(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.

Acknowledgment. This research was supported by Public Health Service Research Grants GM24951 and GM27137 from the National Institute of General Medical Sciences.

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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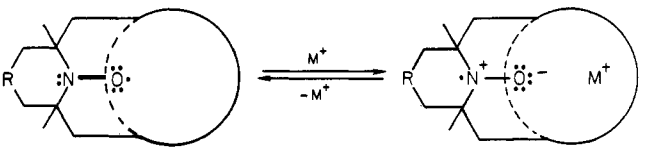
We report the synthesis and complexation properties of several nitroxide spin-labeled crown ethers and cryptands in which the N–O· group, in certain conformations, is thrust toward the cavity of the molecule. While initial approaches involving the cyclization of various unsymmetrically substituted tetraethylene 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-

(1) Weber, E.; Vögtle, F. *Top. Curr. Chem.* **1981**, *98*, 1.
(2) Cram, D. J.; Trueblood, K. N. *Top. Curr. Chem.* **1981**, *98*, 43.
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(5) Lehn, J.-M. *Acc. Chem. Res.* **1978**, *11*, 49.
(6) Lehn, J.-M. *Pure Appl. Chem.* **1978**, *50*, 871.
(7) Blasius, E.; Janzen, K. -P. *Top. Curr. Chem.* **1981**, *98*, 163.
(8) Pacey, G. E.; Wu, Y. P.; Bubnis, B. P. *Synth. Commun.* **1981**, *11*, 323.
(9) Dix, J. P.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 857.
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(11) Nakamura, H.; Takagi, M.; Ueno, K. *Talanta* **1979**, *26*, 921.
(12) Shinkai, S.; Nakaji, T.; Ogawa, T.; Shigematsu, K.; Manabe, O. *J. Am. Chem. Soc.* **1981**, *103*, 111.
(13) Changes in a_N induced by the proximity of a positive charge as an α-amino nitroxide becomes protonated have been used to monitor the pH of aqueous solutions by ESR spectroscopy: Keana, J. F. W.; Acarregui, M. J.; Boyle, S. L. M. *J. Am. Chem. Soc.* **1982**, *104*, 827. Khramtsov, V. V.; Weiner, L. M.; Grigoriev, I. A.; Volodarsky, L. B. *Chem. Phys. Lett.* **1982**, *91*, 69.
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(15) Ishizu, K.; Kohama, H.; Mukai, K. *Chem. Lett.* **1978**, 227.
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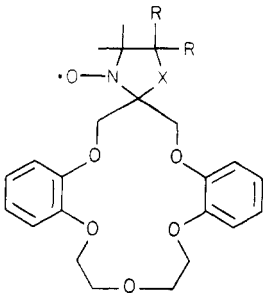
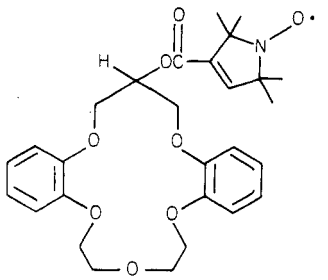
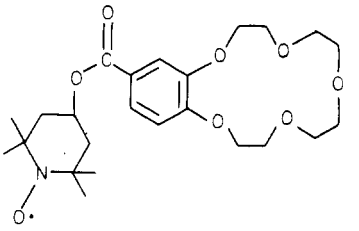
0022-3263/83/1948-2647$01.50/0



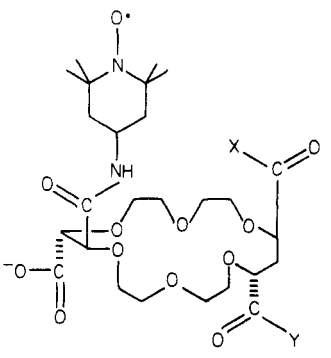
3, R = H; X = O
4, R = Me; X = NH

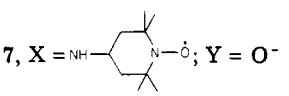


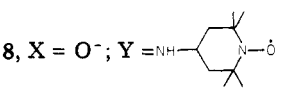
5



6



7, X =  ; Y = O^-

8, X = O^-; Y = 

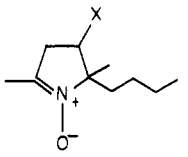
erties of several new nitroxide spin-labeled crown ethers and cryptands in which the N–O group, in certain conformations, is thrust toward the cavity of the molecule.

Results and Discussion

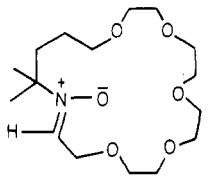
Synthesis of Nitroxide Crown Ethers 48 and 49. Our plan, guided by periodic examination of CPK molecular models,[17] originally called for the construction of a cis or trans azethoxyl nitroxide[18] patterned after schematic structure **1** (R = a single bond). Alcohol **10** and acid **11** were prepared from tetraethylene glycol (**9**) (see Experimental Section), as potential precursors for **13** via a Michael reaction on the corresponding unsaturated ketones **12**, followed by a reductive cyclization. When neither **10** (via oxidation) nor **11** (via reaction with propenyllithium)[19–21] gave useful amounts of **12**, an attempt was made to construct a macrocyclic polyether ring containing nitroxide, cf. **1** (R = H, H), by cyclization of a ω-hydroxyamino group with a terminally generated aldehyde or ketone to give a macrocyclic nitrone for subsequent reac-

$RO(CH_2CH_2O)_4R'$

9, R = R′ = H
10, R = $C_6H_5CH_2$; R′ = $CH_2CH(OH)CH{=}CH_2$
11, R = $C_6H_5CH_2$; R′ = CH_2CO_2H
12, R = $C_6H_5CH_2$; R′ = $CH_2COCH{=}CHX$

13, R = $C_6H_5CH_2$; R′ = 

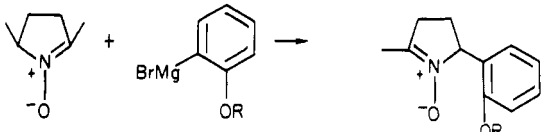
14, R = $(CH_3)_2C(NO_2)(CH_2)_3$; R′ = $CH_2CH(OEt)_2$
15, R = $(CH_3)_2C(NHOH)(CH_2)_3$; R′ = $CH_2CH(OEt)_2$



16

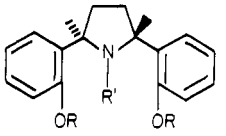
tion with methyllithium. Toward this end, nitro acetal **14** was prepared from **9** and reduced selectively with Zn/NH_4Cl, giving hydroxy amine **15**. Acid-catalyzed hydrolysis afforded what appeared to be impure nitrone **16** by NMR (triplet at δ 7.00) and IR (peak at 1600 cm^{-1}); however, only traces of nitroxide were obtained when crude **16** was treated twice in succession with MeLi followed by an oxidative workup with $Cu(OAc)_2$ and air.[18]

A different, eventually successful, approach to **1** (R = a single bond) involved a sequential addition of appropriate functionality to a preformed pyrroline nitrone. The first objective was the nitroxide bisphenol **24**. To this end,



17 **18**, R = Me; **19**, R = THP

20, R = Me
21, R = THP
22, R = H
23, R = $(CH_2CH_2O)_4$THP



24, R = Me; R′ = O·
25, R = THP; R′ = O·
26, R = H; R′ = O·
27, R = R′ = H

nitrone **17**[22] was allowed to react with Grignard reagent **18** and then $Cu(OAc)_2$–MeOH–O_2,[18] producing nitrone **20**. Repetition of the two-step sequence on **20** gave crystalline bis(methoxyphenyl)pyrrolidinyloxy nitroxide **24** in low yield. The trans configuration is assigned to **24** on the basis of the tendency of the second Grignard addition to take place preferentially from the less hindered site of the pyrroline ring.[18] The assignment was corrborated by the synthesis of the cis stereoisomer **33** by another route (see below). Cleavage of the methoxy groups of **24** to give **26** proved troublesome. While experiments with trimethylsilyl iodide[23] and boron tribromide,[24] for example, led to

