

Yoichi Habata,* Tomomi Saeki, Atsushi Watanabe, and Sadatoshi Akabori

Department of Chemistry, Faculty of Science, Toho University, Funabashi, Chiba 274-8510, Japan

Jerald S. Bradshaw

Department of Chemistry and Biochemistry, Brigham Young University, Provo, UT 84602, USA

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Armed-azacrown ethers having phenols as a side arm were synthesized by the Mannich reaction of 2,6-disubstituted phenols with *N*-methoxymethylmonoaza-12-crown-4 ether. When the groups next to OH of the phenols are Me, *i*-Pr, *t*-Bu, OMe, F, Ph and $-\text{CH}_2\text{CH}=\text{CH}_2$, armed-azacrown ethers **13-20** were obtained. On the other hand, the reaction using dichloro- and dibromophenols gave salts of dihydroxydiphenylmethane with monoaza-12-crown-4 ether **21** and **22**. The oxidized product **23b** of 4,4'-bis(2-methyl-1-hydroxynaphthyl)methane **23a** was obtained when 2-methyl-1-naphthol was allowed to react with *N*-methoxymethylmonoaza-12-crown-4 ether. The structures of these salts and dinaphthylmethane derivatives were confirmed by X-ray crystallography. It is proposed that the acidity and the electrostatic charge of the phenols and naphthols are an indication of the reactivity of the 2,6-disubstituted phenols for the Mannich reaction.

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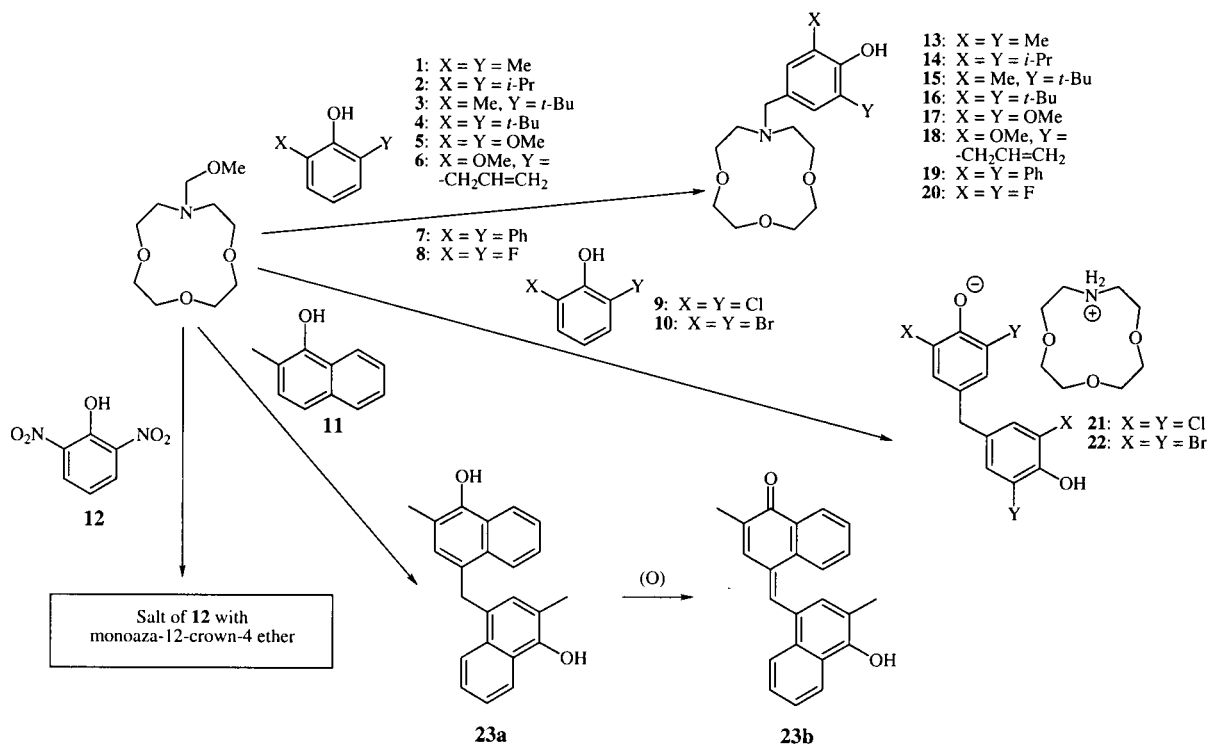
The Mannich reaction [1] is a useful reaction to prepare armed-azacrown ethers and cryptands. A variety of armed- and double armed-azacrown ethers having phenols or naphthols as additional binding sites have been prepared in good yields by treating the appropriate phenols or naphthols with *N*-methoxymethyl-substituted azacrown ethers [2,3]. Recently, we reported that armed-azacrown ether **13** which was prepared by the Mannich reaction of *N*-methoxymethylmonoaza-12-crown-4 ether with 2,6-dimethylphenol (**1**) in benzene forms a polymer-like (2:2)_n complex with rubidium cation [3]. We have prepared many armed-monoaza-12-crown-4 ethers having various groups next to the phenolic OH group in the side arm, because we believe the spatial circumstance around the phenolic OH group would be important in forming a polymer-like complex. In some cases, side reaction products have been obtained instead of the armed-azacrown ethers. Although many armed-azacrown ethers have been synthesized using the Mannich reaction, there is no report on the side reaction products. Here we report the syntheses of *p*-phenol armed-azacrown ethers and the molecular structures of the side reaction products. We propose that *pH* values and electrostatic charges of the 2,6-disubstituted phenols are useful indicators for reactivity for the Mannich reaction.

New armed-azacrown ethers were prepared by the reactions of various 2,6-disubstituted phenols with *N*-methoxymethylmonoaza-12-crown-4 ether (Scheme 1). Using phenols **2-4** and **8** allowed the preparation of the corresponding armed-azacrown ethers **14-16** and **20** in *ca.*

70% yields. When **5-7** were used, the yields of armed-azacrown ethers **17-19** were lower (27-47%) because **17-19** decomposed during separation using column chromatography. Structures of these compounds were confirmed by ¹H nmr, ei-ms and combustion analyses. In all of these reactions, side reaction products were not observed.

