

Novel Crown Ethers with Pendant, Proton-Ionizable, Chromogenic Groups

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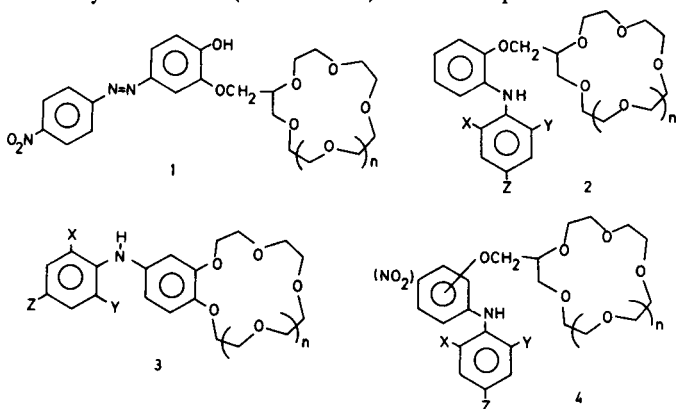
Synthesis of fifteen new chromogenic crown ethers is described in which one phenyl group of diphenylamine has been substituted at the 2-, 4-, and 6-positions with strongly electron-withdrawing groups and the other phenyl group bears an oxymethyl crown ether substituent. Structural variations include the crown ether ring size, identity of the electron-withdrawing groups, acidity of the amine function, and positioning of the oxymethyl crown ether substituent *ortho*, *meta*, and *para* to the amine nitrogen. Preparation of a structurally-related chromogenic bis(crown ether) is also reported.

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The synthesis and properties of crown ethers with pendant azophenol chromogenic units **1** have been summarized by Takagi and Ueno [1]. In such compounds, the deprotonated phenolic group can interact directly with a crown ether-bound metal cation and enhance the binding and chromogenic response.

In our research, we wished to investigate structurally-related crown ethers **2** in which a diphenylamino-type of chromogenic unit is incorporated (X, Y, and Z are strongly electron-withdrawing groups). Although diphenylamine-type chromogenic units already have been utilized in benzocrown compounds **3** [2-4], an examination of CPK space-filling models suggests that the N-H bond in **2** may be oriented directly over the polyether cavity and, upon ionization, provide an opportunity for interaction of a crown ether-complexed metal ion with the anionic nitrogen of the chromophore system. Clearly such interactions would be impossible in the chromogenic benzocrowns **3**.

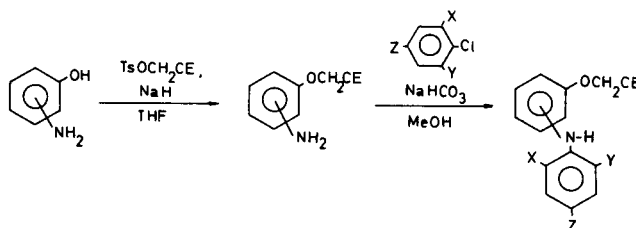
To provide several series of compounds in which the influence of structural variations upon the chromogenic response may be probed, new chromogenic crown ethers **4** have been prepared in which the polyether ring size, identity of the electron-withdrawing groups (X, Y, and Z), acidity of the amine nitrogen, and positioning of the crown ether ring with respect to the amine nitrogen are systematically varied. These syntheses as well as that of a structurally-related bis(crown ether) are now reported.



Results and Discussion.