(17) Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1978**, *11*, 8.
(18) Lee, T. D.; Keana, J. F. W. *J. Org. Chem.* **1978**, *43*, 4226.
(19) For a review see Jorgenson, M. J. *Org. React. (N.Y.)* **1970**, *18*, 1.
(20) Floyd, J. C. *Tetrahedron Lett.* **1974**, 2877.
(21) Seyferth, D.; Vaughan, L. G. *J. Am. Chem. Soc*, **1964**, *86*, 883. Because vinyllithium was not available commercially, we chose propenyllithium as a convenient and acceptable analogue.
(22) Keana, J. F. W. In "Spin Labeling: Theory and Applications"; Berliner, L. J., Ed.; Academic Press: New York, 1979, p 157.
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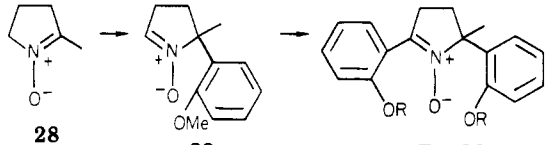
(24) McOmie, J. F. W.; Watts, M. L.; West, D. E. *Tetrahedron* **1968**, *24*, 2289.

many nonparamagnetic products, sodium thioethoxide in dimethylformamide (DMF)[25] led to the amine **27** in 53% yield as the only well-defined product.[26]

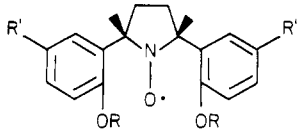
A more easily cleavable protecting group for the phenolic oxygen atom was therefore sought. Reaction of nitrone **17** with Grignard reagent **19** led, after oxidation, to crystalline nitrone phenol **22**. Attempted re-formation of the tetrahydropyranyl (THP) ether **21** from **22** gave material tentatively identified as the hydrate of **21** (addition of water across the C=N group during purification), which failed to give nitroxide **25** or **26** upon application of the Grignard–oxidation sequence of reactions. Though **22** could be converted into polyether **23** by alkylation with the tosylate THP ether derived from tetraethylene glycol, the reaction of **23** with Grignard reagent **19** was not successful.

The synthesis of azethoxyl nitroxide crown ethers **37** and **38** was achieved by using a variation of the above methodology. Reaction of nitrone **28**[27] with Grignard reagent

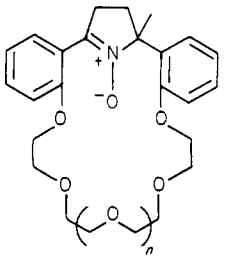


28 **29**

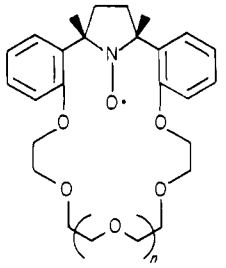
, R = Me
, R = H



32, R = R′ = H
33, R = Me; R′ = H
34, R = H; R′ = Me



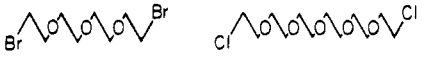
35, n = 1
36, n = 3



37, n = 1
38, n = 3

18 followed by $Cu(OAc)_2$–MeOH–air oxidation gave nitrone **29**. Repetition of the Grignard–oxidation sequence on **29** gave nitrone **30** in 40% overall yield from **28**. Reaction of **30** with MeLi followed by oxidation gave crystalline nitroxide **33**, isomeric with nitroxide **24** described above. The cis stereochemistry is assigned to **33** since the MeLi is expected to add to **30** from the side opposite the bulky methoxyphenyl group (see above).[18]

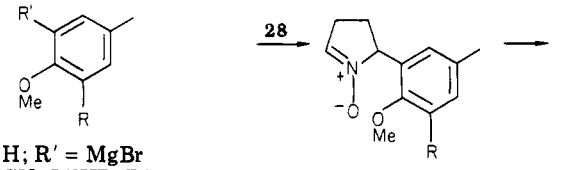
In view of the difficulty in cleaving selectively the methoxy groups of the trans nitroxide **24** (see above), we elected to circumvent nitroxide **32** and assemble the crown ether moiety at the nitrone stage. We were pleased to observe that sodium thioethoxide in DMF, or better, boron tribromide in CH_2Cl_2[24] smoothly afforded the bisphenol **31**. After several abortive attempts to bisalkylate **31** with dibromide **39**[28] and KOH in buty alcohol,[29] success was achieved with **39** and NaH in DMF. Nitrone **35** was thus



39 **40**

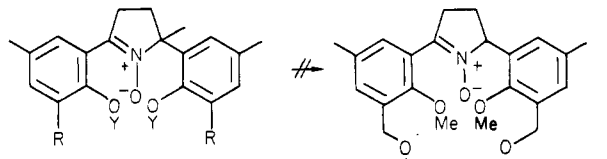
obtained in 38% yield. Reaction of **35** with MeLi followed by oxidation gave nitroxide crown ether **37**, mp 197–199 °C, in 34% yield. The cis configuration is assigned once again on the basis of the expected approach of MeLi to nitrone **35** from the side opposite the bulky phenyl substituent. By an analogous series of reactions using dichloride **40**,[30] nitrone **36** and nitroxide crown ether **38**, mp 94–95 °C, were obtained. Owing to the two additional ethyleneoxy units in **38**, the cavity in this molecule is somewhat larger than that of **37**.

We also briefly investigated approaches toward the nitroxide derived from **50**. This series was modeled after



41, R = H; R′ = MgBr
42, R = CH_2OTHP; R′ = MgBr
43, R = CH_2OTHP; R′ = Br

44



45, R = H; Y = Me
46, R = Y = H
47, R = CH_2OH; Y = H
48, R = CH_2OTHP; Y = Me
49, R = CH_2OH; Y = Me

50

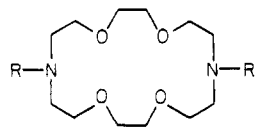
the *m*-teranisyl-containing crown ethers recently reported to bind K^+ better than dicyclohexyl-18-crown-6.[31] Reaction of Grignard reagent **41** with nitrone **28** gave nitrone **44**, which upon reaction with **41** gave the bis(aryl) nitrone **45**. This substance underwent smooth demethylation to bisphenol **46** with boron tribromide in CH_2Cl_2. Interestingly, reaction of *unprotected* **46** with excess MeLi followed by oxidation gave cis nitroxide **34**. Because attempts to prepare bis(hydroxymethyl) derivative **47** from **46** were not successful,[32] the hydroxymethyl groups were introduced at an earlier stage. Thus, reaction of Grignard reagent **42** derived from **43** with **28** followed by oxidation gave the corresponding nitrone **44**, reaction of which with **42** followed by oxidation gave nitrone**48**. Mild hydrolysis of the THP ethers gave crystalline bis(hydroxymethyl) nitrone **49**. Numerous attempts to convert this attractive intermediate into **50** led us to set aside this approach in favor of the nitroxide cryptate chemistry described next.

Synthesis of Nitroxide Cryptand 60. Diaza crown ethers are known to be good complexing agents for metal ions.[9,33] Cryptands are usually prepared from diaza crown ethers by a bisacylation reaction followed by reduction of

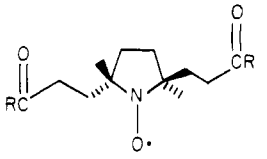
(25) Feutrill, G. I.; Mirrington, R. N. *Aust. J. Chem.* **1972**, *25*, 1719.
(26) This reduction is similar to the reduction of nitroxides to amines reported by Kornblum and Pinnick: Kornblum, N.; Pinnick, H. W. *J. Org. Chem.* **1972**, *37*, 2050.
(27) Brandman, H. A.; Conley, R. T. *J. Org. Chem.* **1973**, *38*, 2236.
(28) Dann, J. R.; Chiesa, P. P.; Gates, J. W. *J. Org. Chem.* **1961**, *26*, 1991.
(29) Pedersen, C. J. *J. Am. Chem. Soc.* **1970**, *92*, 391.
(30) Perry, S. Z.; Hibbert, H. *Can. J. Res., Sect. B* **1936**, *14B*, 77.
(31) Koenig, K. E.; Lein, G. M.; Stuckler, P.; Kaneda, T.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553.
(32) Manasse, D. *Chem. Ber.* **1894**, *27*, 2409.
(33) Frensdorff, H. K. *J. Am. Chem. Soc.* **1971**, *93*, 600. Lehn, J. M.; Sauvage, J. P. *Ibid.* **1975**, *97*, 6700.

the corresponding diamide.[5,6,34] It occurred to us that if the diacid partner were an azethoxyl nitroxide dicarboxylic acid, then the resulting cryptand might be such that the nitroxide oxygen atom would coordinate directly with any complexed metal ions.

