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(*Journal of the Korean Chemical Society*)
Vol. 32, No. 1, 1988
Printed in the Republic of Korea

친핵성 치환 반응에 의한 Dibenzo-18-crown-6의 Nitro 유도체 화합물의 Crown Ether 고리 끊어짐 (제1보)

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(1987. 10. 12 접수)

The Nucleophilic Crown Ether Ring Cleavage of Nitro Derivatives of Dibenzo-18-crown-6 (I)

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(Received October 12, 1987)

요약. 20,21,24,25-Tetranitrodibenzo-18-crown-6에 알코올성 염기를 가하여 친핵성 치환반응을 유도하면 crown ether 화합물을 이루는 polyether 고리가 끊어져서 주생성물로 2,4,5-trialkoxynitrobenzene 유도체, 4,5-dialkoxy-1,2-dinitrobenzene 유도체 그리고 crown ether 고리가 부분적으로 끊어져 생긴 bis[(alkoxynitrophenoxy)ethyl]ether 유도체가 부생성물로 얻어졌다. 이가 알코올성 염기에서는 polyether 고리가 끊어진 생성물과 분자내 치환반응이 다시 진행되어 고리축소 현상이 일어나 12-crown-4의 유도체를 얻게 되거나 출발물질이 도로 생성되었다. 이상의 실험은 다양한 알코올의 농도에서 염기의 종류를 달리하여 그 선택성을 알아보았다.

ABSTRACT. The crown ether ring of 20, 21, 24, 25-tetranitrodibenzo-18-crown-6(TNDB-18-C-6) was cleaved by various alcoholic bases to give 2,4,5-trialkoxynitrobenzene derivatives and 4,5-dialkoxy-1,2-dinitrobenzene derivatives as the major products, and bis[(alkoxynitrophenoxy)-ethyl]ether derivatives from partially cleaved crown ether ring as the minor products. The ring cleavage reaction of TNDB-18-C-6 with ethylene glycolic base resulted ring contraction through intramolecular nucleophilic cyclization of the initially formed ring cleavage product to give nitro derivatives of DB-14-C-4.

It has been well known that *o*-dinitrobenzene undergoes the nucleophilic substitution with strong bases such as OH^-, NH_2^- *etc.* to give *o*-nitrophenol, *o*-nitroaniline respectively.

However tetranitrodibenzo-18-crown-6[1-3], **1** did not react with aqueous NaOH solution even under refluxing temperature.

When this compound was reacted with a strong base, alcoholic NaOH solution, at elevated temperature, the crown ether ring was cleaved to give 4,5-dialkoxy-1,2-dinitrobenzene, **2** and 2,4,5-trialkoxy-1-nitrobenzene, **3** with small amount of **4** in which the crown ether ring was partially cleaved (*Scheme* 1).

Among all primary alcohol having normal carbon chain including allyl and benzyl alcohol reacted with **1** similarly to give similar results. For some alcohols such as methanol in which **1** is poorly soluble, 2-methoxyethanol or dimethoxyethane was used as a cosolvent to enhance

the solubility.

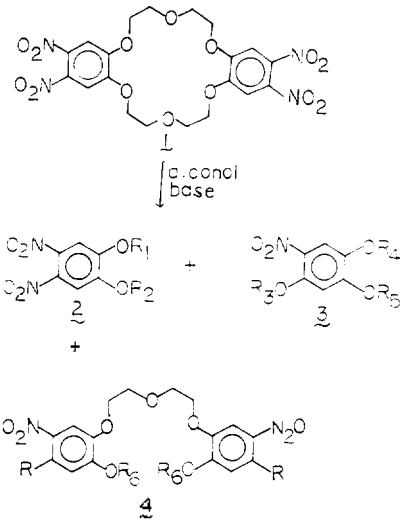
When 2-methoxyethanol was utilized, 2-methoxyethoxy substituted products in the place of some methoxy groups also obtained as the major products. Secondary alcohols did not react under this condition, presumably because of steric effect.