The synthetic route to the new family of chromogenic crown ethers **4** is illustrated in Scheme 1. In this two-step sequence, nucleophilic displacement of phenoxide ions derived from 2-aminophenol, 3-aminophenol, 4-aminophenol, and 2-amino-5-nitrophenol on known (tosyloxy)methyl

Scheme 1



crown ethers [5,6] in tetrahydrofuran gave the corresponding oxymethyl crown ether-substituted anilines **5-14**. Compounds **5-10** are (2-aminophenyl)oxymethyl crown ethers in which the polyether ring size is varied from 15-crown-5 to 16-crown-5 (attachment on the three-carbon bridge) to 18-crown-6 to 19-crown-6 (attachment on a two-carbon bridge) to 21-crown-7 and then to the very large ring of 30-crown-10. With the exception of **6**, for which base-promoted elimination from 3-(tosyloxy)methyl-16-crown-5 to form 3-methyl-16-crown-5 was a serious competing pathway, yields of the (2-aminophenyl)oxymethyl crown ethers were 56-95% (Table I). It is interesting to note that in two series, yields of the 18-crown-6 compound were much higher than that for the corresponding 15-crown-5 derivatives [compare **5** (67%) and **7** (95%) as well as **11** (68%) and **12** (99%)].

For **5**, **11** and **13** which are (aminophenyl)oxymethyl-15-crown-5 compounds with *ortho*, *meta*, and *para* arrangements of the benzene ring substituents, yields were 67, 68, and 69%, respectively. The nearly identical yields of **5**, **11** and **13** indicate that positional variation of the amino group on the attacking phenoxide ion nucleophile does not significantly influence the substitution reaction.

Table 1

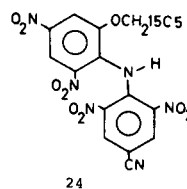
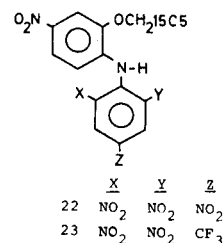
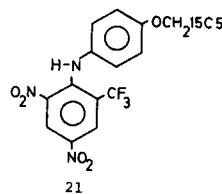
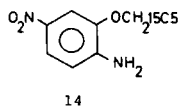
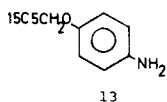
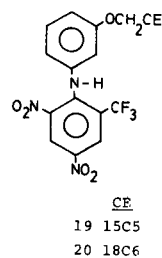
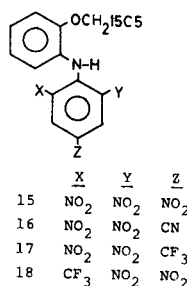
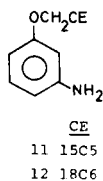
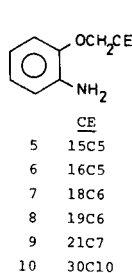
Yields, Physical Properties, Spectral Data and Elemental Analysis Data for Chromogenic Crown Ethers and Intermediates **5-29, 32** and **33**