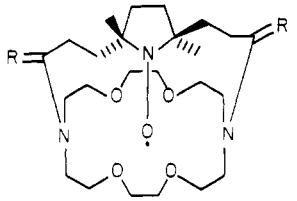
In order to find conditions that efficiently effected the reduction step while being compatible with the presence of a nitroxide free radical,[35] two model studies were first undertaken. Diaza crown ether **51** was converted into the dibenzamide derivative **52** and then reduced to diamine **53**,[36] mp 82.5–83.5 °C, with excess BH_3–THF in THF at reflux. Workup involved destruction of the borane–amine



51, R = H
52, R = C_6H_5CO
53, R = $C_6H_5CH_2$
54, R,R = $O{=}C(CH_2)_8C{=}O$
55, R,R = $(CH_2)_{10}$



56, R = OH
57, R = Cl
58, R = O(C=O)OEt



59, R = O
60, R = H, H

complex by addition of excess tetramethylethylenediamine (TMEDA), a method recently reported by Brown et al.[37] Use of Red-Al (Aldrich) caused cleavage of the C–N bond and formation of starting **51**.

In the second model system sebacoyl chloride was allowed to react with **51** in the presence of Et_3N in dilute benzene solution, affording diamide **54** in 43% yield. Reduction of **54** to diamine **55** (colorless oil) could be effected either with BH_3–THF (96% yield), $LiAlH_4$–THF (93% yield), or Red-Al (90% yield).

trans-Azethoxyl nitroxide diacid **56**, described in the accompanying paper,[38] was converted into the rather unstable diacid chloride **57** via the reaction of the dipotassium salt with oxalyl chloride in ether in the presence of DMF.[39] Reaction of **57** and **51** took place analogously to that of sebacoyl chloride described above, affording nitroxide diamide **59**, mp 205–208 °C, in 25% yield based on starting **56**. Mixed anhydride **58** was generated from **56** and allowed to react with **51**, producing **59** in 13% yield. While reduction of **59** to azethoxyl nitroxide cryptand **60** could also be effected with Red-Al, the reaction proceeded best with BH_3–THF, affording **60** as a yellow oil in near-quantitative yield.

ESR Spectra of Nitroxide Crown Ethers 37 and 38 and Nitroxide Cryptand 60, Their Interaction with $NaBPh_4$, and Their *R* Values and Association Constants (K_a) with Potassium and Sodium Picrates. ESR spectra of nitroxides **37**, **38**, and **60** all show the usual three-line nitroxide spectra (~1 spin per molecule), with a_N = 14.7–15.0 G in $CHCl_3$ and a_N = 14.8–15.4 G in MeOH. The a_N values increased only slightly to 15.4–16.0 G when spectra were run in MeOH which was saturated with KI, NaI, or LiCl. These changes together with some changes in line width are typical effects of increased polarity of the solvent due to the added salts.[40] The striking conclusion is that despite the juxtaposition of the nitroxide group with respect to the ion binding cavity in **37**, **38**, and **60**, if complexation is taking place, it is not reflected by a significant increase in a_N.

In order to determine whether or not complexation in fact was taking place, solutions of nitroxides **37**, **38**, and **60** as well as the hosts **51**, **54**, and **55** in $CDCl_3$ (~0.03 M) were separately treated with excess $NaBPh_4$. $NaBPh_4$ was chosen because the BPh_4^- anion is quite hydrophobic and would therefore facilitate formation of the desired complexes in $CDCl_3$. The salt itself is essentially insoluble in $CDCl_3$, however. The suspension of $NaBPh_4$ and host in $CDCl_3$ were stirred for several minutes and then filtered. The filtrate was examined by IR (~1600 cm^{-1}, an absorption characteristic of $NaBPh_4$) for a qualitative indication of complexation. Integrated NMR spectra were also determined directly on those solutions containing diamagnetic hosts. Lastly, in each case the filtrates were concentrated to dryness, and the presence or absence of complexed $NaBPh_4$ was determined gravimetrically. By these criteria the cryptand nitroxide **60**, cryptand host **55**,[41] and diaza-18-crown-6 **51**[42] all gave a 1:1 complex with $NaBPh_4$. An aliquot of the **60**-$NaBPh_4$ solution was diluted with $CHCl_3$ and its ESR spectrum was measured. The a_N value was essentially the same as that of pure **60** in $CHCl_3$. No evidence of complexation was observed with **37**, **38**, and **54**.

The interaction of $CDCl_3$ solutions of the several hosts herein described with aqueous solutions of either potassium or sodium picrate salts was determined by using the quantitative methodology described by Cram et al.[31,43] Owing to the relatively small amounts available of some of our substrates, the methodology was adapted to accommodate 50-μL volumes of the two phases. The results collected in Table I essentially confirm the IR, NMR, and gravimetric measurements of complexation described above. It is seen that both nitroxide cryptand **60** and host **55** bind Na^+ somewhat better than dicyclohexyl-18-crown-6 (R_{CDCl3} = 0.39 and 0.38, respectively, vs 0.30). K^+ ion is bound significantly better than Na^+ by **60** and **55**, though not as strongly as by dicyclohexyl-18-crown-6. By contrast, the binding of either K^+ or Na^+ by nitroxide crown ethers **37** and **38** is minimal. We are currently working toward the synthesis of alternative nitroxide crown ethers which may reflect the presence of a metal ion in the cavity through significant changes in a_N.

Experimental Section[44]

(16-Hydroxy-2,5,8,11,14-pentaoxaoctadec-17-enyl)benzene (10). A mixture of tetraethylene glycol (**9**) (60 mL, 0.35 mol)

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(35) Keana, J. F. W. *Chem. Rev.* **1978**, *78*, 37.
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(37) Brown, H. C.; Choi, Y. M.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 3153.
(38) Keana, J. F. W.; Seyedrezai, S. E. *J. Org. Chem.*, preceding paper in this tissue.
(39) This is a modification of the method of: Beeby, P. J. *Tetrahedron Lett.* **1977**, 3379.
(40) Knauer, B. R.; Napier, J. J. *J. Am. Chem. Soc.* **1976**, *98*, 4395. Griffith, O. H.; Dehlinger, P. J.; Van, S. P. *J. Membr. Biol.* **1974**, *15*, 159.
(41) The 1:1 complex between **55** and $NaBPh_4$ was isolated as an oil. NMR ($CDCl_3$) δ 1.43 (br s, 16), 2.31–2.70 (m, 12), 3.46 (m, 16), 6.90–7.59 (m, 20).
(42) The 1:1 complex between **51** and $NaBPh_4$ was isolated as white crystals and recrystallized: mp 155.5–157.5 °C (CH_2Cl_2–hexane); NMR ($CDCl_3$) δ 2.41–2.62 (m, 8), 3.23–3.41 (m, 8), 3.49 (s, 8), 6.92–7.54 (m, 20). Reported[34] NMR ($CDCl_3$) for **51**: δ 2.78 (t, 8), 3.58 (t, 8), 3.58 (s, 8).
(43) Moore, S. S.; Tarnowski, T. L.; Newcomb, M.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6398.

and Na metal (4.5 g, 0.20 mol) was stirred at 100 °C until all the Na had dissolved. The solution was cooled to 60 °C and treated with bromoacetaldehyde diethyl acetal (37 mL, 0.25 mol). After a 16-h stir at 60 °C the mixture was cooled, diluted with $CHCl_3$ (100 mL), washed with water, dried (Na_2SO_4), and fractionally distilled to yield the monoalkylated product **61** (not shown) (24 g, 39%) as a colorless liquid, bp 165–170 °C (0.25 mm). A 2.26-g (7.29 mmol) sample was added to a stirred mixture of NaH (284 mg, 11.8 mmol) in dry DMF (10 mL), and after H_2 evolution ceased, benzyl chloride (1.1 mL, 9.6 mmol) was added. The mixture was stirred at 25 °C for 12 h. The usual workup followed by chromatography over silica gel and elution with ether gave the benzyl derivative (1.88 g, 65%) as a colorless oil: NMR δ 1.22 (t, 6), 3.5–3.9 (m, with a spike at 3.72, 18), 4.6–4.8 (m, 3), 7.38 (br s, 5). A 1.00-g (2.50 mmol) sample was stirred in CH_2Cl_2 (10 mL) containing silica gel (3 g) and 12% HCl (0.3 mL) for 24 h, filtered, and concentrated, affording the crude aldehyde (786 mg, 97%) as a colorless oil: NMR δ 3.70 (s, 16), 4.16 (s, 2), 4.60 (s, 2), 7.36 (br s, 5), 9.73 (s, 1); IR ($CHCl_3$) 1715 cm^{-1}. A stirred solution of aldehyde (1.85 g, 5.67 mmol) in THF (35 mL) at 25 °C was treated with vinylmagnesium bromide (5 mL, 1.3 M in THF, 6.5 mmol). After 1 h the usual workup followed by chromatography over silica gel and elution with ether–MeOH (9:1) gave **10** (966 mg, 50%) as a colorless oil: NMR δ 3.3–3.6 (m, 2), 3.61 (s, 16), 4.50–4.55 (m, 3), 5.12 (m, 1), 5.32 (m, 1), 5.80 (m, 1), 7.28 (br s, 5). Anal. Calcd for $C_{19}H_{30}O_6$: C, 64.39; H, 8.53. Found: C, 64.65; H, 8.18.

