Molecular Receptors. Synthesis, X-ray Crystal Structures, and Chemical Properties of Crown Ethers Bearing an Intraannular Phenolic Group

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Abstract: Macrocyclic polyethers having the 1,3-xylyl subunit and an intraannular phenolic group have been synthesised to determine the influence of the proximate oxygen atoms of the crown ether on the chemical behavior of an intraannular substituent and, conversely, the influence of the substituent on the binding properties of the macrocycle. Williamson synthesis between 2,6-bis(bromomethyl)anisole and the sodium salts of tri-, tetra-, and pentaethylene glycol produced the corresponding 15-, 18-, and 21-membered crown ether anisoles which were demethylated with lithium iodide in pyridine affording the 15-, 18-, and 21-membered crown ether phenols **6**, **7**, and **8**, respectively. The pK_a's (H_2O) of these phenols were found to be (**6**) 10.7, (**7**) 10.6, and (**8**) 10.5. The crystal structures of 18-crown phenol (**7**), its *p*-nitro derivative (**10**), and the ammonium salt of **10** have been determined. The crystals of **7** are orthorhombic, space group $Pc2_1b$ with four molecules in the unit cell of dimensions a = 9.779 (2) Å, b = 18.943 (3) Å, and c = 8.915 (2) Å. Crystals of **10** are monoclinic, space group $P2_1/c$ with four molecules in the unit cell of dimensions a = 10.503 (1) Å, b = 9.003 (3) Å, c = 18.924 (3) Å, and β = 101.98 (1)°. Crystals of **16** are also monoclinic, space group $I2/a$ with eight molecules in the unit cell of dimensions a = 20.476 (2) Å, b = 9.092 (3) Å, c = 21.211 (2) Å, and β = 108.92 (1)°. The structures were solved by the direct methods and refined by full-matrix least-squares calculations: for **7** R = 0.053 for 759 observed reflections, for **10** R = 0.032 for 1189 reflections, and for **16** R = 0.053 for 2635 reflections. The analyses establish that in all three structures the phenolic group is oriented toward the center of the macrocyclic cavity; intramolecular O—H···O hydrogen bonding is apparent in **7** (O(1)—H···O(5) 2.856 Å) and **10** (O(1)—H···O(2) 2.707 Å). In **16** the $^+NH_4$ cation is held close to the ring cavity by three N—H···O hydrogen bonds, one to the phenolate oxygen (N···O 2.690 Å) and two to ring oxygens (N···O 2.884 and 2.883 Å). A fourth N—H···O hydrogen bond to the phenolate oxygen of a neighboring molecule (N···O 2.781 Å) yields centrosymmetric hydrogen-bonded dimers. Dimensions for **7**, **10**, and **16** are in accord with expected values. The *p*-nitro group in **10** exerts a considerable structuring effect on the conformation of the macrocycle. Reactions of these phenols with bases including ammonia are discussed, and the isolation of some crystalline phenoxides is reported.

Many polyoxygenated macrocycles of the crown ether variety possess cavities capable of providing a favorable environment for the reception of guest species, notably alkali and alkaline earth metal cations and ammonium and alkylammonium salts.[1-9] Ion–dipole interactions lead to binding, the strength and specificity of which are determined by cation and cavity size, cation–counterion interactions, receptor topology, the number and disposition of the ethereal oxygen atoms, the layer properties of the receptor, and the environmental properties of the system as a whole.[10-17]

The realization that ion-binding characteristics can also be influenced by replacing one or more ethereal oxygen atom of the crown ether by another heteroatom or group capable of electron donation, or by attaching additional binding sites in the form of functional groups to the periphery of the macrocycle, has been an important feature of recent developments with synthetic receptors.[18-26] The emphasis, however, has been on chemically inert receptors, and few systems have evolved in which the reversible reception of a guest species is triggered or facilitated by a reversible chemical change in a strategically placed functional group in the receptor.[27-29] Were such synergism to occur it might be revealed by a change in ion-binding characteristics, a specific ion–counterion interaction between a guest cation and an ionized receptor, or enhanced reactivity of the functional group. Enzymic systems show numerous examples of the enhanced reactivity of functional groups towards guest molecules in highly structured pockets or cavities which provide a favorable environment for both. Convergence of binding sites and functional groups with potential catalytic activity is therefore an important aspect of the design of synthetic receptors capable of imitating enzymes.[30-33]