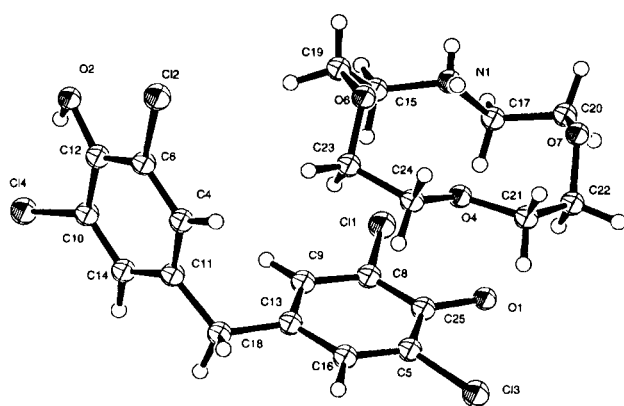
When **9** and **10** were used for the reaction, side reaction products were obtained instead of the desired armed-azacrown ethers. Structures of the side reaction products were confirmed by ¹H nmr, ei-ms and combustion analyses. In the ¹H nmr spectrum of **21**, a singlet at $\delta = 7.02$ for the aromatic protons, four triplets at $\delta = 3.75, 3.69, 3.58$ and 2.85 for the methylene protons of the crown ring, a singlet at $\delta = 3.72$ for the methylene protons of Ph-CH₂-Ph and a broad singlet at $\delta = 3.22$ for the OH and NH₂ protons were observed. In the ei-ms of **21**, peaks at 176, 336, 338 and 340 are assigned for [12-crown-4+H]⁺, [(HO-C₆H₂Cl₂)₂-CH₂-2H]⁺, [(HO-C₆H₂Cl₂)₂-CH₂-2H+2]⁺ and [(HO-C₆H₂Cl₂)₂-CH₂-2H+4]⁺, respectively. The structure of **22** was confirmed in the same manner. In order to investigate the detailed structures of the side reaction products, X-ray crystal studies were performed. Figure 1 shows the ORTEP diagrams, selected bond lengths and bond angles of compounds **21** and **22**. Two hydrogens on the N atoms in the crown ethers and a hydrogen of the phenolic OH group were found by the difference syntheses in the X-ray analysis. Compounds **21** and **22** consist of two parts; one is a diphenylmethane derivative and the other is monoaza-12-crown-4 ether.

Scheme 1

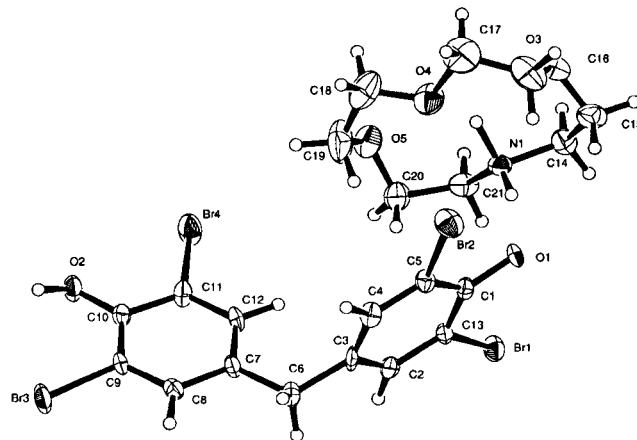


Two phenol units are bridged at position 4 by CH₂ to form diphenylmethane derivatives. One phenolic OH group of the diphenylmethane forms a salt with the amine moiety of monoaza-12-crown-4 ether such as [R₂NH₂]⁺

[HOPh-CH₂-Ph-O]⁻. The bond lengths O (phenolic OH)-C (benzene) for **21** and **22** are in the range 1.30-1.34 Å. The bond lengths C (bridge carbons: C19 in **21**, C6 in **22**)-C (bridgehead carbons of phenyl group) are in the



O1-C25: 1.34(1), O2-C12: 1.33(1),
 C8-C9: 1.39(1), C5-C16: 1.36(1),
 C13-C18: 1.51(1), C11-C18: 1.51(1),
 ∠ C11-C18-C13: 115.3(8)

21

O1-C1: 1.30(1), O2-C10: 1.34(1),
 C4-C5: 1.38(1), C2-C13: 1.39(1),
 C3-C6: 1.51(1), C6-C7: 1.53(1),
 ∠ C3-C6-C7: 115.0(9)

22

Figure 1. The ORTEP drawings, selected bond lengths (Å) and bond angles (°) of **21** and **22**.

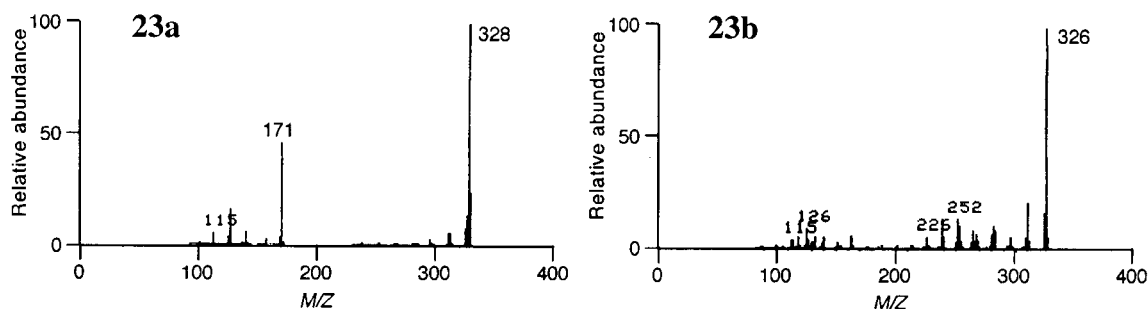


Figure 2. Mass spectra of **23a** and **23b**.

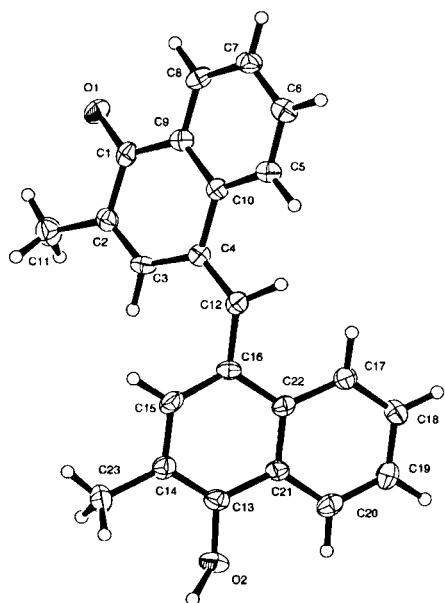
range 1.51-1.53 Å. The angles C11-C18-C13 for **21** and C3-C6-C7 for **22** are 115.3 and 115.0°, respectively.