16-Phenyl-3,6,9,15-tetraoxahexadecanoic Acid (11). From Na metal (2.93 g, 0.127 mol) **9** (45 mL, 0.26 mol), and benzyl chloride (12 mL, 0.104 mol) there was obtained 30.8 g (85%) of the monobenzyl ether: NMR δ 2.7–2.9 (br s, 1), 3.60 (s, 16), 4.57 (s, 2), 7.34 (br s, 5). A 9.53-g (33.4 mmol) sample was added to a stirred suspension of NaH (1.05 g, 43.8 mmol) in dry DMF (50 mL) at 25 °C. After H_2 evolution had ceased, ethyl bromoacetate (5.0 mL, 45 mmol) was added, and the mixture was stirred for 20 h at 25 °C. The usual workup followed by silica gel chromatography and elution with ether–pentane (1:1) gave **11** ethyl ester (4.509 g, 36%): NMR δ 1.27 (t, 3), 3.73 (s, 16), 4.2–4.4 (m, 4), 4.61 (s, 2), 7.38 (br s, 5); IR ($CHCl_3$) 1760 cm^{-1}. This ester (3.19 g, 8.62 mmol) was heated at reflux with 10% aqueous NaOH (50 mL) for 2 h. The mixture was cooled and extracted with ether, giving 0.603 g of recovered ester. The aqueous layer was acidified and worked up with $CHCl_3$, affording 1.68 g (79%) of acid **11** as a colorless oil: NMR δ 3.72 (s, 16), 4.18 (s, 2), 4.72 (s, 2), 7.38 (s, 5). Anal. Calcd for $C_{17}H_{26}O_7$: C, 59.64; H, 7.65. Found: C, 59.36; H, 7.75.

4-Ethoxy-22-methyl-22-nitro-3,6,9,12,15,18-hexaoxatricosane (14). A mixture of dimethoxyethane (35 mL), NaH (306 mg, 12.8 mmol), and acetal **61** (3.94 g, 12.7 mmol) (see **10**) was stirred at 25 °C until H_2 evolution ceased. Then the mesylate (3.05 g, 13.5 mmol, mp 68–69 °C) prepared by methanesulfonation (95%) of 2-methyl-2-nitropentan-1-ol was added. After a 36-h stir at 25 °C the usual workup gave 5.36 g (96%) of **14**. An analytical sample was obtained by chromatography over silica gel and elution with $CHCl_3$–MeOH (99:1): colorless oil; NMR δ 1.21 (t, 6), 1.4–1.7 (m, with a spike at 1.58, 8), 1.85–2.1 (m, 2), 3.3–3.8 (m, with a spike at 3.77, 20), 4.72 (t, 1). Anal. Calcd for $C_{20}H_{41}NO_9$: C, 54.64; H, 9.42; N, 3.19. Found: C, 54.49; H, 9.40; N, 3.19.

4-Ethoxy-22-(hydroxyamino)-22-methyl-3,6,9,12,15,18-hexaoxatricosane (15). A stirred mixture of **14** (1.30 g, 2.96 mmol), water (2.5 mL), and NH_4Cl (171 mg, 3.20 mmol) was cooled to 0 °C, and Zn (787 mg, 12 mmol) was added portionwise over 1 h. After a 3-h stir, the mixture was filtered and the precipitate was washed with MeOH. The combined filtrate and wash were concentrated to 3 mL and extracted with $CHCl_3$. Chromatography of the extract over silica gel and elution with $CHCl_3$–MeOH (95:5) gave 819 mg (65%) of **15** as a colorless oil: NMR δ 1.06 (s, 6), 1.20 (t, 6), 1.35–1.8 (m, 4), 3.4–3.8 (m, with a spike at 3.74, 20), 4.72 (t, 1). Anal. Calcd for $C_{20}H_{43}NO_8$: C, 56.45; H, 10.18; N, 3.29. Found: C, 56.88; H, 9.52; N, 2.93.

2,5-Dimethyl-2-(2-methoxyphenyl)-3,4-dihydro-2*H*-pyrrole 1-Oxide (20). Grignard reagent **18** (prepared from 2.0 g of Mg turnings, 6.2 mL of *o*-bromoanisole, and 140 mL of THF) was added to a stirred solution of nitrone **17**[22] in THF (100 mL). After 2 h at 25 °C the reaction was quenched by the addition of NH_4Cl (2.8 g) in water (40 mL). The usual workup gave an oil, which was dissolved in MeOH (250 mL) containing concentrated NH_4OH (6 mL) and $Cu(OAc)_2 \cdot H_2O$ (2 g) and stirred under O_2 until the pale yellow solution became dark blue. The solution was concentrated and the residue was treated with $CHCl_3$ and saturated aqueous $NaHCO_3$. The usual workup gave 9.8 g of crude **20** as a brownish oil suitable for the next reaction: IR (film) 1594 cm^{-1}; NMR δ 1.87 (s, 3), 2.15 (s, 3), 2.60 (br m, 4), 3.82 (s, 3), 6.8–7.4 (m, 4).

***trans*-2,5-Dimethyl-2,5-bis(2-methoxyphenyl)tetrahydropyrrolyl-1-oxy (24).** To nitrone **20** (9.8 g) in THF (100 mL) was added Grignard reagent **18** (prepared exactly as described above). After a 1.5-h stir at 25 °C the reaction was quenched with NH_4Cl (2.8 g) in water (80 mL). The usual workup gave an oil, which was dissolved in MeOH (250 mL) containing concentrated NH_4OH (5 mL) and $Cu(OAc)_2 \cdot H_2O$ (1.2 g) and stirred under O_2 for 10 min. The usual workup gave a brown oil (12 g), which was chromatographed over silica gel. Elution with CCl_4–EtOAc (20:1) gave a yellow fraction, which was crystallized from $CHCl_3$–hexane, affording **24** (530 mg, 4% overall from nitrone **17**) as yellow crystals: mp 169–171 °C; ESR (MeOH) 3 lines, a_N = 14.1 G; MS, *m/e* 326.175 (calcd for $C_{20}H_{24}NO_3$, 326.176). Anal. Calcd for $C_{20}H_{24}NO_3$: C, 73.58; H, 7.41; N, 4.29. Found: C, 73.35; H, 7.59; N, 4.20.

***trans*-2,5-Dimethyl-2,5-bis(2-hydroxyphenyl)tetrahydropyrrole (27).** Ethanethiol (62 mg, 1.0 mmol) in dry DMF (1 mL) was added to a stirred suspension of NaH (24 mg, 1.0 mmol) in DMF (1 mL). After 10 min nitroxide **24** (33 mg) in DMF (1 mL) was added and the mixture was heated at 145 °C for 3 h and then cooled to 0 °C. Acetic acid (0.2 mL) was added and the mixture was concentrated under vacuum. The residue was triturated with ether and the extract was purified by preparative TLC over silica gel ($CHCl_3$–MeOH, 20:1) to give 20 mg of crude **27**. Crystallization from $CHCl_3$–MeOH gave **27** (15 mg) as colorless crystals: mp 135–136 °C; NMR δ 1.52 (s, 3), 1.98 (s, 3), 2.15–2.60 (m, 4), 6.75–7.20 (m, 6); 8.1 (br s, 2); MS, *m/e* 283.157 (25) (calcd for $C_{18}H_{21}NO_2$, 283.157), 268 (100), 252 (5), 190 (3), 60 (83).