Compound No.	Yield %	mp, °C	¹ H NMR Spectra (60 MHz), ppm	IR Spectra, cm ⁻¹	Elemental Analysis		
					Theory	Found	
5	67	37.5-39.5 yellow crystals	3.35-4.2 (m, 23H), 6.73 (br s, 4H)	3460, 3356 (N-H), 1126 (C-O)	C H	59.81 7.97	59.64 8.01
6	26 [a]	oil	—	—	—	—	—
7	95	oil	3.45-4.2 (m, 27H), 6.55-6.85 (br s, 4H)	3456, 3360 (N-H), 1115 (C-O)	C H	59.20 8.11	59.09 8.22
8	72	oil	1.80 (pentet, 2H), 3.2-4.15 (m, 27H), 6.66 (br s, 4H)	3462, 3360 (N-H), 1116 (C-O)	C H	60.10 8.33	60.09 8.29
9	56	pale yellow oil	3.4-4.2 (m, 31H), 6.5-7.85 (m, 4H)	3460, 3356 (N-H), 1116 (C-O)	C H	58.73 8.21	58.51 8.44
10	68	pale yellow oil	3.3-4.2 (m, 43H), 6.69 (br s, 4H)	3460, 3360 (N-H), 1113 (C-O)	C [b] H	56.83 8.48	56.91 8.56
11	68	brown oil	3.5-4.15 (m, 23H), 6.1-7.15 (m, 4H)	—	C [b] H	58.27 8.05	58.21 7.85
12	99	pale yellow oil	3.45-4.15 (m, 27H), 6.15-6.4 (m, 3H), 6.8-7.05 (m, 1H)	3445, 3362 (N-H), 1105 (C-O)	C H	59.20 8.11	59.12 8.20
13	69	pale yellow oil	3.5-4.0 (m, 21H), 6.6-6.7 (dd, 4H)	—	C [b] H	58.27 8.06	58.39 8.38
14	85	97.5-98.5 yellow solid	3.45-4.3 (m, 21H), 5.00 (br s, 2H), 6.62 (d, 1H), 7.6-7.9 (m, 2H)	3475, 3345 (N-H), 1520, 1319 (NO ₂), 1122 (C-O)	C H	52.84 6.78	52.62 6.94
15	89	119-121 orange crystals	3.35-4.20 (m, 21H), 6.8-7.35 (m, 4H), 9.02 (s, 2H), 10.31 (s, 1H)	3306 (N-H), [c] 1537 (NO ₂), 1120 (C-O)	C H	50.00 5.11	50.20 5.17
16	92	red glass	3.35-4.20 (m, 21H), 6.8-7.35 (m, 4H), 8.4 (s, 2H), 10.13 (s, 1H)	3312 (N-H), [c] 2233 (C≡N), 1537 (NO ₂), 1122 (C-O)	C H	54.13 5.30	54.39 5.55
17	96	red oil	3.4-4.2 (m, 21H), 6.8-7.3 (m, 4H), 8.41 (s, 2H), 9.96 (s, 1H)	3323 (N-H), 1543 (NO ₂), 1130 (C-O)	C H	50.09 4.90	50.14 4.93
18	90	72.5-74.5 red crystals	3.2-4.2 (m, 21H), 6.6-7.35 (m, 4H), 7.78 (br s, 1H), 8.5-8.9 (m, 2H)	3418, 3315 (N-H), [c] 1540 (NO ₂), 1130 (C-O)	C H	50.09 4.90	50.31 5.09
19	69	red oil	3.55-4.1 (m, 21H), 6.45-7.35 (m, 4H), 7.60 (s, 1H), 8.75 (dd, 2H)	3416, 3302 (N-H), 1545 (NO ₂), 1126 (C-O)	C H	50.09 4.90	50.04 4.90
20	67	red oil	3.35-4.3 (m, 25H), 6.75-7.3 (m, 4H), 7.75 (s, 1H), 8.80 (dd, 2H)	3427, 3300 (N-H), 1547 (NO ₂), 1120 (C-O)	C H	50.40 5.21	50.65 5.60
21	74	red oil	3.45-4.05 (m, 21H), 6.75 (s, 4H), 7.65 (s, 1H), 8.63 (dd, 2H)	3416, 3302 (N-H), 1545 (NO ₂), 1136 (C-O)	C [d] H	47.84 5.18	48.05 5.13
22	47	red oil	3.3-4.5 (m, 21H), 6.7 (m, 2H), 7.2 (m, 2H), 8.88 (s, 2H), 9.00 (s, 1H)	3306 (N-H), 1538 (NO ₂), 1167, 1093 (C-O),	C [g] H	44.88 4.75	44.76 4.58
23	10 [e] 48 [f]	red glass	3.4-4.35 (m, 21H), 6.90 (d, 1H), 7.65-7.95 (m, 2H), 8.53 (s, 2H), 9.90 (s, 1H)	3320 (N-H), 1543 (NO ₂), 1132 (C-O)	C H	46.46 4.38	46.32 4.41
24	80	164-166 yellow solid	3.35-4.25 (m, 21H), 8.02 (d, 1H), 8.45-8.8 (m, 3H), 11.40 (s, 1H)	3260 (N-H), 2238 (C≡N), 1537 (NO ₂), 1126 (C-O)	C H	46.31 4.21	46.38 4.52
25	47 [h]	orange oil	2.0-2.6 (m, 1H), 3.25-3.9 (m, 20H), 4.10 (d, 2H), 6.65-7.35 (m, 3H), 7.80 (s, 1H), 8.55-8.9 (m, 2H)	3416, 3312 (N-H), 1547 (NO ₂), 1132-1128 (C-O)	C H	50.93 5.13	50.83 5.28