On the other hand, the reaction of 2-methyl-1-naphthol with the *N*-methoxymethyl crown ether gave two compounds; 4,4'-bis(2-methyl-1-hydroxynaphthyl)methane (**23a**) and its oxidized analog **23b**. The structure of **23a** was confirmed by ^1H nmr spectroscopy and ei-ms. Combustion analysis was not measured because **23a** is easily oxidized to give **23b**. The structure of the oxidized compound **23b** was confirmed by ^1H nmr, ei-ms, combustion analysis and X-ray crystallography. In the ^1H nmr spectrum, five signals for the aromatic protons of **23a** appeared at $\delta = 8.21$ (d), 7.95 (d), 7.50 (t), 7.43 (t), and 6.84, (s), while the signals for the aromatic protons of **23b** were more complicated than those of **23a** (see Experimental). Figure 2 shows the mass spectra of **23a** and **23b**. Peaks at 171 and 328 in the spectrum of **23a** and a peak at 326 in the spectrum of **23b** are assigned for $[\text{M}-\text{C}_{11}\text{H}_9\text{O}]^+$ and $[\text{M}]^+$ of **23a** and $[\text{M}]^+$ of **23b**, respectively. These ms peaks indicate that **23b** is the oxidized form of **23a**. The ORTEP diagram of **23b** is

shown in Figure 3. The bond lengths O1-C1, C2-C3 and C4-C12 are 1.246, 1.342 and 1.357 Å, respectively, and the angle C4-C12-C16 is 127.6°. The O2-C13 bond length in the naphthol ring is 1.359 Å. These results show that the O1-C1 bond is a C=O double bond and the C2-C3 and C4-C12 bonds are C=C double bonds.

When 2,6-dinitrophenol (**12**) was used in the reaction, a salt of monoaza-12-crown-4 ether with **12** was recovered in a 14% yield.

It is well known that the formation process of an iminium ion from a primary amine with formaldehyde in the Mannich reaction is a reversible reaction [1]. Also, the reaction of phenols with formaldehyde have been used for the preparation of diphenylmethane derivatives such as 5,5'-dichloro-2,2'-dihydroxydiphenylmethane and 2,2'-dihydroxy-3,5,6,3',5',6'-hexachlorodiphenylmethane which are well known as disinfectants [4]. Therefore, it is reasonable to assume that *N*-methoxymethylmonoaza-12-crown-4 ether is dissociated by some of the acidic phenols to form monoaza-12-crown-4 ether and formaldehyde,



O1-C1: 1.246(8),
 O2-C13: 1.359(9),
 C2-C3: 1.342(9),
 C9-C10: 1.413(9),
 C4-C12: 1.357(9),
 C12-C16: 1.457(10),
 \angle C4-C12-C16: 127.6(8)

Figure 3. The ORTEP drawing, selected bond lengths (Å) and bond angle (°) of **23b**.

Table 1
pH Values in Methanol (1.0 mole/l, 25°C) and Electrostatic Charges at Position 4 Carbons (AM1 level)
 of 2,6-Disubstituted Phenols and 2-Methyl-1-naphthol

Compound No.	Substituted groups at positions 2 and 6	<i>pH</i>	Electrostatic charge (electrons)
1	(X = Y = Me)	7.3	-0.11
2	(X = Y = <i>i</i> -Pr)	6.7	-0.15
3	(X = Me, Y = <i>t</i> -Bu)	6.8	-0.13
4	(X = Y = <i>t</i> -Bu)	6.9	-0.10
5	(X = Y = OMe)	6.6	-0.15
6	(X = OMe, Y = -CH ₂ CH=CH ₂)	6.7	-0.12
7	(X = Y = Ph)	7.3 [a]	-0.13
8	(X = Y = F)	5.2	-0.10
9	(X = Y = Cl)	4.5	-0.22
10	(X = Y = Br)	4.6	-0.26
11	2-methyl-1-naphthol	4.3	-0.22
12	(X = Y = NO ₂)	1.8	-0.23

[a] The *pH* value of 7 was measured in a mixed solution of methanol and benzene (1:1), because 7 did not dissolve in methanol.

and the formaldehyde reacts with the phenols to form the dihydroxydiphenylmethane derivatives. To investigate the acidity of these 2,6-disubstituted phenols, *pH* values in methanol solution (or a mixed solution of methanol and benzene (1:1)) of the phenols and 2-methyl-1-naphthol

were measured. As shown in Table 1, the phenols which gave the Mannich products show slightly acidic-neutral *pH* values (*pH* = 5.2-7.3), while the *pH* values of 2,6-dichloro- and 2,6-dibromophenols and 2-methyl-1-naphthol are lower (4.5, 4.6 and 4.3, respectively). In addition,

Table 2
 Crystal and Selected Experimental Data for Compounds 21, 22 and 23b

	21	22	23b
Formula	C ₂₁ H ₂₅ NO ₅ Cl ₄	C ₂₁ H ₂₅ NO ₅ Br ₄	C ₂₃ H ₁₈ O ₂
<i>M</i>	513.24	691.05	326.39
Crystal system	orthorhombic	monoclinic	monoclinic
Space group	Pna2 ₁	P2 ₁ /n	P2 ₁ /n
<i>a</i> /Å	23.657(6)	11.790(4)	18.488(6)
<i>b</i> /Å	8.435(10)	8.44(1)	4.981(6)
<i>c</i> /Å	11.672(7)	24.981(4)	19.218(5)
β/°		92.78(2)	109.03(2)
<i>U</i> /Å ³	2328(4)	2481(3)	1673(1)
<i>Z</i>	4	4	4
<i>D_c</i> /g cm ⁻³	1.464	1.849	1.296
<i>F</i> (000)	1064.00	1352.00	688.00
μ(Mo-Kα)/cm ⁻¹	5.40	65.38	0.81
Crystal dimensions/mm	0.40x0.20x0.40	0.20x0.05x0.75	0.10x0.10x0.50
No. of reflections for unit cell determination (2θ range)/°	25 (21.8-29.8)	22 (25.6-29.6)	19 (20.4-24.0)
Scan width/°	1.47+0.30tanθ	0.79+0.30tanθ	0.94+0.30tanθ
No. reflections measured	3063	6383	4425
unique (R _{int})	3061 (0.099)	6097 (0.057)	4298 (0.141)
used [<i>I</i> > 3.00σ(<i>I</i>), N _o]	1110	1964	914
R	0.040	0.046	0.056
R'	0.044	0.049	0.058
Goodness of fit [a]	1.22	1.26	1.56
No. parameters, N _p	292	280	226
Maximum shift/error in final cycle	0.05	0.01	0.01
Maximum, minimum peaks in final difference map/e Å ⁻³	0.20, -0.16	0.65, -0.48	0.32, -0.26

[a] Details in common: ω-2θ scan; scan range 2θ 0-55°; R = Σ||*F_o*|-|*F_c*||/Σ|*F_o*|, R'=[Σw(|*F_o*|-|*F_c*||)²Σw*F_o*²]^{1/2}, goodness of fit [Σw(|*F_o*|-|*F_c*||)²/(N_o-N_p)]^{1/2}.