2,5-Dimethyl-2-(2-hydroxyphenyl)-3,4-dihydro-2*H*-pyrrole 1-Oxide (22). Grignard reagent **19** (prepared from 0.5 g of Mg turnings, 3.08 g of *o*-bromophenyl tetrahydropyranyl ether, and 20 mL of THF) was added to a stirred solution of nitrone **17** (1.13 g) in 20 mL of THF. After 2 h the reaction was quenched with saturated aqueous NH_4Cl, worked up with ether, and oxidized in MeOH as described for **20**, giving 1.92 g of an oil from which **22** (300 mg) crystallized. The mother liquors were chromatographed over silica gel. Elution with $CHCl_3$–MeOH (20:1) gave another 100 mg (total yield, 20%) of crystalline **22**: mp 178–179 °C; MS, *m/e* 205.110 (100) (calcd for $C_{12}H_{15}NO_2$, 205.110), 188 (56), 163 (27), 131 (31), 91 (24). Anal. Calcd for $C_{12}H_{15}NO_2 \cdot {}^1/_3H_2O$: C, 68.20; H, 7.48; N, 6.63. Found: C, 68.25; H, 7.47; N, 6.55.

2,5-Dimethyl-2-{2-[(12-tetrahydropyranyloxy)-1,4,7,10-tetraoxadodecanyl]phenyl}-3,4-dihydro-2*H*-pyrrole 1-Oxide (23). To a stirred solution of **22** (205 mg) and *O*-tosyl-*O*-tetrahydropyranyltetraethylene glycol (432 mg, prepared by sequential conversion of **9** into its monobenzoate, bp 83–90 °C (0.01 mm), THP ether benzoate, mono THP ether, and finally tosylate) in DMF (15 mL) was added NaH (50 mg), and the mixture was heated for 2 h at 60 °C. The mixture was concentrated and extracted with $CHCl_3$. This gave a brownish oil which was chromatographed over silica gel ($CHCl_3$–MeOH, 10:1), giving **23** (340 mg, 73%) as a yellowish oil: NMR δ 1.4–1.95 (m, 6), 1.90 (s, 3), 2.15 (s, 3), 2.5–2.8 (m, 4), 3.4–3.9 (m, 16), 4.16 (t, 2), 4.62 (m, 1), 6.8–7.0 (m, 2), 7.08–7.4 (m, 2); MS, *m/e* 465.275 (1.2) (calcd for $C_{25}H_{39}NO_7$, 465.272), 464 (1.3), 381 (24), 232 (55), 216 (76), 205 (100).

2-Methyl-2-(2-methoxyphenyl)-3,4-dihydro-2*H*-pyrrole 1-Oxide (29). A stirred solution of nitrone **28**[27] (650 mg, 6.5 mmol) in THF (15 mL) was treated with (*o*-methoxyphenyl)magnesium

(44) 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.

(45) Brown, H. C.; Singaram, B. *Inorg. Chem.* **1980**, *19*, 455.

bromide (prepared from 0.5 g of Mg turnings and 1.56 mL of *o*-bromoanisole in 20 mL of THF). After 2 h the reaction was quenched with aqueous NH_4Cl. The usual workup followed by oxidation (see preparation of **20**) gave crude **29** (1.1 g) as a green-brownish oil suitable for the next reaction: NMR δ 1.88 (s, 3), 2.0–2.85 (m, 4), 3.84 (s, 3), 6.84–7.44 (m, 5).

2-Methyl-2,5-bis(2-methoxyphenyl)-3,4-dihydro-2*H*-pyrrole 1-Oxide (30). A solution of nitrone **29** (1.1 g) in THF (10 mL) was treated as above with (*o*-methoxyphenyl)magnesium bromide and then oxidized (see preparation of **20**) to give **30** (0.81 g, 40% overall yield from **28**) as an oil: NMR δ 1.94 (s, 3), 2.38–4.16 (m, 4), 3.82 (s, 3), 3.86 (s, 3), 6.8–7.45 (m, 7), 8.44–8.6 (m, 1); MS, *m/e* 312 (7), 311.153 (32) (calcd for $C_{19}H_{21}NO_3$, 311.152), 296 (14), 295 (15), 294 (27), 281 (11), 280 (35), 85 (67), 83 (100).

***cis*-2,5-Dimethyl-2,5-bis(2-methoxyphenyl)tetrahydropyrrolyl-1-oxy (33).** To a stirred solution of nitrone **30** (93 mg) in THF (2 mL) at 25 °C was added MeLi (1.5 mL, 1.4 M in ether). After 5 min, the reaction was quenched with saturated aqueous NH_4Cl, worked up, and oxidized (see preparation of **24**). Preparative TLC ($CHCl_3$–hexanes, 3:1) over silica gel followed by recrystallization from ether–hexane gave **33** as yellow crystals: mp 149–150 °C. Anal. Calcd for $C_{20}H_{24}NO_3$: C, 73.58; H, 7.41; N, 4.29. Found: C, 73.37; H, 7.21; N, 4.23.

2-Methyl-2,5-bis(2-hydroxyphenyl)-3,4-dihydro-2*H*-pyrrole 1-Oxide (31). To a stirred solution of **30** (31 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) was added a solution of BBr_3 in CH_2Cl_2 (3 mL, 0.1 M, 0.3 mmol). After a 24-h stir at 25 °C, the mixture was poured over ice containing concentrated NH_4OH (0.5 mL) and worked up with ether. Preparative TLC over silica gel ($CHCl_3$–MeOH, 20:1) followed by crystallization from $CHCl_3$–hexane gave **31** (20 mg, 74%) as a white powder: mp 193–194 °C; NMR δ 1.98 (s, 3), 2.95–3.10 (m, 4), 6.74–7.50 (m, 8), 10.0 (s, 1), 11.5 (s, 1); MS, *m/e* 283.121 (100) (calcd for $C_{17}H_{17}NO_3$, 283.121), 266 (35), 211 (18), 196 (25), 148 (21), 91 (27). Anal. Calcd for $C_{17}H_{17}NO_3 \cdot {}^1/_3H_2O$: C, 70.59; H, 6.11; N, 4.84. Found: C, 70.76; H, 6.03; N, 4.85.

2,3:17,18-Dibenzo-1-methyl-4,7,10,13,16-pentaoxa-22-azabicyclo[17.2.1]docosa-2,17,19(22)-triene 22-Oxide (35). To NaH (10 mg, 0.4 mmol) in DMF (4 mL) was added nitrone **31** (57 mg, 0.20 mmol) in DMF (4 mL). After a 15-min stir, the mixture was diluted with DMF (15 mL), and dibromide **39**[28] (64 mg, 0.20 mmol) in DMF (15 mL) was added dropwise over 2 h while the mixture was refluxed. The resulting mixture was heated at 103 °C for 5 h and then 80 °C for 12 h. The solvent was evaporated in vacuo and the residue was extracted with $CHCl_3$. The extract was washed with water, dried ($MgSO_4$), concentrated, and purified by preparative TLC over silica gel ($CHCl_3$–MeOH, 20:1), affording **35** (34 mg, 38%) as an oil sufficiently pure for the next experiment: NMR δ 1.95 (s, 3), 2.8–3.1 (m, 4), 3.3–3.9 (m, 12), 4.1–4.3 (m, 4), 6.8–7.6 (m, 7), 8.86–9.0 (m, 1).

***cis*-2,3:17,18-Dibenzo-1,19-dimethyl-4,7,10,13,16-pentaoxa-22-azabicyclo[17.2.1]docosa-2,17-dienyl-22-oxy (37).** To a stirred solution of nitrone **35** (34 mg, 0.077 mmol) in THF (4 mL) at 0 °C was added MeLi (0.5 mL, 1.3 M in ether). After a 10-min stir, the reaction was quenched with saturated aqueous NH_4Cl. The usual workup with ether gave a residue which was dissolved in MeOH (15 mL) containing $Cu(OAc)_2 \cdot H_2O$ (5 mg) and one drop of concentrated NH_4OH and stirred for 12 h. The usual workup followed by preparative TLC over silica gel ($CHCl_3$–MeOH, 100:1) and crystallization from $CHCl_3$–hexane gave **37** (12 mg, 34%) as yellow crystals: mp 197–199 °C; ESR (MeOH) 3 lines, a_N = 15.4 G; MS, *m/e* 456.238 (42) (calcd for $C_{26}H_{34}NO_6$, 456.239), 442 (21), 426 (100). Anal. Calcd for $C_{26}H_{34}NO_6 \cdot (1/2)H_2O$: C, 67.05; H, 7.58; N, 3.01. Found: C, 67.20; H, 7.33; N, 2.99.