Table 1 (continued)

Compound No.	Yield %	mp, °C	¹ H NMR Spectra (60 MHz), ppm	IR Spectra, cm ⁻¹	Elemental Analysis	
					Theory	Found
26	67	red oil	3.3-4.45 (m, 25H), 6.8-7.25 (br s, 4H), 7.6-8.0 (br s, 1H), 8.75 (dd, 2H)	3427, 3300 (N-H), 1547 (NO ₂), 1120 (C-O)	C H	48.98 5.38 48.72 5.35
27	94	red oil	1.80 (pentet, 2H), 3.2-4.25 (m, 25H), 6.7-7.3 (m, 4H), 7.70 (s, 1H), 8.45-8.90 (m, 2H)	3420, 3312 (N-H), 1547 (NO ₂), 1120 (C-O)	C H	51.18 5.41 51.34 5.52
28	51	red oil	3.4-4.25 (m, 29H) 6.7-7.35 (m, 4H), 7.75 (br s, 1H), 8.5-8.9 (m, 2H)	3416, 3310 (N-H), 1547 (NO ₂), 1118 (C-O)	C [d] H	51.32 6.08 51.65 5.59
29	66	red oil	3.4-4.3 (m, 41H), 6.65-7.3 (m, 4H), 7.70 (br s, 1H), 8.5-8.9 (m, 2H)	3420, 3313 (N-H), 1545 (NO ₂), 1118 (C-O)	C H	51.32 6.08 51.01 6.40
32	86	yellow oil	3.4-4.35 (m, 50H), 6.95 (d, 1H), 7.7-8.0 (m, 2H)	1514 (NO ₂), 1109 (C-O)	C H	54.30 7.55 54.50 7.55
33	71	red oil	3.35-4.2 (m, 50H), 6.25-7.45 (m, 4H), 8.2-8.65 (m, 2H)	3526, 3300 (N-H), 1514 (NO ₂), 1126 (C-O)	C [g] H	50.37 6.29 49.98 6.01

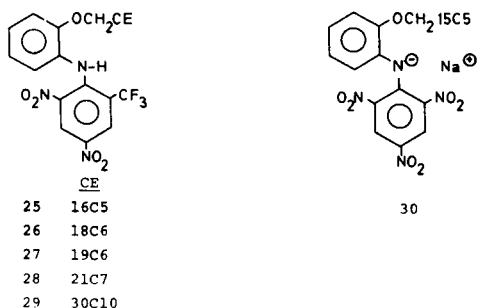
[a] Product was slightly contaminated with 3-methylene-16-crown-5 and was used directly for the preparation of **25**. [b] Analyzed as a 0.5 hydrate. [c] Deposit on a sodium chloride plate. [d] Analyzed as a 1.5 hydrate. [e] Yield obtained from **14**. [f] Yield obtained from nitration of **17**. [g] Analyzed as a hydrate. [h] Overall yield from 2 steps.



In the second step of the synthetic sequence, (amino-phenyl)oxymethyl crown ethers were coupled with highly-activated aryl chlorides in methanol to produce the chromogenic crown ethers **15-21** and **25-29**. Reactions of

(2-aminophenyl)oxymethyl-15-crown-5 (**5**) with picryl chloride, 1-chloro-4-cyano-2,6-dinitrobenzene, 1-chloro-2,6-dinitro-4-trifluoromethylbenzene and 1-chloro-2,4-dinitro-6-trifluoromethylbenzene gave high yields (89-96%) of the corresponding chromogenic compounds **15-18**. These compounds provide a series of chromogenic 15-crown-5 derivations with four different combinations of strongly

electron-attracting substituents. For the preparation of chromogenic crown compounds **19-21** and **25-29**, the highly-activated aryl halide coupling component was restricted to 1-chloro-2,4-dinitro-6-trifluoromethylbenzene.