The products were identified through elemental analysis, mass and nmr spectroscopy. In the case of 2, 4, 5-trimethoxynitrobenzene, **5**, the molecular ion peak appears at m/e : 213.3 in the mass spectrum which corresponds to the formula $C_9H_{11}NO_5$(213) (*Fig.* 1).

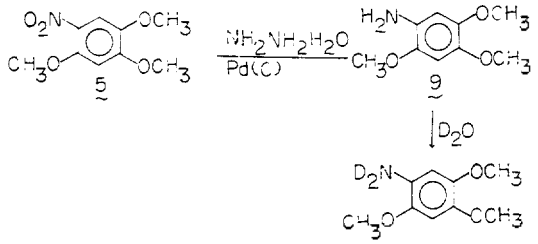
The nmr spectrum of **5** shows two aromatic proton signals, each corresponds to a single proton at 7.53 and 6.87 respectively as singlets, and two methoxy methyl proton signals corresponding six and three protons respectively at 3.94 and 3.87. Since the protons of two methyl groups at C_4 and C_5 are expected to have same chemical shift, the signal at 3.94 could be assigned to these protons. These results unequivocally support the structure of **5** to be 2, 4, 5-trimethoxynitrobenzene[4] (*Fig.* 2).

Further evidence were obtained from the reduction product, **9** from **5** with hydrazine hydrate on palladium catalyst. In **9**, the methoxy proton at 3.94 was shifted to upfield and splitted two narrowly spaced singlets at 3.65 and 3.63. A new signal due to amino proton appeared at 3.34 which was confirmed through deuterium exchange experiment (*Scheme* 2) and (*Fig.* 3).

When **1** was reacted with ethylene glycol and NaOH, a ring contraction occurred on the crown ether ring and gave dibenzo-12-crown-4 derivatives **24** and **25** (*Scheme* 3).



Scheme 1



Scheme 2

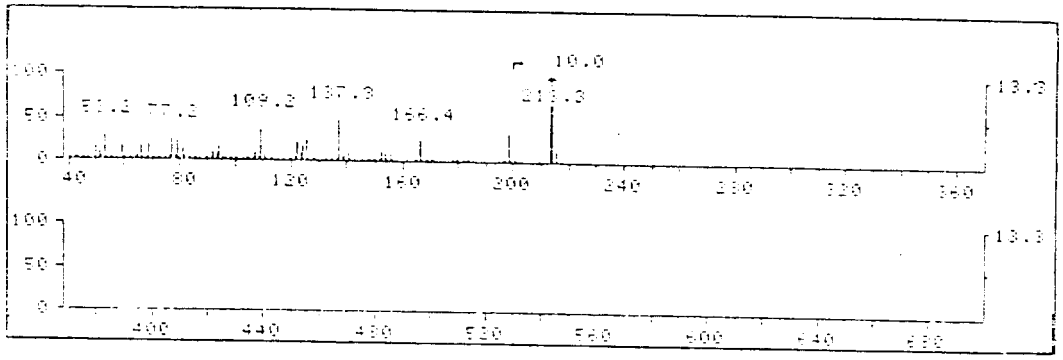


Fig. 1. Mass spectrum of 2, 4, 5-trimethoxybenzene, **5**.