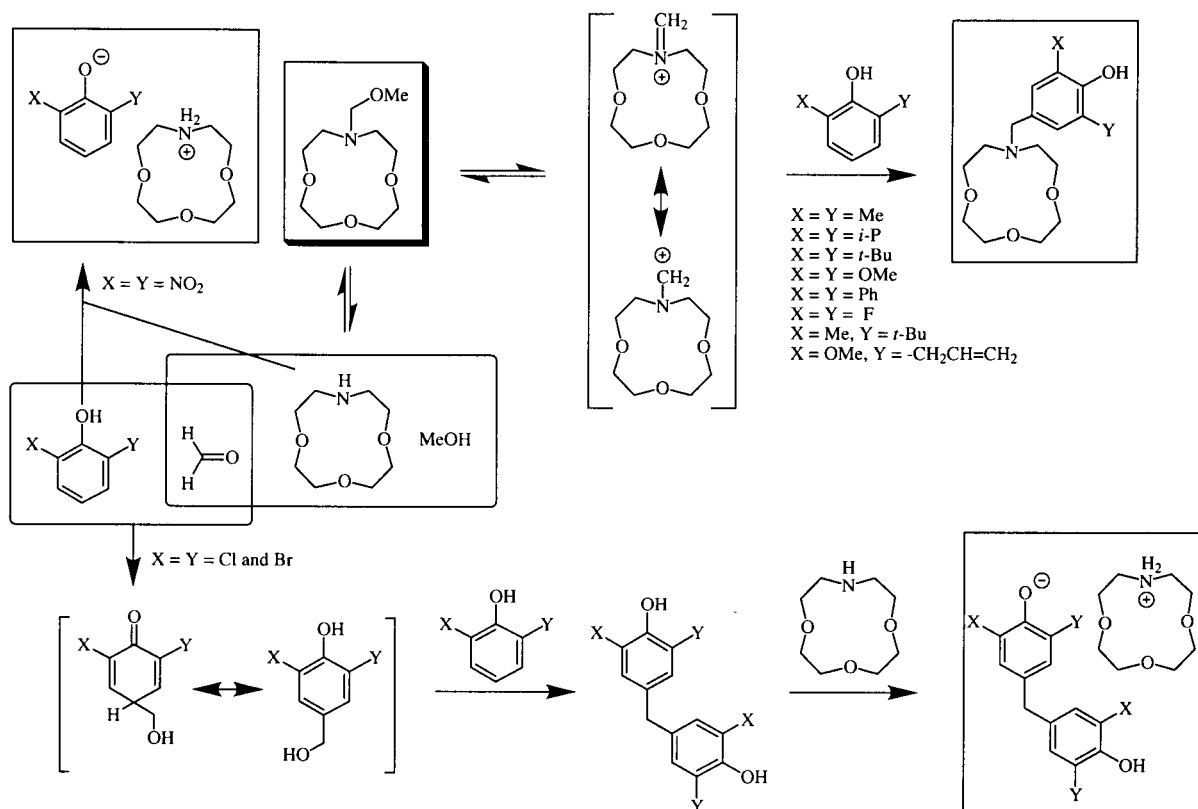


Figure 4. A postulated reaction mechanism to form the Mannich reaction and the side reaction products.

2,6-dinitrophenol, which did not give any reaction product, is a strong acid ($\text{pH} = 1.8$). Thus, the 2,6-disubstituted phenols which do not undergo the Mannich reaction are also the strongest acids. These results indicate that *N*-methoxymethylmonoaza-12-crown-4 ether is probably dissociated into formaldehyde and monoaza-12-crown-4 ether by the medium-strong acidic phenols.

In order to understand the difference in the reactivity of the 2,6-disubstituted phenols and the naphthol, the electrostatic charge at the position 4 carbon atom of the phenols and naphthol were calculated. The electrostatic charge is a scheme whereby atomic charges are chosen to best match the electrostatic potential at points surrounding a molecule, subject to overall charge balance [5]. Relative electron density of the carbon at position 4 in a series of 2,6-disubstituted phenols can be compared by the values of the electrostatic charge, and the electrostatic charge would be an indicator of the reactivity. The electrostatic charges at the position 4 carbon of the 2,6-disubstituted phenols were calculated in the AM1 level and are summarized in Table 1. The values for the position 4 carbons differ distinctly between **1-8** (in the range $-0.10 \sim -0.15$ electrons) and **9-12** (in the range $-0.22 \sim -0.26$ electrons). The electrostatic charges at the position 4 carbons of the 2,6-disubstituted phenols having Cl and Br at the 2,6-posi-

tions to the phenolic OH group are lower than that of the 2,6-dialkyl-, 2,6-difluoro-, and 2,6-dimethoxy- substituted phenols. Thus, 2,6-dichloro- and 2,6-dibromophenols and 2-methyl-1-naphthol, which have higher electron densities at the position 4 carbon, react with formaldehyde to give the dihydroxydiphenylmethane derivatives. 2,6-Dinitrophenol did not give the corresponding dihydroxydiphenylmethane derivative, because 2,6-dinitrophenol forms a stable salt with monoaza-12-crown-4 ether because of its very strong acidity.

The results of the *pH* measurements and calculations of electrostatic charge lead us to describe a reaction mechanism for the Mannich and the side reaction products (Figure 4). First, when the 2,6-disubstituted phenols which have low acidity are used, the phenols readily react with the iminium ion derived from *N*-methoxymethylmonoaza-12-crown-4 ether to give the Mannich products **13-20**. Second, in the case of using the more acidic 2,6-disubstituted phenols, the *N*-methoxymethylmonoaza-12-crown-4 ether dissociates into formaldehyde and monoaza-12-crown-4 ether, and the formaldehyde reacts with the phenols having lower electrostatic charge (higher reactivity toward formaldehyde) at the position 4 carbon to give hydroxymethylphenol and/or hydroxymethylquinone intermediates leading to the dihydroxy-

diphenylmethane derivatives **21-23a**. Third, a very strong acid such as **12** does not form either the Mannich or the

side reaction products. If the postulated reaction mechanism is correct, a mixture of formaldehyde, monoaza-12-