With the intention of exploring synergism between a strategically placed reactive functional group and a macrocyclic receptor, we have synthesized a series of crown ethers, **6–11**, bearing an intraannular phenolic group, and have studied their reactions, particularly with bases, to determine the influence of the proximate oxygen atoms of the ring on the chemical activity of the functional

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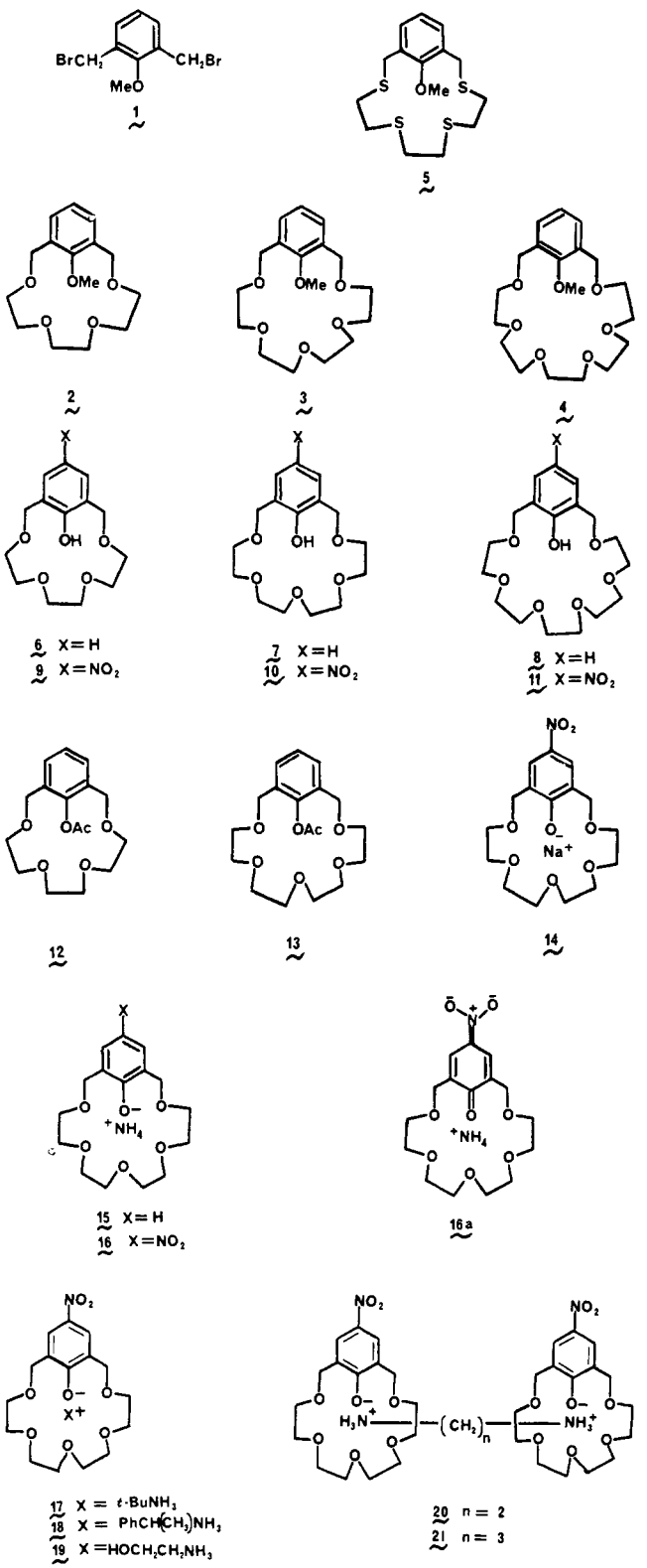
Chart I



group. Conversely, we also sought information on how phenolic groups might influence the ion-binding properties of the receptor.

Prior to the publication of a preliminary communication on this work,[34] the chemistry of crown ether phenols of type **6–11** was unexplored. Three bis(phenols) in the binaphthyl crown ether series had been described by Cram,[35] though the chemical activity of the functional group was not discussed. In each case the phenolic group was found to inhibit binding of alkylammonium and alkali metal cations, an effect attributed to the existence of strong intramolecular hydrogen bonding in the guest-free receptor. Phenolic groups play an important function in the structuring of some natural, unimolecular receptors capable of binding metal ions, e.g., as in the barium salt of the antibiotic X-537A (Lasalocid A).[36] Phenolic groups held together by intramolecular hydrogen bonding are also important in the structuring of the calixarenes,[37] and many crystalline *multimolecular* inclusion complexes based on (*p*-hydroxyphenyl)-2,2,4-trimethylchroman (Dianin's compound) and related molecules owe their existence to strong intermolecular hydrogen bonding between phenolic groups.[38] Crown ethers in the binaphthyl series bearing "arms" terminating in carboxyl groups have been reported by Cram;[35] these structures represent the first examples of crown ethers bearing counterionic functional groups in which the arms are able to project into the cavity. Lehn and his co-workers have investigated the binding properties of non-benzoic crown ethers substituted with carboxyl groups acting as counterionic complexing agents.[22,23] A series of lariat crown ethers have been developed by Gokel and his coworkers in which the macrocycle bears a flexible side chain containing one or more neutral donor groups that, if in a suitable geometric arrangement, provide additional sites for coordination to a guest cation in the cavity.[24]