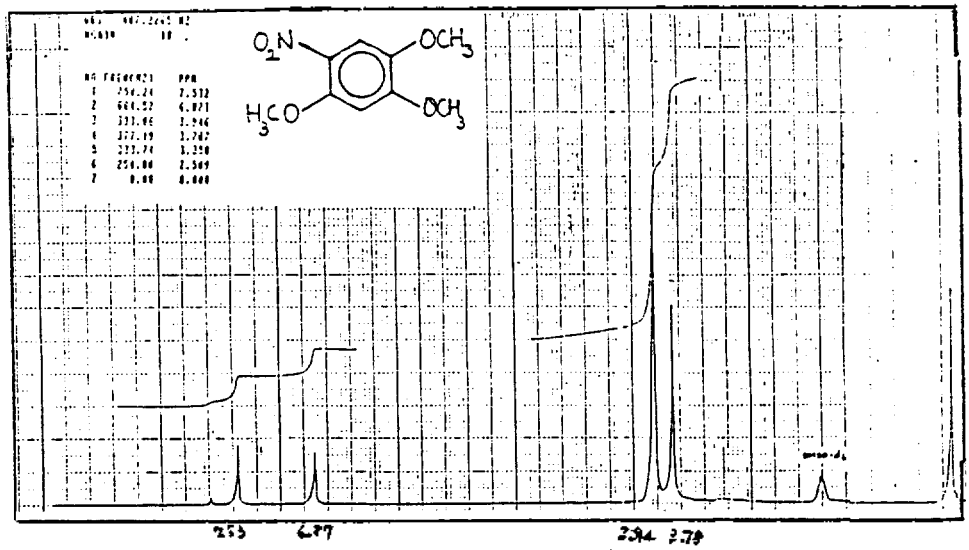


Fig. 2. ^{1}H NMR spectrum of 2, 4, 5-trimethoxybenzene, **5**.

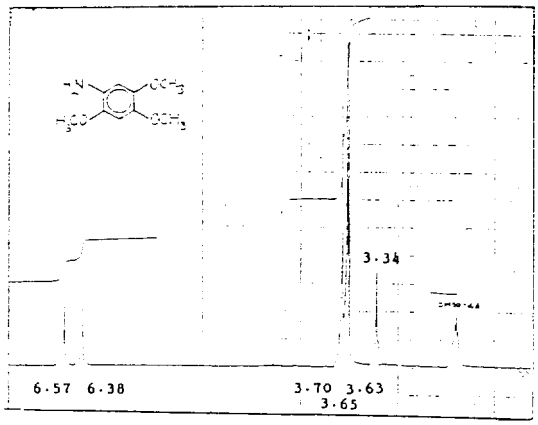
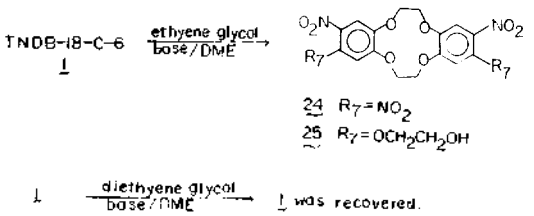


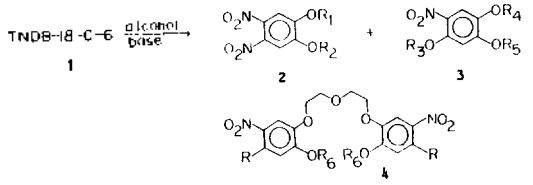
Fig. 3. ^{1}H NMR spectrum of 2, 4, 5-trimethoxyaniline[5], **9**.



Scheme 3

In the mass spectrum of **24**, the most prominent peak is $m/e=226$ corresponding to the formular of $C_8H_6N_2O_6$(226). The symmetrically

Table 1.



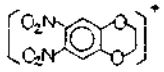
Product	Substituted groups on the products	Alcohol
5	$R_3=R_4=R_5=CH_3$	MeOH/ 2-methoxyethanol
6	$R_3=R_4=CH_3$	〃
7	$R_1=R_2=CH_2CH_2OCH_3$	〃
8	$R_3=R_4=R_5=CH_2CH_2OCH_3$	〃
9	2, 4, 5-Trimethoxyaniline	
10	$R_1=R_2=CH_3$	MeOH
11	$R=OCH_3$, $R_6=CH_3$	〃
12	$R_1=R_2=CH_2CH_3$	EtOH
13	$R_3=R_4=R_5=CH_2CH_3$	〃
14	2, 4, 5-Triethoxyacetamide	
15	$R_1=R_2=CH_2CH_2CH_3$	1-PrOH
16	$R_3=R_4=R_5=CH_2CH_2CH_3$	〃
17	$R=NO_2$, $R_6=CH_2CH_2CH_3$	〃
18	$R_1=R_2=CH_2CH_2CH_2CH_3$	1-BuOH
19	$R_3=R_4=R_5=CH_2CH_2CH_2CH_3$	〃
20	$R=NO_2$, $R_6=CH_2CH_2CH_2CH_3$	〃
21	$R_1=R_2=CH_2CH=CH_2$	Allyl alcohol
22	$R=NO_2$, $R_6=CH_2CH=CH_2$	〃
23	$R_3=R_4=R_5=CH_2C_6H_5$	Benzyl alcohol