Table 3
Atomic Coordinates and B_{iso}/B_{eq} for **21**

atom	x	y	z	B_{eq}
Cl(1)	0.78054(10)	0.0997(3)	0.615(2)	4.41(6)
Cl(2)	0.8830(1)	0.5735(3)	1.087(2)	5.08(7)
Cl(3)	0.9562(1)	0.3223(4)	0.371(2)	5.96(8)
Cl(4)	0.8899(1)	-0.0504(3)	1.177(2)	5.50(8)
O(1)	0.8354(3)	0.2201(9)	0.413(2)	4.1(2)
O(2)	0.8474(3)	0.2781(8)	1.202(2)	3.5(2)
O(4)	0.8669(3)	0.6718(10)	0.553(2)	5.5(2)
O(6)	0.8399(3)	0.765(1)	0.776(2)	6.0(2)
O(7)	0.7715(4)	0.7381(9)	0.414(2)	5.3(2)
N(1)	0.7534(4)	0.637(1)	0.643(2)	3.7(2)
C(4)	0.9338(4)	0.358(1)	0.951(2)	3.4(3)
C(5)	0.9277(4)	0.258(1)	0.500(2)	3.1(2)
C(6)	0.9018(4)	0.379(1)	1.050(2)	2.8(2)
C(8)	0.8509(3)	0.162(1)	0.606(2)	2.8(2)
C(9)	0.8837(4)	0.153(1)	0.704(2)	3.6(2)
C(10)	0.9056(4)	0.110(1)	1.086(2)	3.1(2)
C(11)	0.9500(4)	0.208(1)	0.918(2)	3.5(3)
C(12)	0.8839(4)	0.255(1)	1.118(2)	2.8(2)
C(13)	0.9403(4)	0.197(1)	0.700(2)	3.6(3)
C(14)	0.9358(4)	0.082(1)	0.989(2)	3.8(3)
C(15)	0.7725(5)	0.553(1)	0.747(2)	4.7(3)
C(16)	0.9611(4)	0.250(1)	0.595(2)	4.1(2)
C(17)	0.7411(4)	0.530(1)	0.542(2)	4.1(3)
C(18)	0.9786(4)	0.183(1)	0.803(2)	5.0(3)
C(19)	0.7985(5)	0.666(2)	0.827(2)	6.0(4)
C(20)	0.7303(5)	0.628(2)	0.438(2)	5.4(3)
C(21)	0.8721(6)	0.730(2)	0.438(3)	7.2(4)
C(22)	0.8223(7)	0.671(2)	0.371(3)	6.2(4)
C(23)	0.8904(6)	0.685(2)	0.749(3)	6.9(4)
C(24)	0.9086(5)	0.732(2)	0.629(3)	7.3(4)
C(25)	0.8711(4)	0.213(1)	0.503(2)	2.9(2)
H(1)	0.9436	0.4526	0.9030	3.7928
H(2)	0.8682	0.1106	0.7734	4.1778
H(3)	0.9478	-0.0246	0.9618	5.3244
H(4)	1.0015	0.2747	0.5861	4.8677
H(5)	1.0098	0.2527	0.7914	7.0806
H(6)	0.9946	0.0743	0.8009	7.0806
H(7)	0.7418	0.4992	0.7819	6.0942
H(8)	0.8002	0.4730	0.7246	6.0942
H(9)	0.7733	0.4631	0.5277	5.0288
H(10)	0.7095	0.4637	0.5583	5.0288
H(11)	0.8171	0.6040	0.8882	7.2149
H(12)	0.7703	0.7273	0.8611	7.2149
H(13)	0.6949	0.6879	0.4473	6.3055
H(14)	0.7215	0.5629	0.3705	6.3055
H(15)	0.8740	0.8450	0.4418	8.8883
H(16)	0.9089	0.6959	0.4093	8.8883
H(17)	0.8199	0.5547	0.3695	7.4473
H(18)	0.8260	0.6983	0.2874	7.4473
H(19)	0.9191	0.7057	0.8091	8.1718
H(20)	0.8854	0.5706	0.7502	8.1718
H(21)	0.9474	0.7038	0.6204	9.6572
H(22)	0.9101	0.8536	0.6356	9.6572
H(24)	0.846(4)	0.18(1)	1.196(9)	3.3(5)
H(25)	0.727(4)	0.67(1)	0.66(1)	4.2(4)
H(26)	0.776(3)	0.726(8)	0.634(7)	0.6(8)

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^* \cos\gamma + 2U_{13}aa^*cc^* \cos\beta + 2U_{23}bb^*cc^* \cos\alpha)$$

Table 4
Atomic Coordinates and B_{iso}/B_{eq} for **22**

atom	x	y	z	B_{eq}
Br(1)	0.27933(8)	0.1206(2)	0.76236(4)	3.70(3)
Br(2)	0.2469(1)	-0.1923(2)	0.96183(5)	5.05(4)
Br(3)	-0.51984(9)	-0.2375(2)	0.80120(6)	5.54(4)
Br(4)	-0.2519(1)	0.3013(2)	0.85605(6)	5.81(4)
O(1)	0.3418(5)	0.0297(9)	0.8782(2)	3.2(2)
O(2)	-0.4639(5)	0.1106(9)	0.8396(3)	3.8(2)
O(3)	0.4365(7)	0.330(1)	1.0072(3)	5.1(2)
O(4)	0.2100(7)	0.231(1)	0.9996(3)	6.0(3)
O(5)	0.0802(7)	0.395(1)	0.9218(4)	5.9(3)
N(1)	0.3166(7)	0.331(1)	0.9072(3)	3.4(2)
Cl(1)	0.2516(7)	-0.040(1)	0.8605(4)	2.7(2)
C(2)	0.1016(8)	-0.085(1)	0.7903(4)	3.1(3)
C(3)	0.0427(7)	-0.186(1)	0.8227(4)	3.1(3)
C(4)	0.0885(8)	-0.216(1)	0.8743(4)	3.0(3)
C(5)	0.1885(8)	-0.144(1)	0.8918(4)	2.9(3)
C(6)	-0.0687(8)	-0.258(1)	0.8025(4)	4.0(3)
C(7)	-0.1739(7)	-0.157(1)	0.8118(4)	2.9(3)
C(8)	-0.2814(8)	-0.226(1)	0.8046(4)	3.0(3)
C(9)	-0.3768(7)	-0.137(1)	0.8135(4)	3.1(3)
C(10)	-0.3747(8)	0.018(1)	0.8305(4)	2.8(3)
C(11)	-0.2644(8)	0.086(1)	0.8360(4)	3.3(3)
C(12)	-0.1675(8)	0.001(2)	0.8264(4)	3.4(3)
C(13)	0.2026(7)	-0.016(1)	0.8089(4)	2.4(2)
C(14)	0.4337(9)	0.398(1)	0.9153(4)	4.2(3)
C(15)	0.496(1)	0.311(2)	0.9599(5)	5.1(4)
C(16)	0.398(1)	0.190(2)	1.0321(6)	7.0(5)
C(17)	0.280(1)	0.214(2)	1.0478(5)	7.9(5)
C(18)	0.095(1)	0.259(2)	1.0049(7)	8.1(5)
C(19)	0.040(1)	0.266(2)	0.9506(7)	8.7(6)
C(20)	0.1222(10)	0.362(2)	0.8711(5)	5.5(4)
C(21)	0.2405(10)	0.418(1)	0.8690(4)	4.2(3)
H(1)	0.3380	0.2217	0.8999	6.2852
H(2)	0.0725	-0.0616	0.7531	3.8075
H(3)	0.0510	-0.2905	0.8984	3.5866
H(4)	-0.2883	-0.3396	0.7939	3.7873
H(5)	-0.0933	0.0524	0.8294	3.7436
H(6)	-0.0661	-0.2811	0.7652	5.1301
H(7)	-0.0781	-0.3599	0.8207	5.1301
H(8)	0.4723	0.3934	0.8827	5.1592
H(9)	0.4291	0.5110	0.9249	5.1592
H(10)	0.5732	0.3488	0.9655	6.0870
H(11)	0.5014	0.1996	0.9507	6.0870
H(12)	0.4017	0.0984	1.0052	7.9574
H(13)	0.4524	0.1544	1.0604	7.9574
H(14)	0.2826	0.3097	1.0693	8.9168
H(15)	0.2583	0.1291	1.0702	8.9168
H(16)	0.0594	0.1841	1.0274	9.2246
H(17)	0.0830	0.3641	1.0220	9.2246
H(18)	-0.0404	0.2646	0.9488	10.3586
H(19)	0.0619	0.1660	0.9306	10.3586
H(20)	0.1217	0.2472	0.8647	6.7282
H(21)	0.0742	0.4075	0.8430	6.7282
H(22)	0.2405	0.5311	0.8768	4.8637
H(23)	0.2662	0.4074	0.8331	4.8637
H(24)	-0.5209	0.0219	0.8588	6.2852
H(25)	0.2823	0.3436	0.9501	6.2852