Chromogenic crown ethers **18**, **19**, and **21** are structural isomers which possess common 15-crown-5 polyether rings but different attachment sites of the oxymethyl crown ether unit with respect to the amine nitrogen. The yield of chromogenic crown ether **18** which has an ortho arrangement was considerably higher (90%) than those for **19** (69%) and **21** (74%) in which there are meta and para relationships, respectively.

The structural variation for chromogenic crown ethers **19**, **20** and **18**, **25-29** is the crown ether ring size. For **19** and **20** in which the polyether unit is bonded meta to the amine nitrogen, the ring size variation was limited to 15-crown-5 and 18-crown-6. Both compounds were formed in very similar yields. For the more extended series of **18**, **25-29**, the polyether unit is attached ortho to the amine nitrogen and the ring size variation includes 15-crown-5, 16-crown-5, 18-crown-6, 19-crown-6, 21-crown-7, and 30-crown-10. Yields of the coupling reaction varied from 51-94% with no apparent relationship between the crown ether ring size and the yield.

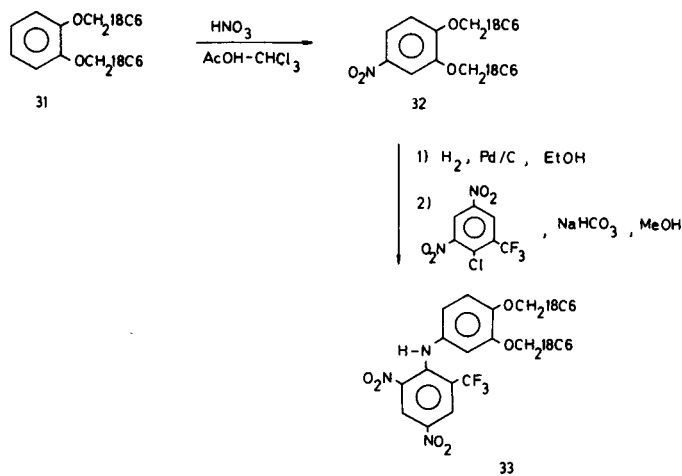
It was anticipated that the addition of nitro groups to the benzene ring which bears the crown ether unit would enhance the acidity of the amino group. Coupling of **14** with 1-chloro-2,6-nitro-4-trifluoromethylbenzene gave only a 10% yield of the desired chromogenic crown ether **23**. On the other hand, nitration of chromogenic crown ether **17** with fuming nitric acid in acetic acid-chloroform gave a 48% yield of **23**. Similarly, nitration of **15** gave a 47% yield of **22**. Under the same conditions, **16** gave an 80% yield of the dinitration product **24**.

Reaction of chromogenic crown ethers **15** with sodium hydride in tetrahydrofuran produced a 95% yield of the sodium inner salt **30** as a dark brown solid.

Molecules which contain two crown ether units are designated (bis)crown ethers. Monocyclic crown ethers and bis(crown ethers) may exhibit significantly different cation complexation behavior [7]. Chromogenic bis(crown ethers) with an azophenol group have been reported [8]. Therefore the preparation of a bis(crown ethers) was undertaken which incorporates the same type of chromogenic unit as the new chromogenic crown ethers described above. Reaction of catechol with potassium hydride and two equiva-

lents of (tosyloxy)methyl-18-crown-6 in tetrahydrofuran produced a 65% yield of bis(crown ether) **31**. Nitration of **31** with fuming nitric acid in acetic acid-chloroform gave **32**. Subsequent reduction of the nitro group with hydrogen in the presence of palladium on carbon catalyst and coupling with 1-chloro-2,4-dinitro-6-trifluoromethylbenzene gave the novel, chromogenic, bis(crown ether) **33** in 71% overall yield (Scheme 2).