Table 2. Yield and data of the products prepared

Products	Yield (%)	m. p(°C) (*Lit.* data)	M. S. *m/e*(M^+)	H-NMR($CDCl_3$/TMS) δ(ppm)
5	14[a] 52[b]	120~121 (128~129[4])	213	7.53(s, 1H, Ar), 6.87(s, 1H, Ar), 3.95(s, 9H, $-OCH_3$) 3.75(s, 3H, $-OCH_3$).
6	17[a]	113~115	257	7.55(s, 1H, Ar), 6.78(s, 1H, Ar), 4.00(s, 3H, $-OCH_3$) 4.25(m, 2H, $ArOCH_2CH_2OCH_3$), 3.80(m, 2H, $ArOCH_2CH_2OCH_3$).
7	21[a]	76~78	316	7.48(s, 2H, Ar), 4.30(m, 4H, $ArOCH_2CH_2OCH_3$). 3.80(m, 4H, $ArOCH_2CH_2OCH_3$), 3.37(s, 6H, $-OCH_3$).
8	28[a]	70~70.5	345	7.53(s, 1H, Ar), 6.67(s, 1H, Ar), 4.15(m, 6H, $ArOCH_2CH_2OCH_3$). 3.75(m, 6H, $ArOCH_2CH_2OCH_3$), 3.48(s, 9H, $-OCH_3$).
9	42	88~89 (92~93 C)		6.57(s, 1H, Ar), 6.38(s, 1H, Ar), 3.70(s, 3H, $-OCH_3$), 3.65(s, 3H, $-OCH_3$), 3.63(s, 3H, $-OCH_3$), 3.34(s, 2H, NH_2).
10	3[b]	127~128 (129~131[6])	228	7.30(s, 2H, Ar), 3.98(s, 6H, $-OCH_3$).
11	4[b]	151~153	468	7.60(s, 2H, Ar), 6.50(s, 2H, Ar), 4.18(m, 8H, $ArOCH_2CH_2OR$), 3.95(s, 12H, $-OCH_3$).
12	23	54~56		7.18(s, 2H, Ar), 4.15(q, 4H, $-OCH_2CH_3$), 1.43(t, 6H, $-OCH_2CH_3$).
13	32	59~60	255	7.55(s, 1H, Ar), 5.45(s, 1H, Ar), 4.08(m, 6H, $-OCH_2CH_3$), 1.45(t, 6H, $-OCH_2CH_3$).
14		133~134.5		8.18(s, 1H, Ar), 7.75(br. s, 1H, Ar), 4.08(q, 6H, $-OCH_2CH_3$), 2.20(s, 3H, $-COCH_3$), 1.30(t, 9H, $-OCH_2CH_3$).
15	3	113	284	7.30(s, 2H, Ar), 4.05(t, 4H, $-CH_2C_2H_5$), 1.88(m, 4H, $-OCH_2CH_2CH_3$), 1.05(t, 6H, $-OCH_2CH_2CH_3$).