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^* \cos\gamma + 2U_{13}aa^*cc^* \cos\beta + 2U_{23}bb^*cc^* \cos\alpha)$$

Table 5
Atomic Coordinates and B_{iso}/B_{eq} for **23b**

atom	x	y	z	B_{eq}
O(1)	0.8475(3)	0.694(1)	0.9620(3)	4.6(2)
O(2)	0.3744(3)	-0.095(1)	0.6112(3)	4.2(1)
C(1)	0.7776(4)	0.701(2)	0.9274(4)	3.0(2)
C(2)	0.7442(4)	0.529(2)	0.8638(4)	3.1(2)
C(3)	0.6679(4)	0.526(2)	0.8316(4)	3.2(2)
C(4)	0.6141(4)	0.694(2)	0.8515(4)	2.7(2)
C(5)	0.6022(4)	1.070(2)	0.9360(4)	3.2(2)
C(6)	0.6339(5)	1.243(2)	0.9926(4)	3.7(2)
C(7)	0.7125(5)	1.244(2)	1.0288(4)	3.6(2)
C(8)	0.7574(4)	1.065(2)	1.0074(4)	3.5(2)
C(9)	0.7265(4)	0.889(2)	0.9494(4)	2.8(2)
C(10)	0.6468(4)	0.886(2)	0.9123(4)	2.7(2)
C(11)	0.7984(5)	0.355(2)	0.8406(4)	4.6(2)
C(12)	0.5372(4)	0.663(2)	0.8212(4)	3.1(2)
C(13)	0.4149(4)	0.094(2)	0.6592(4)	3.3(2)
C(14)	0.4691(0)	0.253(2)	0.6440(4)	3.3(2)
C(15)	0.5100(4)	0.438(2)	0.6989(4)	3.7(2)
C(16)	0.4962(4)	0.471(2)	0.7651(4)	2.9(2)
C(17)	0.4149(4)	0.341(2)	0.8417(4)	3.3(2)
C(18)	0.3595(5)	0.181(2)	0.8536(4)	3.6(2)
C(19)	0.3226(4)	-0.009(2)	0.8018(5)	4.0(2)
C(20)	0.3390(4)	-0.037(2)	0.7376(5)	3.7(2)
C(21)	0.3959(4)	0.123(2)	0.7249(4)	2.9(2)
C(22)	0.4358(4)	0.316(2)	0.7771(4)	2.8(2)
C(23)	0.4874(4)	0.228(2)	0.5741(4)	5.7(3)
H(1)	0.8129	1.0681	1.0342	4.1970
H(2)	0.7353	1.3655	1.0713	4.4221
H(3)	0.6006	1.3723	1.0075	4.4916
H(4)	0.5460	1.0733	0.9108	3.5803
H(5)	0.6452	0.3914	0.7920	3.7102
H(6)	0.7878	0.1618	0.8451	4.6494
H(7)	0.7934	0.3773	0.7888	4.6494
H(8)	0.8506	0.3815	0.8684	4.6494
H(9)	0.5064	0.7984	0.8492	3.9625
H(10)	0.3483	-0.0648	0.5525	3.9625
H(11)	0.5506	0.5481	0.6888	3.5087
H(12)	0.4420	0.4752	0.8801	4.1456
H(13)	0.3163	0.2065	0.8980	4.2035
H(14)	0.2827	-0.1205	0.8117	4.1840
H(15)	0.3102	-0.1770	0.7023	4.5244
H(16)	0.4430	0.2542	0.5302	5.1779
H(17)	0.5063	0.0470	0.5678	5.1779
H(18)	0.5262	0.3500	0.5693	5.1779

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^* \cos\gamma + 2U_{13}aa^*cc^* \cos\beta + 2U_{23}bb^*cc^* \cos\alpha)$$

crown-4 ether and 2,6-dimethylphenol (**1**) should give armed-azacrown ether **13**, while a mixture of formaldehyde, monoaza-12-crown-4 ether and 2,6-dibromophenol (**10**) should give the salt of the dihydroxydiphenylmethane derivative with monoaza-12-crown-4 ether **22**. As expected, compounds **13** and **22** were obtained in 61% and 43% yields, respectively, in these one-pot reactions. These results suggest that formaldehyde does not react under these conditions with 2,6-dimethylphenol ($pH = 7.3$, Electrostatic charge = -0.11 electrons) directly, and formaldehyde does not form the iminium ion leading to

the Mannich product in the presence of 2,6-dibromophenol ($pH = 4.6$, Electrostatic charge = -0.26 electrons). Therefore, the products in these reactions depend on both the acidity and the electron density at the position 4 carbon atom of the phenols.

In conclusion, we have demonstrated that the Mannich reaction of 2,6-disubstituted phenols with *N*-methoxymethylmonoaza-12-crown-4 ether give the Mannich product or dihydroxydiphenylmethane derivatives. We propose that the pH value and the electrostatic charge at the position 4 carbon of the 2,6-disubstituted phenols are an indication of the reactivity of the 2,6-disubstituted phenols for the Mannich reaction. These results may provide a guideline for the synthesis of new armed-macrocycles using the Mannich reaction.

EXPERIMENTAL

Material and Apparatus.

N-Methoxymethyl-1,4,7-trioxa-10-azacyclododecane was prepared as reported [3]. 2,6-Dinitrophenol was dried with an Abderhalden's dryer (70°, 0.1 Torr) for 2 hours. The other phenols were used without further purification. The 1H nmr spectra were measured in deuteriochloroform on a Bruker AC-250 (250 MHz) spectrometer. The ei-ms were performed using the Hitachi M-80 spectrometer. Elemental analyses were performed on a Perkin-Elmer CHN-2400. Decomposition point of the salt of **12** with monoaza-12-crown-4 ether was measured using Rigaku TG-DTA. Other melting and decomposition points were taken on the Mel TempTM melting point apparatus and are uncorrected.