2,3:23,24-Dibenzo-1-methyl-4,7,10,13,16,19,22-heptaoxa-28-azabicyclo[23.2.1]octacosa-2,23,25(28)-triene 28-Oxide (36). The procedure used to prepare nitrone **35** was adapted. From nitrone **31** (57 mg) and dichloride **40**[30] (64 mg) there was obtained nitrone **36** (51 mg, 48%) as an oil sufficiently pure for the next experiment: NMR δ 1.98 (s, 3), 2.75–3.45 (m, 4), 3.6–4.0 (m, 20), 4.1–4.25 (m, 4), 6.84–7.46 (m, 7), 8.7–8.82 (m, 1).

***cis*-2,3:23,24-Dibenzo-1,25-dimethyl-4,7,10,13,16,19,22-heptaoxa-28-azabicyclo[23.2.1]octacosa-2,23-dienyl-28-oxy (38).** The procedure used to prepare nitroxide **37** was adapted. From nitrone **36** (51 mg) there was obtained, after recyrstallization from $CHCl_3$–hexane, nitroxide **38** (11 mg, 21%) as yellow crystals: mp 94–95 °C; ESR (MeOH) 3 lines, a_N = 15.3 G; MS, *m/e* 544.293 (7) (calcd for $C_{30}H_{42}NO_8$, 544.291), 530 (11), 514 (100), 292 (11), 150 (50). Anal. Calcd for $C_{30}H_{42}NO_8 \cdot {}^2/_3H_2O$: C, 64.70; H, 7.85; N, 2.52. Found: C, 64.55; H, 7.79; N, 2.46.

2-Methyl-2-(2-methoxy-5-methylphenyl)-3,4-dihydro-2*H*-pyrrole 1-Oxide (44, R = H). The procedure used to prepare nitrone **20** was adapted. From nitrone **28**[27] (5.0 g) and 2-bromo-4-methylanisole (12.5 g) there was obtained, after filtration through a neutral alumina column, 8.5 g of a 3:7 mixture of 4-methylanisole and the title nitrone, NMR δ 1.89 (s, 3), 2.30 (s, 3), 2.10–2.85 (m, 4), 3.83 (s, 3), 6.76 (t, 1), 6.82–7.30 (m, 3), suitable for the next experiment.

2-Methyl-2,5-bis(2-methoxy-5-methylphenyl)-3,4-dihydro-2*H*-pyrrole 1-Oxide (45). The procedure used to prepare nitrone **30** was adapted. From the above 4-methylanisole–nitrone mixture (8.5 g) there was obtained nitrone **45** (4.1 g, 24% based on **28**) as an oil: NMR δ 1.94 (s, 3), 2.28 (s, 3), 2.34 (s, 3), 3.82 (s, 3), 3.84 (s, 3), 6.75–7.25 (m, 5), 8.34 (m, 1); MS, *m/e* 339.183 (19) (calcd for $C_{21}H_{25}NO_3$, 339.183), 324 (9), 323 (19), 322 (17), 309 (11), 308 (36), 204 (83), 83 (100).

2-Methyl-2,5-bis(2-hydroxy-5-methylphenyl)-3,4-dihydro-2*H*-pyrrole 1-Oxide (46). The procedure used for the preparation of **31** was adapted. From nitrone **45** (3.5 g) and BBr_3 (7.5 g), there was obtained nitrone **46** (2.8 g, 90%) as a brownish foam. The analytical specimen was obtained by preparative TLC ($CHCl_3$–MeOH, 100:5) followed by crystallization from $CHCl_3$–hexane: mp 148–151 °C; NMR δ 2.00 (s, 3), 2.30 (s, 6), 2.2–2.4 (m, 2), 3.0–3.3 (m, 2), 6.8–7.2 (m, 8); MS, *m/e* 312 (7), 311.152 (16) (calcd for $C_{19}H_{21}NO_3$, 311.152), 295 (10), 294 (9), 280 (12), 83 (100).

***cis*-2,5-Dimethyl-2,5-bis(2-hydroxy-5-methylphenyl)-tetrahydropyrrolyl-1-oxy (34).** The procedure used to prepare nitroxide **33** was adapted. From nitrone **46** (62 mg) there was obtained, after preparative TLC ($CHCl_3$–MeOH, 100:1) and recrystallization from ether–hexane, nitroxide **34** (15 mg, 23%) as yellow crystals: mp 187–189 °C; MS, *m/e* 326.176 (17) (calcd for $C_{20}H_{24}NO_3$, 326.175), 311 (7), 296 (32), 280 (15), 148 (100).

2-Bromo-4-methyl-6-((tetrahydropyranyloxy)methyl)-anisole (43). To a stirred solution of 4-methylanisole (28 g) in benzene (100 mL) was added 37% hydrochloric acid (80 mL) and then the mixture was saturated with HCl gas at 0 °C. Formaldehyde (20 mL, 37% aqueous) and 37% hydrochloric acid (80 mL) were added and stirring was continued at 25 °C for 4 h. The organic phase was washed with cold water and aqueous $NaHCO_3$, dried ($MgSO_4$), concentrated, and distilled, giving 2-chloromethyl-4-methylanisole (30.4 g, 78%) as a colorless oil: bp 56–58 °C (0.1 mm). A 28.9-g (0.17 mol) sample was dissolved in $CHCl_3$ and treated with Br_2 (27.2 g, 0.17 mol) dropwise at 0 °C. During the addition the cooling bath was removed and the reaction mixture was then stirred for 12 h at 25 °C. The usual workup followed by vacuum distillation gave 36.6 g (~80%) (bp 72–90 °C (0.05 mm) of a mixture of chloromethylated and bromomethylated 2-bromo-4-methylanisoles. A 36-g sample of this mixture was added to water (300 mL) containing K_2CO_3 (25 g) and the resulting mixture was refluxed for 12 h. The usual workup with $CHCl_3$ followed by vacuum distillation gave 2-bromo-4-methyl-6-(hydroxymethyl)anisole (20.3 g, 52% overall yield): bp 101–103 °C (0.04 mm); NMR δ 2.35 (s, 3), 3.91 (s, 3), 4.73 (s, 2), 7.11–7.20 (m, 1), 7.31–7.38 (m, 1). A 6.9-g sample was dissolved in CH_2Cl_2 (50 mL) containing dihydropyran (4.1 mL) and *p*-toluenesulfonic acid (5 mg), and the solution was stirred for 1 h at 25 °C. A color change from colorless to purple to blue to light yellow was observed. The solution was washed with 1 N NaOH (20 mL), dried (K_2CO_3), evaporated, and distilled, giving **43** (8.4 g, 89%) as a colorless oil: bp 123–128 °C (0.005 mm); NMR δ 1.45–1.90 (m, 6), 2.30 (s, 3), 3.45–4.05 (m, 2), 3.84 (s, 3), 4.4–4.9 (ABq + m, 3), 7.15–7.35 (m, 2); MS, *m/e* 316.050 (9) (calcd for $C_{14}H_{19}BrO_3$, 316.050), 314 (9), 216 (10), 215 (24), 214 (10), 213 (24), 185 (5), 183 (5), 85 (100).

2-Methyl-2-(2-methoxy-3-((tetrahydropyranyloxy)-methyl)-5-methylphenyl)-3,4-dihydro-2*H*-pyrrole 1-Oxide (44, R = CH_2OTHP). The procedure used for the preparation of nitrone **29** was adapted. From nitrone **28** (2.0 g) and **43** (7.0 g) there was obtained 6.0 g of a mixture of the title compound and 2-[(tetrahydropyranyloxy)methyl]-4-methylanisole, which was suitable for use in the next experiment.

2-Methyl-2,5-bis(2-methoxy-3-((tetrahydropyranyloxy)-methyl)-5-methylphenyl)-3,4-dihydro-2*H*-pyrrole 1-Oxide (48). The procedure used for the preparation of nitrone **30** was adapted. From the above mixture (6.0 g) and **43** (7.0 g) there was obtained after the oxidation step a brown oil (10.7 g), which was chromatographed over silica gel ($CHCl_3$–acetone, 20:1), giving 3.1 g of a green oil. This was dissolved in ether, washed with aqueous ethylenediaminetetraacetic acid (EDTA) disodium salt, water, and brine, dried ($MgSO_4$), and evaporated, giving 2.2 g of a yellow oil (2 spots on TLC). Rechromatography gave pure **48** (1.35 g, 12% based on **28**) as a light yellow foam: NMR δ 1.5–1.9 (m, 12), 2.00 (s, 3), 2.32 (s, 3), 2.40 (s, 3), 2.5–3.2 (m, 4), 3.4–4.1 (m, 4), 3.74 (s, 3), 3.88 (s, 3), 4.5–4.9 (m, 6), 7.1–7.3 (br s, 4); MS, *m/e* 551.328 (3) (calcd for $M^+ - O$, 551.325), 550 (5), 536 (5), 467 (15), 466 (42), 465 (18), 449 (11), 448 (8), 85 (100).