Scheme 2



All new compounds were characterized by nmr and ir spectra and by elemental analysis (Table 1).

Partial analytical evaluation of the new chromogenic compounds has been presented elsewhere [9].

EXPERIMENTAL

Melting points were taken with either a Mel-Temp or Fisher-Johns melting point apparatus and are uncorrected. The ir spectra were obtained with a Nicolet MX-S spectrometer and are reported in reciprocal centimeters. The pmr spectra were recorded with Varian EM360 or EM360A spectrometers in deuteriochloroform and chemical shifts are reported in parts per million (δ) downfield from TMS. Elemental analysis was performed by Galbraith Laboratories, Inc. (Knoxville, Tennessee).

Unless specified otherwise, reagent grade reactants and solvents were used as received. Tetrahydrofuran was purified by distillation from lithium aluminum hydride. Dimethylformamide was stored over molecular sieves (5 Å). Pentane was stored over potassium hydroxide pellets and was distilled prior to use. The (tosyloxy)methyl crown ethers were available from earlier work [5,6].

Preparation of Oxymethyl Crown Ether-Substituted Anilines 5-14.

Under nitrogen, sodium hydride (50% in mineral, 0.17 g, 3.60 mmoles) was washed with pentane and suspended in 4 ml of tetrahydrofuran. A solution of the appropriate aminophenol (3.20 mmoles) in 10 ml of tetrahydrofuran was added and the mixture was stirred at room temperature for 1 hour. A solution of the (tosyloxy)methyl crown ether (3.20 mmoles) in 10 ml of tetrahydrofuran was added and the mixture was refluxed to 48 hours. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography on alumina with chloroform-ethanol (100:1) as eluent to give the pure product.

Preparation of Chromogenic Crown Ethers 15-21, 23, and 33.

A mixture of the oxymethyl crown ether-substituted aniline (2.50 mmoles), the appropriate activated aryl chloride (2.80 mmoles) and sodi-

um bicarbonate (0.25 g) in 3 ml of absolute methanol was refluxed overnight. The solvent was removed *in vacuo* and the residue was purified by column chromatography on alumina with ethyl acetate as eluent to afford the pure product.

Preparation of Chromogenic Crown Ethers 22-24 by Nitration.

For synthesis of **22**, **23** and **24**, 0.40 mmole of the precursor **15**, **17** or **16**, respectively, was dissolved in 8 ml of chloroform and 1.5 ml of a solution of fuming nitric acid, acetic acid and chloroform (1:1:1) was added dropwise at room temperature. After 10 minutes, water was added and the organic layer was washed several times with water. The solvent was removed *in vacuo* and the residue was chromatographed on an alumina column with ethyl acetate-methanol (5:1) as eluent to give the pure product.

Preparation of Internal Sodium Salt 30 of Chromogenic Crown Ether 15.

Sodium hydride (50% in mineral oil 0.038 g, 0.80 mmole) was washed with pentane and suspended in 2 ml of tetrahydrofuran. A solution of 0.39 g (0.70 mmole) of **15** in 5 ml of tetrahydrofuran was added dropwise and the mixture was stirred for 48 hours at room temperature. The excess sodium hydride was removed by filtration and the solvent was removed *in vacuo* from the filtrate to afford 0.38 g (95%) of **30** as a dark-brown solid with mp 115° dec; ir (deposit on a sodium chloride disk): 1116, 1097 cm^{-1} (C-O); ^1H nmr (deuteriochloroform): δ 3.0-4.35 (m, 21H), 6.3-6.9 (m, 4H), 8.65 (s, 2H); uv (chloroform): λ max 443 nm, ϵ 16,040.

Anal. Calcd. for $\text{C}_{23}\text{H}_{17}\text{N}_4\text{NaO}_{12}$: C, 48.09; H, 4.74. Found: C, 48.03; H, 4.99.

Preparation of Bis(crown Ether) 31.