General Procedure for the Reaction of Phenol or Naphthol Derivatives with *N*-Methoxymethyl-1,4,7-trioxa-10-azacyclododecane.

A mixture of *N*-methoxymethyl-1,4,7-trioxa-10-azacyclododecane (5.5 mmoles) and phenol or naphthol derivative (5.5 mmoles) in absolute benzene (15 ml) was refluxed under a nitrogen atmosphere for 24 hours. The reaction mixture was cooled and then concentrated under reduced pressure. The residual oil was separated and purified by silica-gel and then gel-permeation column chromatography to give the following products.

N-(4-Hydroxy-3,5-diisopropylbenzyl)-1,4,7-trioxa-10-azacyclododecane (**14**).

This compound was isolated in a 73% yield as white crystals, mp 90-93°; 1H nmr: δ 7.04 (s, 2H), 4.74 (s, 1H), 3.82-3.59 (m, 14H), 2.72 (t, 4H, $J = 4.7$ Hz), 1.27-1.24 (d, 12H, $J = 6.8$ Hz); ms: ei (m/z) 362 (100%, $[M]^+ + 1$).

Anal. Calcd. for $C_{21}H_{35}NO_4 \cdot 0.5H_2O$: C, 67.35; H, 9.69; N, 3.74. Found: C, 67.55; H, 9.62; N, 3.67.

N-(4-Hydroxy-3-*tert*-butyl-5-methylbenzyl)-1,4,7-trioxa-10-azacyclododecane (**15**).

This compound was isolated in a 68% yield as white crystals, mp 82-85°; δ 7.10 (s, 1H), 7.00 (s, 1H), 4.72 (s, 1H), 3.82-3.56 (m, 14H), 2.73 (t, 4H, $J = 4.8$ Hz), 2.21 (s, 3H), 1.40 (s, 9H); ms: ei (m/z) 352 (100%, $[M]^+ + 1$).

Anal. Calcd. for $C_{20}H_{33}NO_4$: C, 68.34; H, 9.46; N, 3.99. Found: C, 68.14; H, 9.82; N, 3.55.

N-(4-Hydroxy-3,5-di-*tert*-butylbenzyl)-1,4,7-trioxa-10-azacyclododecane (**16**).

This compound was isolated in a 47% yield as white crystals; mp 102-104°; δ 7.15 (s, 2H), 5.10 (s, 1H), 3.59-3.74 (m, 12H), 2.73 (t, 4H, $J = 4.8$ Hz), 1.43 (s, 18H); ms: ei (m/z) 394 (100%, $[M]^+ + 1$).

Anal. Calcd. for $C_{23}H_{39}NO_4$: C, 70.19; H, 9.99; N, 3.56. Found: C, 70.01; H, 10.18; N, 3.61.

N-(4-Hydroxy-3,5-dimethoxybenzyl)-1,4,7-trioxa-10-azacyclododecane (**17**).

This compound was isolated in a 47% yield as a pale yellow oil; 1H nmr: δ 6.69 (s, 2H), 3.89 (s, 6H), 3.79-3.67 (m, 8H), 3.64-3.60 (m, 6H), 2.73 (t, 4H, $J = 4.7$ Hz); ms: ei (m/z) 342 (52%, $[M]^+ + 1$), 167 (100%, $[HOC_6H_2(OMe)_2CH_2]^+$).

Anal. Calcd. for $C_{17}H_{27}NO_6$: C, 59.81; H, 7.97; N, 4.10. Found: C, 59.57; H, 8.03; N, 3.98.

N-(4-Hydroxy-3-allyl-5-methoxybenzyl)-1,4,7-trioxa-10-azacyclododecane (**18**).

This compound was isolated in a 27% yield as a pale yellow oil; 1H nmr: δ 6.96 (s, 1H), 6.76 (s, 1H), 6.06-5.92 (m, 1H), 5.60 (s, 1H), 5.11-5.02 (m, 2H), 3.89 (s, 3H), 3.79-3.67 (m, 8H), 3.63-3.59 (m, 6H), 3.39 (d, 2H, $J = 6.5$ Hz), 2.72 (t, 4H, $J = 4.8$ Hz); ms: ei (m/z) 352 (8%, $[M]^+ + 1$), 177 (100%, $[HOC_6H_2(OMe)(CH_2CH=CH_2)]^+$).

Anal. Calcd. for $C_{19}H_{29}NO_5$: C, 64.93; H, 8.32; N, 3.99. Found: C, 64.99; H, 8.38; N, 3.87.

N-(4-Hydroxy-3,5-diphenylbenzyl)-1,4,7-trioxa-10-azacyclododecane (**19**).

This compound was isolated in a 36% yield as a colorless oil; 1H nmr: δ 7.59-7.35 (m, 10H), 7.29 (s, 2H), 5.37 (broad s, 1H), 3.69-3.65 (m, 14H), 2.79 (t, 4H, $J = 4.8$ Hz); ms: ei (m/z) 434 (18%, $[M]^+ + 1$), 259 (100%, $[HOC_6H_2(Ph)_2CH_2]^+$).

Anal. Calcd. for $C_{27}H_{31}NO_4$: C, 74.80; H, 7.21; N, 3.23. Found: C, 74.76; H, 7.29; N, 2.99.

N-(4-Hydroxy-3,5-difluorobenzyl)-1,4,7-trioxa-10-azacyclododecane (**20**).

This compound was isolated in a 68% yield as a pale yellow oil; 1H nmr: δ 6.98-6.82 (m, 2H), 3.75-3.55 (m, 15H), 2.75 (t, 4H, $J = 4.7$ Hz); ms: ei (m/z) 318 (100%, $[M]^+ + 1$).

Anal. Calcd. for $C_{15}H_{21}NO_4F_2 \cdot 0.5H_2O$: C, 55.21; H, 6.79; N, 4.29. Found: C, 55.54; H, 6.93; N, 4.06.

The Salt of Bis(3,5-dichloro-4-hydroxyphenyl)methane with 1,4,7-Trioxa-10-azacyclododecane (**21**).

This compound was isolated in a 62% yield as colorless crystals, mp 185.5-186° dec; 1H nmr: δ 7.02 (s, 4H), 3.75 (t, 4H, $J = 4.7$ Hz), 3.72 (s, 2H), 3.69 (t, 4H, $J = 4.7$ Hz), 3.58 (t, 4H, $J = 4.7$ Hz), 3.22 (broad s, 3H, this peak disappeared by addition of deuterium oxide), 2.85 (t, 4H, $J = 4.7$ Hz); ms: ei (m/z) 176 (100%, $[12\text{-crown-4+H}]^+$), 336 (4.2%, $[(HOC_6H_2Cl_2)_2CH_2-2H]^+$), 338 (5.3%, $[(HOC_6H_2Cl_2)_2CH_2-2H+2]^+$), 340 (2.6%, $[(HOC_6H_2Cl_2)_2CH_2-2H+4]^+$).

