m, 5) (see text for discussion of high-field ^1H and ^{19}F NMR spectra); MS, m/e 383.156 (0.5) (calcd for M - CH_2CH_2CN, 383.158), 296 (0.4), 279 (0.6), 259 (0.5), 241 (0.4), 235 (1.7), 232 (1.1), 220 (6.0), 191 (2.9), 190 (27), 189 (100).

***trans*-2,5-Dimethyl-2,5-bis(2-carboxyethyl)pyrrolidinyl-1-oxy (14).** A solution of 224 mg (1.0 mmol) of **12** and 11 mL of 2.5 N NaOH was heated at reflux for 44 h. The cooled solution (0 °C) was acidified with chilled 3 N HCl and then extracted four times with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. The crystalline residue was recrystallized from EtOAc–hexane to give 188 mg (73%) of nitroxide diacid **14** as yellow crystals: mp 127–131 °C; ESR ($CHCl_3$) 3 lines, a_N = 14.3 G; MS, m/e 258.135 (calcd for $C_{12}H_{20}NO_5$, 258.134). Anal. Calcd for $C_{12}H_{20}NO_5$: C, 55.84; H, 7.81; N, 5.43. Found: C, 55.64; H, 7.82; N, 5.20.

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Registry No. **4**, 28765-36-8; **6**, 86335-47-9; *cis*-**7**, 86350-28-9; *trans*-**7**, 86335-48-0; *cis*-**8**, 86335-49-1; *trans*-**8**, 86363-08-8; *cis*-**9**, 86335-50-4; *trans*-**9**, 86335-51-5; *cis*-**10**, 86335-52-6; *trans*-**10**, 86335-53-7; *cis*-**11**, 86335-54-8; *trans*-**11**, 86335-55-9; **12**, 86335-56-0; **13** (isomer 1), 86335-57-1; **13** (isomer 2), 86363-09-9; **14**, 86335-58-2; 3-bromopropan-1-yl tetrahydropyranyl ether, 33821-94-2.

Azethoxyl Nitroxide Spin-Labeled Crown Ethers and Cryptands with the N–O• Group Positioned near the Cavity

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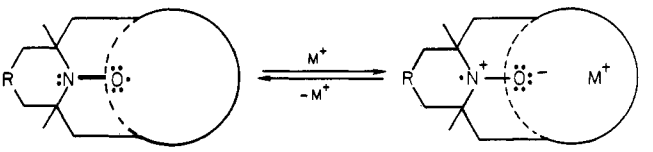
We report the synthesis and complexation properties of several nitroxide spin-labeled crown ethers and cryptands in which the N–O· group, in certain conformations, is thrust toward the cavity of the molecule. While initial approaches involving the cyclization of various unsymmetrically substituted tetraethylene glycols (e.g, **10**, **11**, and **15**) were not promising, success was achieved by the sequential addition of substituted phenyl groups to nitrone **28**, leading to nitroxide crown ethers **37** and **38**. Nitroxide cryptand **60** was prepared by diacylation of diaza-18-crown-6 **51** with azethoxyl nitroxide diacid chloride **57** followed by reduction. The ESR spectrum a_N values of these nitroxides were not sensitive to the presence of K^+, Na^+, or Li^+ in MeOH. While diaza-18-crown-6, decamethylene cryptand **55**, and nitroxide cryptand **60** formed 1:1 complexes with $NaBPh_4$ in $CDCl_3$, nitroxide crown ethers **37** and **38** and amide **54** did not. Adaptation of the quantitative methodology of Cram et al. showed that **55** and **60** bind Na^+ somewhat better than dicyclohexyl-18-crown-6. K^+ is bound better than Na^+ by **55** and **60**, though not as strongly as dicyclohexyl-18-crown-6. The binding of K^+ and Na^+ by **37** and **38** is minimal.

Crown ethers[1-4] and cryptands[5-7] are being investigated extensively, owing to their ability to complex selectively ions and neutral molecules. With an eye toward analytical applications, chromophoric analogues that respond spectrophotometrically to the presence of a guest within the cavity[7-12] have been developed. We envisaged a series of nitroxide spin-labeled crown ethers and cryptands in which the nitroxide oxygen atom might participate directly in the complexation interactions with the host metal ion. The presence of a metal ion within the cavity may be expected to increase the electron spin resonance (ESR) hyperfine splitting parameter, a_N, substantially over that of the uncomplexed nitroxide due to changes in the distribution of unpaired spin density upon complexation, shown schematiclly in **1** ⇄ **2**.[13] ESR spectroscopy on such nitroxides might therefore constitute a simple, ion-selective, highly sensitive method for monitoring the concentration of alkaline and alkaline earth metal ions in aqueous solution without the usual requirement of optical transparency of the sample.



1 (small a_N) **2** (large a_N)

The synthesis of nitroxide spin-labeled crown ethers **3–5**,[14] **6**,[15] **7**,[16] and **8**[16] have been described by others. Crowns **3–5** turn out to be poor complexing agents. An X-ray structure of **3** showed that the hydrogen atoms of one methylene group of the propylene bridging unit protruded into the cavity.[14] Ester **6** showed little change in the ESR spectrum upon treatment with NaSCN in EtOH. However, addition of 0.5 equiv of KSCN led to a sandwich complex involving two crown molecules and one K^+ ion, as shown by spin–spin interactions in the ESR spectrum. Continued addition of KSCN led to a return of the usual three-line spectra.[15] Spin–spin interactions increased as a function of [KSCN] for syn isomer **7** but not for anti isomer **8**.[16] In none of these derivatives is the N–O group particularly situated such that direct interaction with the complexed metal ion is fostered by structural constraints. Herein, we report the synthesis and complexation prop-

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