Under nitrogen, sodium hydride (50% in mineral oil, 0.26 g, 5.4 mmoles) was washed with pentane and suspended in 4 ml of tetrahydrofuran. A solution of catechol (0.27 g, 2.4 mmoles) in 5 ml of tetrahydrofuran was added dropwise at room temperature. After 1 hour, a solution of (tosyloxy)methyl-18-crown-6 (2.19 g, 4.9 mmoles) in 5 ml of tetrahydrofuran was added and the mixture was refluxed for 48 hours. The solvent was evaporated *in vacuo* and 30 ml of water was added. The residue was extracted with methylene chloride (2 \times 20 ml). The combined extracts were dried over magnesium sulfate and evaporated *in vacuo*. The residue was purified by column chromatography on alumina with ethyl acetate-methanol (50:1 then 20:1) as eluent to give 1.05 g (65%) of **31** as an extremely hygroscopic, colorless oil; ir (neat): 1128 cm^{-1} (C-O); ^1H nmr (deuteriochloroform): δ 3.5-4.3 (s + m, 50H), 6.89 (s, 4).

Anal. Calcd. for $\text{C}_{22}\text{H}_{14}\text{O}_{14}$: C, 57.99; H, 8.21. Found: C, 57.83; H, 8.23.

Nitration of Bis(crown Ether) 31 To Form 32.

To a solution of **31** (0.53 g, 0.80 mmole) in 15 ml of chloroform-acetate (1:1), 1.1 ml of concentrated nitric acid was added dropwise at room temperature and the reaction mixture was stirred overnight. After addition of sodium bicarbonate to neutralize the excess of nitric acid, the organic layer was separated and the aqueous layer was washed twice with chloroform. The combined chloroform layers were dried with magnesium sulfate and evaporated *in vacuo*. Column chromatography of the residue on alumina with ethyl acetate-methanol (20:1) as eluent gave 0.48 g (86%) of **32** as a pale yellow, viscous, hygroscopic oil; ir (neat): 1549 (NO_2), 1109 (C-O) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 3.4-4.35 (m, 50H), 6.95 (d, 1H), 7.7-8.0 (m, 2H).

Anal. Calcd. for $\text{C}_{22}\text{H}_{13}\text{NO}_{16}$: C, 54.30; H, 7.55. Found: C, 54.50; H, 7.55.

Preparation of Chromogenic Bis(crown Ether) 33.

The nitrated bis(crown ether) **32** (0.45 g, 0.60 mmole) was dissolved in 5 ml of dimethylformamide and 50 mg of 10% palladium on carbon was added. After hydrogenation under 45 psi of hydrogen at room temperature for 12 hours, the catalyst was filtered and the solvent was removed *in vacuo* to give the crude amino compound which was used directly in the next step.

The crude amino compound was dissolved in 3 ml of absolute methanol and 0.17 g (0.60 mmole) of 1-chloro-2,4-dinitro-6-trifluoromethylbenzene and 0.1 g of sodium bicarbonate were added. After refluxing overnight, the methanol was evaporated *in vacuo* and the residue was passed through a short alumina column with ethyl acetate-methanol (20:1) as eluent. The eluted material was absorbed on a column of silica gel. Elution with ethyl acetate-methanol (10:1) removed the impurities. Contents of the silica gel column were transferred to a beaker and water was added. The resulting slurry was extracted repeatedly with ethyl acetate. The combined extracts were dried over magnesium sulfate and evaporated *in vacuo* to give 0.41 g (71%) of chromogenic bis(crown ether) **33** as a dark red, viscous oil; ir (neat): 3526 and 3300 (N-H), 1514 (NO_2), 1126 (C-O) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 3.35-4.2 (m, 50H), 6.25-7.45 (m, 4H), 8.2-8.65 (m, 2H).

Anal. Calcd. for $\text{C}_{29}\text{H}_{26}\text{F}_3\text{N}_3\text{O}_{18}\cdot\text{H}_2\text{O}$: C, 50.37; H, 6.29. Found: C, 49.98; H, 6.01.

Acknowledgement.

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