Anal. Calcd. for $C_{21}H_{25}NO_5Cl_4$: C, 49.14; H, 4.91; N, 2.73. Found: C, 48.78; H, 4.65; N, 2.59.

The Salt of Bis(3,5-dibromo-4-hydroxyphenyl)methane with 1,4,7-Trioxa-10-azacyclododecane (**22**).

This compound was isolated in a 45% yield as colorless crystals, mp 190.5-192° dec; 1H nmr: δ 7.21 (s, 4H), 3.76 (t, 4H, $J = 4.9$ Hz), 3.74 (s, 2H), 3.69 (t, 4H, $J = 4.9$ Hz), 3.59 (t, 4H, $J = 4.9$ Hz), 2.85 (t, 4H, $J = 4.9$ Hz), 2.53 (broad s, 3H, this peak disappeared by addition of deuterium oxide); ms: ei (m/z) 176 (100%, $[12\text{-crown-4+H}]^+$), 514 (1.6%, $[(HOC_6H_2Br_2)_2CH_2-2H]^+$), 516 (2.5%, $[(HOC_6H_2Br_2)_2CH_2-2H+2]^+$), 518 (1.6%, $[(HOC_6H_2Br_2)_2CH_2-2H+4]^+$).

Anal. Calcd. for $C_{21}H_{25}NO_5Br_4$: C, 36.64; H, 3.37; N, 1.89. Found: C, 36.50; H, 3.65; N, 2.03.

4,4'-Bis(2-methyl-1-hydroxynaphthyl)methane (**23a**) and Oxidized Compound **23b**.

2-Methyl-1-naphthol was allowed to react with *N*-methoxymethyl-1,4,7-trioxa-10-azacyclododecane in benzene under a nitrogen atmosphere for 24 hours as described above. After the reaction mixture was treated in the usual manner, the residual oil was chromatographed on silica-gel using benzene/ethyl acetate (200:1) as eluent to give two fractions. The first fraction was concentrated under reduced pressure to give a pale-yellow solid **23a** in a 14% yield; 1H nmr: δ 8.21 (d, 2H, $J = 7.7$ Hz), 7.95 (d, 2H, $J = 7.7$), 7.50 (t, 2H, $J = 7.7$ Hz), 7.43 (t, 2H, $J = 7.7$ Hz), 6.84 (s, 2H), 4.98 (s, 2H), 4.68 (s, 2H), 2.28 (s, 6H); ms: ei (m/z) 171 ($[M-C_{11}H_9O]^+$, 48%), 328 ($[M]^+$ of **23a**, 100%). Combustion analysis could not be measured, because **23a** was easily oxidized in 24 hours at room temperature (color of the solid changed to red within 24 hours). The ei mass spectrum of the red compound changed to (m/z) 326 ($[M]^+$ of **23b**, 100%). From the second fraction, a red solid was obtained, **23b**; mp 204-206° dec; 1H nmr: δ 8.45 (s, 1H), 8.35 (dd, 1H, $J = 1.3$ Hz, $J = 7.8$ Hz), 8.25 (dd, 1H, $J = 2.5$ Hz, $J = 7.1$ Hz), 8.20 (d, 1H, $J = 8.3$ Hz), 7.93 (dd, 1H, $J = 2.3$ Hz, $J = 7.2$ Hz), 7.67 (dd, 1H, $J = 1.6$ Hz, $J = 7.1$ Hz), 7.64 (s, 1H), 7.58-7.53 (m, 3H), 7.32 (s, 1H), 5.42 (s, 1H), 2.50 (s, 3H), 2.11 (s, 3H); ms: ei (m/z) 326 ($[M]^+$ of **23b**, 100%). Samples for X-ray crystallography were twice recrystallized from acetonitrile.

Anal. Calcd. for $C_{23}H_{18}O_2 \cdot 1/3H_2O$: C, 83.11; H, 5.66. Found: C, 83.00; H, 5.60.

Reaction of **12** with Monoaza-12-crown-4 Ether.

When **12** was treated as above with monoaza-12-crown-4, a 14% yield of yellow crystals were isolated; mp 189° dec, TG-DTA; 1H nmr: δ 7.99 (d, 2H, $J = 8.1$ Hz), 6.26 (t, 4H, $J = 8.1$ Hz), 3.97 (t, 4H, $J = 4.7$ Hz), 3.83 (t, 4H, $J = 4.3$ Hz), 3.67 (t, 4H, $J = 4.3$ Hz), 3.23 (t, 4H, $J = 4.7$ Hz). The spectral data is exactly same as that of a 1:1 mixture of **12** and monoaza-12-crown-4 ether.

The One-Pot Reaction of Monoaza-12-crown-4 Ether, Formaldehyde and 2,6-Dimethylphenol (**1**).

A mixture of the monoazacrown ether (0.88 mmole), paraformaldehyde (0.95 mmole) and **1** (0.97 mmole) in absolute benzene (20 ml) was refluxed for 1 day. The residual solid was treated in the manner described above to give compound **13** in 61% yield.

The One-Pot Reaction of Monoaza-12-crown-4 Ether, Formaldehyde and 2,6-Dibromophenol (**10**).

A mixture of the monoazacrown ether (0.44 mmole), paraformaldehyde (0.48 mmole) and **10** (0.44 mmole) in absolute benzene (20 ml) was refluxed for 2 days. The residual

solid was treated in the manner described above to give compound **22** in 43% yield.

Crystallography.

The crystallographic and experimental data are listed in Table 2. Each of the single crystals was mounted in a glass capillary. All measurements were made at 298 K on a Rigaku AFC5S four-circle diffractometer with graphite-monochromated MoK α radiation (λ 0.71069 Å) and a 12kW rotating-anode generator. Cell contacts and an orientation matrix for data collection were obtained from a least-squares refinement. The data were collected using the 2- θ scan technique to an above maximum 2θ value of 55.0°. All intensities were corrected for Lorentz and polarization effects. The structure was solved by direct methods (SIR92) [6]. The non-hydrogen atoms were refined anisotropically. The coordinates of all hydrogen atoms except the hydrogen atoms of the phenolic OH and NH₂⁺ groups were calculated at ideal positions and were refined. Neutral atom scattering factors were taken from Cromer and Waber [7] Anomalous dispersion effects were included in Fc [8], the values for Δf and $\Delta f'$ were those of Cromer and Waber [7]. All calculations were carried out on a Silicon Graphics Indigo with the TEXSAN crystallographic software package [9].

Calculation of Electrostatic Charges.

The semi-empirical AM1 calculations [10] using SYBYL/X geometry [11] were performed on a Power Macintosh 7600/200. Mac Spartan PlusTM [12] was used as the computer-modeling software.

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