2-Methyl-2,5-bis(2-methoxy-3-(hydroxymethyl)-5-methylphenyl)-3,4-dihydro-2*H*-pyrrole 1-Oxide (49). To nitrone **48** (1.25 g) in MeOH (100 mL) was added *p*-toluenesulfonic acid (250 mg). After a 2-h stir at 25 °C, the usual workup afforded a foam (0.85 g), which crystallized from $CHCl_3$–ether, affording nitrone **49** (0.60 g, 68%) as light yellow crystals: mp 178–180 °C; NMR δ 1.96 (s, 3), 2.27 (s, 3), 2.35 (s, 3), 2.5–3.1 (m, 4), 3.70 (s, 3), 3.80 (s, 3), 4.64–4.80 (m, 4), 7.08–7.25 (m, 3), 8.18–8.25 (m, 1); MS, *m/e* 399.207 (37) (calcd for $C_{23}H_{29}NO_5$, 399.205), 382 (47), 368 (50), 350 (36), 166 (66), 159 (62), 84 (100). Anal. Calcd for $C_{23}H_{29}NO_5 \cdot {}^1/_2H_2O$: C, 67.62; H, 7.40; N, 3.43. Found: C, 67.88; H, 7.46; N, 3.28.

7,16-Dibenzyl-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (53). To a stirred solution of 52 mg of diaza crown ether **51**, 100 μL of pyridine, and 5 mL of CH_2Cl_2 was added 46 μL of benzoyl chloride. After 2 h at 25 °C, the usual workup followed by silica gel chromatography (CH_3Cl–MeOH, 95:5) gave 73 mg (78%) of dibenzamide **52**. A 35-mg sample was dissolved in 3 mL of THF and added to 300 μL of 1 M BH_3–THF solution with stirring. The solution was refluxed for 2 h, cooled, and concentrated. The residue was treated with 2 mL of TMEDA, stirred for 2 h at 25 °C, and concentrated. The residue was triturated with ether, leaving the insoluble TMEDA·$2BH_3$ complex, mp 183–185 °C (lit.[45] mp 182.5–184 °C). The ether extract was concentrated, and the residue was recrystallized from ether–hexane to give 30 mg (91%) for **53**[36] as colorless crystals: mp 82.5–83.5 °C. Anal. Calcd for $C_{26}H_{38}O_4N_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.11; H, 8.49; N, 6.52.

15,18,23,26-Tetraoxa-2,11-dioxo-1,12-diazabicyclo[10.8.8]-octacosane (54). To 100 mL of stirred dry benzene was added dropwise simultaneously from two addition funnels[34] over 2 h a solution of 72 mg (0.30 mmol) of sebacoyl chloride in 25 mL of benzene and a solution of 79 mg (0.30 mmol) of **51** and 61 mg (0.60 mmol) of Et_3N in 25 mL of benzene. The resulting cloudy mixture was stirred at 25 °C for 20 h, filtered, and concentrated. Chromatography of the residue over silica gel ($CHCl_3$–MeOH, 94:6) gave a solid which was crystallized from toluene–hexane to give 114 mg (43%) of diamide **54** as colorless needles: mp 98–100 °C; IR ($CDCl_3$) 1632 and 1120 cm^{-1}; MS, *m/e* 429 (13), 428.284 (53) (calcd for $C_{22}H_{40}N_2O_6$, 428.289), 427 (26), 385 (20), 383 (21), 367 (16), 360 (33), 354 (23), 353 (100). Anal. Calcd for $C_{22}H_{40}N_2O_6$: C, 61.65; H, 9.41; N, 6.54. Found: C, 61.73; H, 9.57; N, 6.59.

15,18,23,26-Tetraoxa-1,12-diazabicyclo[10.8.8]octacosane (55). To a stirred solution of 0.70 mL of 1 M BH_3–THF was added 75 mg of **54** in 5 mL of THF. After a 5-h reflux period the reaction was worked up with TMEDA as described for **53** above, affording 67 mg (96%) of **55** as a colorless oil: MS, *m/e* 401 (21), 400.332 (81) (calcd for $C_{22}H_{44}N_2O_4$, 400.330), 340 (26), 339 (89), 326 (20), 325 (100).

Nitroxide Diamide 59. To a stirred solution of 39 mg (0.15 mmol) of nitroxide diacid **56**[38] in 0.5 mL of MeOH was added 0.38 mL (0.31 mmol) of 0.83 M KOH. The solution was concentrated and the solid dipotassium salt was dried by azeotropic distillation of MeOH–benzene and then high vacuum. This was suspended in 4 mL of dry ether and treated with excess (100 μL) of oxalyl chloride and 6 μL of DMF[39] at 0 °C. The solution was stirred in the dark at 0 °C for 4 h and then concentrated (IR in $CHCl_3$, 1790 cm^{-1}). The residue was dissolved in 20 mL of dry benzene and transferred to an addition funnel attached to flask containing 70 mL of stirred dry benzene.[34] A second addition funnel was charged with 335 mg (0.13 mmol) of **51**, 31 mg (0.30 mmol) of Et_3N, and 20 mL of benzene and attached to the flask. The two solutions were added simultaneously dropwise over 100 min to the stirred benzene. The cloudy mixture was stirred at 25 °C for 20 h and concentrated. The residue was purified by preparative TLC (silica gel, $CHCl_3$–MeOH, 94:6), affording after recrystallization from toluene–hexane 18 mg (25% based on **56**) of **59** as yellow needles: mp 205–208 °C; IR ($CHCl_3$) 1645 and 1120 cm^{-1}; ESR ($CHCl_3$) 3 broadened lines, a_N = 14.06 G; MS, *m/e* 485 (15), 484.304 (42) (calcd for $C_{24}H_{42}N_3O_7$, 484.302), 454 (8), 169 (17), 168 (100). Anal. Calcd for $C_{24}H_{42}N_3O_7$: C, 59.48; H, 8.74; N, 8.67. Found: C, 59.74; H, 8.57; N, 8.99.

Table I. Thermodynamic Parameters for the Association of Relevant Hosts and Nitroxides 37, 38, and 60 with Potassium and Sodium Picrates in $CDCl_3$ at 24 °C

host	cation	R[a]	$K_a \times 10^{-3}$ M^{-1} [b]	$-\Delta G°$, kcal/mol
dicyclohexyl-18-crown-6	K	0.809[c]	200000	11.32
		0.82	120000	11.0
	Na	0.308[c]	2300	8.68
		0.30	1900	8.5
nitroxide cryptand **60**[d]	K	0.52	6000	9.2
	Na	0.39	3700	8.9
cryptand **55**[d]	K	0.50	5300	9.1
	Na	0.38	3100	8.8
dibenzo-18-crown-6	K	0.44	3300	8.9
	Na	0.10	311	7.5
nitroxide crown ether **38**	K	0.077	149	7.0
	Na	0.020	47	6.4
nitroxide crown ether **37**	K	0.054	94	6.8
	Na	0.020	47	6.4

[a] Guest to host molar ratio.[31,43] [b] Association constant as defined in ref 31 and 43 (see Experimental Section). [c] Reference 31. [d] A 1:1 complex between this host and either potassium or sodium picrate could be isolated as an oil (see text and ref 41).

Nitroxide Cryptand 60. To a stirred solution of 100 μL of 1 M BH_3–THF was added 2.0 mg of diamide **59** in 2 mL of THF. After a 10-h reflux period, the reaction mixture was worked up with TMEDA as described for **53** above, affording 2 mg (~100%) of **60** as a yellow oil: IR ($CHCl_3$) 1120 cm^{-1}; ESR ($CHCl_3$) a_N = 15.0 G; MS, *m/e* 458 (25), 457.351 (100) (calcd for $C_{24}H_{47}N_3O_5$, 457.352, M + 1), 456 (7), 440 (7), 180 (12), 154 (28), 138 (25), 136 (18).