16	53	78	297	7.55(s, 1H, Ar), 6.53(s, 1H, Ar), 4.00(m, 6H, $-OCH_2CH_2CH_3$), 1.85(m, 6H, $-OCH_2CH_2CH_3$), 1.05(m, 9H, $-OCH_2CH_2CH_3$).
17	4	147	554	7.40(s, 4H, Ar), 4.28(m, 4H, $ArOCH_2CH_2OR$), 3.85(m, 8H, $ArOCH_2C_2ORH$ and $-OCH_2CH_2CH_3$), 1.83(m, 4H, $-OCH_2CH_2CH_3$), 1.05(m, 6H, $-OCH_2CH_2CH_3$).
18	12	116~117		7.28(s, 2H, Ar), 4.13(t, 4H, $-OCH_2(CH_2)CH_3$), 1.65(m, 8H, $-OCH_2(CH_2)_2CH_3$), 1.03(t, 6H, $-OCH_2(CH_2)_2CH_3$.
19	58	77.5~79	339	7.58(s, 1H, Ar), 6.53(s, 1H, Ar), 4.03(m, 6H, $-OCH_2(CH_2)_2CH_3$), 1.72(m, 12H, $-OCH_2(CH_2)_2CH_3$). 1.00(t, 9H, $-OCH_2(CH_2)_2CH_3$.
20	3	151	582	7.45(s, 4H, Ar), 4.30(m, 4H, $ArOCH_2CH_2OR$), 4.00(m, 8H, $-OCH_2(CH_2)_2CH_3$ and $ArOCH_2CH_2OR$), 1.63(m, 8H, $-OCH_2(CH_2)_2CH_3$), 1.00(t, 6H, $-OCH_2(CH_2)_2CH_3$).
21	23	81~83	280	7.35(s, 2H, Ar), 6.40(m, 2H, $-OCH_2CH=CH_2$), 5.40(d of d, 4H $-OCH_2CH=CH_2$), 4.08(d, 4H, $-OCH_2CH=CH_2$).
22	11	131~132	550	7.28(s, 4H, Ar), 6.00(m, 2H, $-OCH_2CH=CH_2$). 5.50(m, 2H, $-OCH_2CH=CH_2$), 5.00(s, 2H, $-OCH_2CH=CH_2$), 4.62(d, 4H, $-OCH_2CH=CH_2$), 4.22(m, 4H, $ArOCH_2CH_2OR$), 3.95(m, 4H, $ArOCH_2CH_2OR$).
23	62	128	441	7.68(s, 1H, Ar), 7.38(s, 15H, Ar), 6.70(s, 1H, Ar), 5.10(s. 6H, $-OCH_2-\phi$).
24	23	119~120	(*m/e*)226 (100%)	7.40(s, 4H, Ar), 4.40(s, 8H, crown ether ethylene).
25	35	106~107	(*m/e*)241 (100%)	7.50(s, 2H, Ar), 6.82(s, 2H, Ar), 4.92(t, 1H, OH), 4.35(s, 8H, crown ether ethylene). 4.12(m, 4H, $ArOCH_2CH_2OH$), 3.75(m, 4H, $ArOCH_2CH_2OH$).