Interaction of $NaBPh_4$ with 37, 38, 51, 54, 55, and 60. Solutions (0.03 M) of the title substrates in $CDCl_3$ (0.5 mL) were separately treated with excess $NaBPh_4$ (15 mg). The suspensions were stirred at 25 °C in a closed vial for 15 min and then filtered. Filtrates were examined for evidence of complex formation by IR, NMR, and/or gravimetric analysis. The results are described in the text.

Determination of the Guest to Host Molar Ratio (R) and the Association Constant (K_a) for the Interaction of Relevant Hosts and Nitroxides 37, 38, and 60 with Potassium and Sodium Picrates. The procedures of Cram and co-workers[31,43] were adapted to accommodate small samples as follows. A 0.3-mL Reacti-Vial (cone capacity 0.1 mL) (Pierce Co.) was charged with 50 μL of a 0.015 M solution of the host in $CDCl_3$ by means of a gas-tight syringe. To this was added 50 μL of either aqueous potassium picrate (0.0162 M) or sodium picrate (0.0161 M). The mixture was tightly capped and stirred at 24 °C for 15 min. The layers were allowed to separate. From each layer was taken 10 μL, and each was diluted to 5.00 mL was CH_3CN (HPLC grade) in a volumetric flask. The absorbance was then measured for each sample at 380 nm. Three measurements were taken, an average absorbance, A, was calculated, and this was used for the calculation of R_{CDCl_3}, K_a, and ΔG (Table I) using the expression derived by Cram and co-workers[31,43] shown below.

$$R_{CDCl_3} = [\{[G_i^+]_{H_2O} - A(D/\epsilon)\}(V_{aq}/V_{org})]/[H_i^*]$$

$[G_i^+]_{H_2O}$ is the initial concentration of potassium or sodium picrate in water, D is the dilution factor (500 in these experiments), ϵ = 16 900 M^{-1}/cm^{-1} for potassium or sodium picrate in CH_3CN

at 380 nm,[43] $V_{aq} = V_{org} = 50$ μL, and $[H_i^*]$ is the initial concentration of host (0.015 M in these experiments).

$$K_a = R_{CDCl_3}/[(1 - R_{CDCl_3})K_d\{[G_i^+]_{H_2O} - R_{CDCl_3}[H_i^*]_{CDCl_3}(V_{CDCl_3}/V_{H_2O})\}^2]$$

K_a[31] is the association constant corresponding to the equilibrium

$$host_{CDCl_3} + M^+ picrate^-_{CDCl_3} \rightleftarrows M^+ \cdot host \cdot picrate^-_{CDCl_3}$$

K_d is the distribution constant between $CDCl_3$ and water for potassium picrate ($K_d = 2.55 \times 10^{-3}$ M^{-1}) or sodium picrate ($K_d = 1.74 \times 10^{-3}$ M^{-1}).[43]

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Registry No. **9**, 112-60-7; **9** monobenzyl ether, 86259-87-2; **10**, 86259-55-4; **11**, 86259-56-5; **14**, 86259-57-6; **15**, 86259-58-7; **17**, 28765-36-8; **20**, 86259-59-8; **22**, 86259-60-1; **23**, 86259-61-2; **24**, 86259-62-3; **27**, 86259-63-4; **28**, 6931-10-8; **29**, 86259-64-5; **30**, 86259-65-6; **31**, 86259-66-7; **33**, 86259-67-8; **34**, 86259-68-9; **35**, 86259-69-0; **36**, 86259-70-3; **37**, 86259-71-4; **38**, 86259-72-5; **39**, 31255-26-2; **40**, 52559-90-7; **43**, 86259-73-6; **44** (R = H), 86259-74-7; **44** (R = CH_2OTHP), 86259-77-0; **45**, 86259-75-8; **46**, 86259-76-9; **48**, 86259-78-1; **49**, 86259-79-2; **51**, 23978-55-4; **52**, 81897-78-1; **53**, 69703-25-9; **54**, 86259-80-5; **55**, 86259-81-6; **56**, 86259-92-9; **59**, 86259-82-7; **60**, 86259-83-8; **61**, 86259-84-9; **61** benzyl derivative, 86259-85-0; **61**-ol benzyl derivative, 86259-86-1; $NaBPh_4$, 143-66-8; *o*-bromoanisole, 578-57-4; *o*-bromophenyl tetrahydropyranyl ether, 57999-46-9; 2-methyl-2-nitropentan-1-ol mesylate, 86259-88-3; *O*-tosyl-*O*-tetrahydropyranyltetraethylene glycol, 86259-89-4; 2-chloromethyl-4-methylanisole, 7048-41-1; 2-bromo-4-methyl-6-(bromomethyl)anisole, 86259-90-7; 2-bromo-4-methyl-6-(hydroxymethyl)anisole, 86259-91-8; bromoacetaldehyde diethyl acetal, 2032-35-1; vinyl bromide, 593-60-2; ethyl bromoacetate, 105-36-2; 2-bromo-4-methylanisole, 22002-45-5; 4-methylanisole, 104-93-8; sebacoyl chloride, 111-19-3; potassium picrate, 573-83-1; sodium picrate, 3324-58-1.

Potent Hydrophilic Dienophiles. Synthesis and Aqueous Stability of Several 4-Aryl- and Sulfonated 4-Aryl-1,2,4-triazoline-3,5-diones and Their Immobilization on Silica Gel

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The purpose of this investigation is the development of a series of sulfonated 4-aryl-1,2,4-triazoline-3,5-diones (TADs) useful as potent dienophiles for Diels–Alder reactions in aqueous solution and capable of providing a TAD moiety immobilized on an insoluble support. TADs **4**, **5**, **23**, **24**, and **29** were all prepared by oxidation of the corresponding urazoles with N_2O_4. The urazole precursors were prepared by chlorosulfonation of the appropriate 4-arylurazole, followed in some cases by hydrolysis and neutralization. While TAD sulfonic acids **5** and **29** were not stable toward isolation, the presence of the bulky isopropyl groups in **23** and **24** rendered these TADs isolable in pure form and sufficiently stable in water to allow Diels–Alder reactions to compete successfully with attack on the TAD moiety by the solvent (see following paper). Urazolesulfonyl chlorides **2**, **18**, and **19** reacted with aminopropylsilylated silica gel **31** to give the corresponding immobilized sulfonamides, which were readily oxidized to TAD silica gels **33** (red) and **34** (purple). TAD acid **23** and **31** gave silica gel **35** in which the TAD moiety was attached to the gel via an ionic bond. 1,3-Dienes were selectively and quantitatively removed from solution by these silica gels and could be recovered quantitatively therefrom.

1,2,4-Triazoline-3,5-diones (TADs) are among the most reactive dienophiles known for the Diels–Alder reaction.[1,2] Inert solvents such as benzene and CH_2Cl_2 are normally used, owing to the incompatibility of the TAD moiety with hydroxylic solvents. 4-Phenyl TAD, for example, decomposes rapidly in water[3] and alcohols,[4] the initial attack of the solvent postulated as being at one of the carbonyl groups of the TAD. In connection with the development[5] of a new class of 1,3-diene-containing detergents that can be modified by a Diels–Alder reaction under mild *aqueous* conditions,[6] we undertook to develop water soluble TADs that were sufficiently stable in water to allow a Diels–Alder reaction to compete successfully with decomposition. The new sulfonated 4-aryl TADs herein described not only fulfill this requirement but also permit for the first time the immobilization[7] of the TAD moiety on an insoluble matrix such as silica gel.[8] The resulting colorful TAD-

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(6) Few examples of Diels–Alder reactions in aqueous solution are available. Recently, Rideout and Breslow (Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816) have observed rate enhancements for certain Diels–Alder reactions run in aqueous solvent as compared with organic solvents.
(7) The immobilization of reagents or substrates on an insoluble inorganic (McKillop, A.; Young, D. W. *Synthesis* **1979**, 401 and 481) or organic (Akelah, A.; Sherrington, D. C. *Chem. Rev.* **1981**, *81*, 557) matrix is a widely exploited technique.
(8) Silica gel has served as a support, for example, for inductrially important catalysts (Yermakov, Yu. I.; Kuznetsov, B. N.; Zakharov, V. A. "Catalysis by Supported Complexes", Elsevier, New York, 1981), phase-transfer catalysis (Tundo, P.; Venturello, P. *J. Am. Chem. Soc.* **1981**, *103* 856), and the automated synthesis of deoxyoligonucleotides (Matteucci, M. D.; Caruthers, M. H. *J. Am. Chem. Soc.* **1981**, *103*, 3185).

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