[a] From methanol and 2-methoxyethanol mixed. [b] From methanol only.

substituted crown ethers usually gives a peak corresponding a half of the molecule as the most prominent peak in their mass spectrum.

In this case, it is  $m/e=226$.

Same phenomena was observed with **25** which gave prominent peak at 241 (*Fig.* 4).

The nmr spectrum of **24** is quite simple with only twe singlet proton signals at 7.40(4H) and 4.40(8H) which correspond to two each aromatic protons and methylene protons in the crown ether ring respectively (*Fig.* 5).

The reaction with diethylene glycol was also examined. In this reaction only the starting material **1** was recovered. These results indicated that the cleaved crown ether went through recyclization subsequently form a crown ether ring again, presumably following the sequence as bellow (*Scheme* 4).

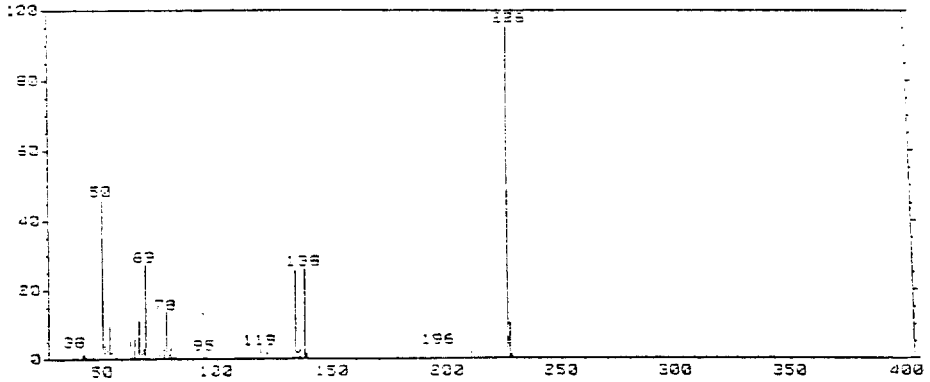


Fig. 4. Mass spectrum of tetranitrodibenzo-14-crown-4.

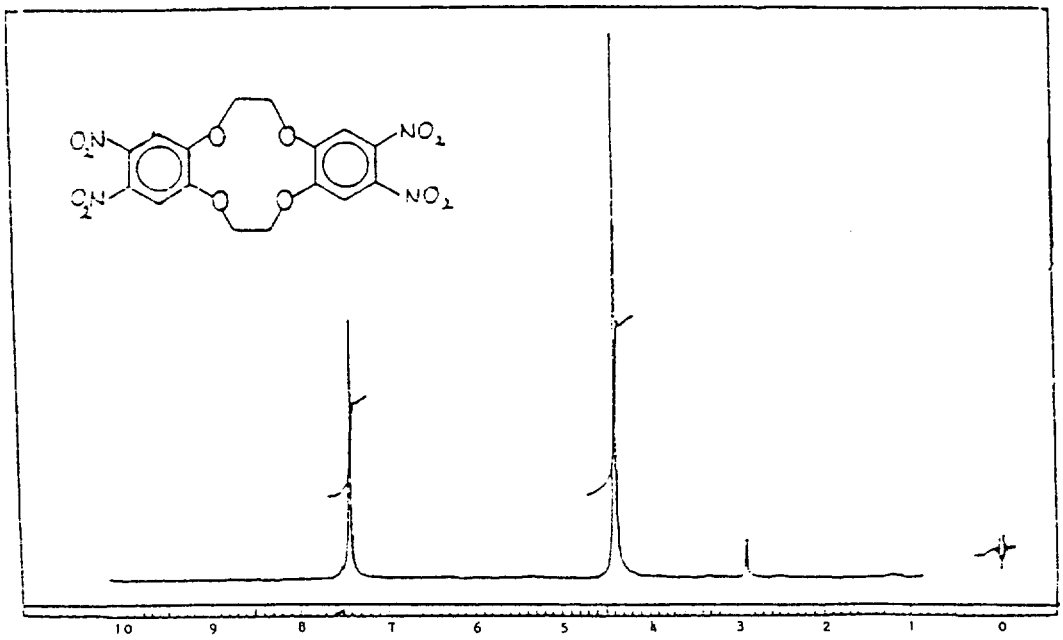
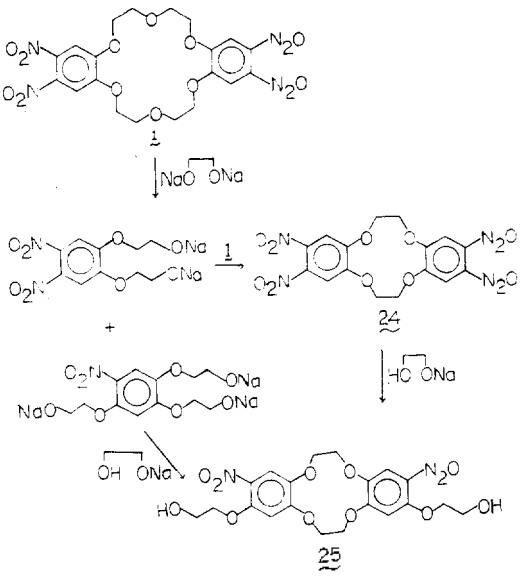
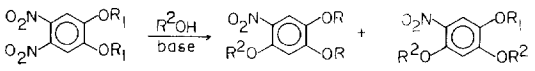


Fig. 5. ^{1}H NMR spectrum of tetranitrodibenzo-14-C-4. **24**.



Scheme 4



Scheme 5

The effects of molar ratio of NaOH/alcohol and reaction temperature were also examined. The best results were obtained for the molar ratio beween 1 : 10 and 1 : 20 in most cases. Prolonged heating at high temperature resulted darkening of the reaction mixture and accordingly diminishing of the yield. The best result obtained at the temperature range between 60 ~80°C, and the reaction time for 10~18 hrs. For the lower temperature and shorter reaction time, disubstitution prevailed. This presumption was supported from the fact that when the purified **2** was further treated with alcoholic NaOH solution, one of the nitro groups was substituted with an alkoxyl group to give **3** (*Scheme* 5).

The type of compounds, 2, 4, 5-trialkoxyanilines or phenol are usually difficult to obtain so that not many of them were known yet. The nucleophilic substitution reaction described here offers a convenient route to synthesize these kinds of compounds.

EXPERIMENTAL

Melting point were determined on Gallenkamp capillary melting point apparatus and were uncorrected. IR spectra were obtained with Perkin-Elmer 710B and 283 spectrometers. NMR spectra were recorded on varian EM-360 A spectrometer and JEOL, JNM-FX 100FT-NMR spectrometer. Mass spectra and elemental analysis were provided courtesy of Mr. D. Shin (Lucky Chem. Lab.) and Dr. P. Cho (Univ. of Cal.). Tetranitrodibenzo-18-crown-6 was synthesized from dibenzo-18-crown-6 according to the previously reported procedure. All of the reaction were carried out in a nitrogen atmosphere.

Preparation of 5, 6, 7 and 8.

5 : 2, 4, 5-Trimethoxynitro benzene.

6 : 2, 5-Dimethoxy-4-(2-methoxyethoxy)nitrobenzene.

7 : 1, 2-Di-(2-methoxyethoxy)-4, 5-dinitrobenzene.

8 : 2, 4, 5-tri-(2-methoxyethoxy) nitrobenzene.

2-Methoxyethanol(20m*l*) was added to 1.08g (2mmol) of TNDB-18-C-6 : **1**. 3% methanolic NaOH(10m*l*) was added dropwise to the mixture. Temperature was raised slowly and refluxed for 1hr. Yellow colored reaction mixture became a dark red solution by the end. Most of the alcohol was removed *in vacuo*. It was neut ralized with d-HCl and diluted with water. It was extracted with methylene chloride and washed with water, and dried over anhydrous $MgSO_4$. Solvent evaporation gave reddish gum. It was chromatographed on silica gel column to give four products from pet. ether : methylene chloride(1 : 2) and more polar fractions.

Preparation of 9: 2, 4, 5-trimethoxyaniline.

Ethanol(10m*l*) was added to 102mg(0.5mmol)

of **5**. To this 3-4 drops of 64% hydrazine hydrate and 20mg of Pd(C) were added, was and refluxed for 20min. After filteration of the used catalyst, the filterate was concentrated to give small volume *in vacuo*. After being diluted with water, it was extracted with methylene chloride and washed with water, and solvent evaporation, gave colorless solid. It was recrystallized from pet. ether and ethyl acetate as needles.

Preparation of 10 and 11.

10 : 1, 2-Dimethoxy-4, 5-dinitrobenzene.

11 : Bis[(2, 4-dimethoxy-5-dinitrophenoxy)-ethyl]ether.

DME(15m*l*) was added to 540mg(1mmol) of **1**. and 80mg(2mmol) of powdered NaOH and 0.8m*l* of dried methanol were added to the mixture. Temperature was raised slowly and refluxed for 3hrs. The workup was carried out by almost same procedure described in prep. of **5**. The major product (52% by weight) was **5** and the two minor products were **10** and **11**.

Preparation of 12 and 13.

12 : 4, 5-Diethoxy-1, 2-dinitrobenzene.

13 : 2, 4, 5-Triethoxynitrobenzene.

DME(10m*l*) was added to 540mg(1mmol) of **1**. 80mg(2mmol) of powdered NaOH and 2.9m*l* of abs. ethanol were added to the mixture. Temperature was raised slowly and refluxed for 3hrs. The workup was carried out by almost same procedure described before. Silica gel column chromatography afforded two products which were recrystallized from cold ethanol as needles.

Preparation of 14: 2,4,5-triethoxyacetanilide.

Ethanol(10m*l*) was added to 128mg(0.5mmol) of **13**. To this, 3 drops of 64% hydrazine hydrate and 20mg of Pd(C), were added, and refluxed for 20min. After filteration of used catalyst, the filterate was evaporated to give small volume. After dilution with water, it was extracted with methylene chloride, and the extract was washed with water and dried. The concentrated product showed the presence of aniline in nmr spectrum. To the product 3m*l* of acetic acid and a drop of acetic anhydride were added. To the resulting solution aqeous sodium acetate, were added. It afforded white precipitates. It was dissolved in methylene chloride and washed with water. Solvent evaporation gave a white powder.

Preparation of 15, 16 and 17.

15 : 4, 5-Dipropoxy-1, 2-dinitrobenzene.

16 : 2, 4, 5-Tripropoxynitrobenzene.

17 : Bis[(4, 5-dinitro-2-propoxyphenoxy) ethyl] ether.

DME(15m*l*) were added to 540mg of **1**. Powdered 80mg of NaOH and 1.20g of dried 1-propanol were added to the mixture. Temperature was raised slowly to 70°C, stirred for 18 hrs. The workup was carried out by almost same procedure described before.

Preparation of 18, 19 and 20.

18 : 4, 5-Dibutoxy-1, 2-dinitrobenzene.

19 : 2, 4, 5-Tributoxynitrobenzene.

20 : Bis[(2-butoxy-4, 5-dinitrophenoxy)ethyl] ether.

1-Butanol(15m*l*) and 56mg of KOH were added to 540mg of **1**. Temperature was raised slowly to 80°C and stirred for 2hrs. The workup was carried out by almost same procedure described before. It was chromatographed on silica gel column to give three products from pet. ether : ethyl acetate (1 : 2), (1 : 4) and successive increment of the solvent porality.

Preparation of 21 and 22.

21 : 4, 5-Diallyloxy-1, 2-dinitrobenzene.

22 : Bis[(2-allyloxy-4, 5-dinitrophenoxy)ethyl]ether.

KOH (56mg) and 20m*l* of ally alcohol were added to 540mg of TNDB-18-C-6. Temperature was raised to 80°C and stirred for 2hrs. The workup was carried out by almost same procedure described before. The isolated gum was

cheomatographed on alumina to give two products from hexane : ethyl acetate(1 : 2), ethyl acetate : methylene chloride : methanol (2 : 1 : 0.1) successively.

Preparation of 23 : 2, 4, 5-Tribenzyloxynitrobenzene.

DME(15m*l*) was added to 540mg of **1**. Powdered 80mg of NaOH and 4.32g of benzyl alcohol were added in small portion. Temperature was raised slowly to 80 C and stirred for 18hrs. The reaction mixture was neutralized with d-HCl. The solvent and benzyl alcohol were removed in vacuo. Cold water-ethanol mixture (5 : 1) was added to produce yellow precipitates which was crystallized from pet. ether and ethyl acetate mixture as needles.

Preparation of 24 and 25.

24 : 16, 17, 20. 21-TNDB-12-C-4.

25 : 17, 20-Di-(2'-hydroxyethoxy)-16, 21-DNDB-12-c-4.

DME(15m*l*) was added to 540mg of **1**. 80 mg of NaOH and 1.24g of ethylene glycol were added to the reaction mixture. It was stirred at 70C for 18hrs. The reaction mixture was neutralized with d-HCl. Solvent was evaporated under reduced pressure and diluted with water. It was extracted with methylene chloride several times and the extract was dried with anhydrous $MgSO_4$. Solvent evadoration gave solid which was purified with silica gel column chromatography.

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