The macrocyclic polyethers chosen for this study are based on the 1,3-xylyl subunit because (a) a functional group attached to the 2-position can easily adopt an intraannular orientation and thereby project into or toward the center of the cavity defined by the macroring, (b) depending on ring size, the macroring can have sufficient mobility to allow the benzene ring to tilt out of the general plane defined by the ethereal oxygen atoms in which case the phenolic group might be able to act cooperatively as an additional binding site, (c) through para-substitution it should be possible to make controlled changes in the chemical activity of the phenolic group without altering the constitution of the macroring, and (d) such macrocycles should be easily assembled from 2-substituted 1,3-difunctionalized xylenes and polyethylene glycols, using the Williamson ether synthesis. Other intraannular substituents attached to the 2-position of 1,3-xylyl-based crown

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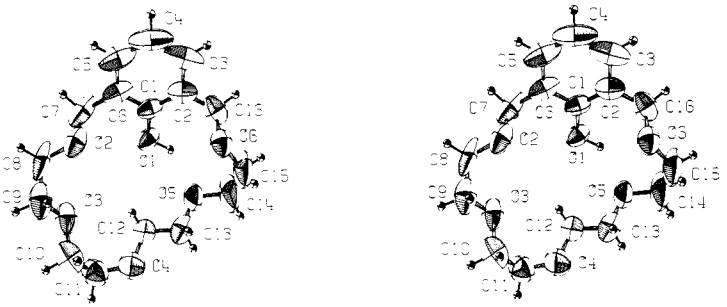

Figure 1. Stereoview of a molecule of **7** with the crystallographic numbering scheme.

ethers whose effects on ion-binding properties have been studied include carboxyl,[20] methoxycarbonyl,[20,35] and methoxy.[35,39,40]

Results and Discussion

Synthesis and Structure. In order to take advantage of the Williamson ether synthesis in the preparation of phenols **6–11**, protection of the hydroxyl group was necessary. The corresponding methyl ethers were chosen because of the relatively small steric requirement of the methoxy group and its stability toward strongly basic conditions. Condensation of 2,6-bis(bromomethyl)anisole (**1**) with the appropriate polyethylene glycol in hot tetrahydrofuran containing sodium hydride produced the methoxy-15-crown-4 (**2**) (45%), the methoxy-18-crown-5 (**3**) (58%), and the methoxy-21-crown-6 (**4**) (75%). All three crown anisoles were readily purified by distillation, and the larger two were crystalline solids, mp 50.0–50.5 and 82.0–82.5 °C, respectively.

Differences in intramolecular crowding in the vicinity of the benzylic hydrogen atoms of the macroring and the methoxy group were apparent from the NMR spectra of the three crown anisoles. In **2**, the benzylic hydrogens appeared as an AB system, suggesting that the size of the cavity is too small to permit easy movement of the methoxy group relative to the mean plane of the 15-membered ring at ordinary temperatures. At 200 °C, however, this AB system was replaced by a singlet in the NMR spectrum. Vogtle has observed a similar degree of temperature-dependent intramolecular overcrowding in the related 15-membered thiamacrocycle **5**.[41] The benzylic hydrogen atoms in **3** and **4**, on the other hand, appeared as singlets in the NMR spectra even at room temperature, indicating that the 18- and 21-membered rings have cavities sufficiently large to permit easy movement of the encirculing atoms relative to the intra-annular methoxy group.

Difficulties with the use of conventional acidic reagents for the release of the phenolic group by demethylation of these three crown ether anisoles were anticipated because in addition to the molecules being 2,6-disubstituted (and therefore hindered), they are also benzylic ethers and cleavage of the macroring was therefore considered a likely complication. Nevertheless, we found that use of anhydrous lithium iodide, a dealkylating agent introduced originally for demethylation of methyl esters[42] and later extended by Harrison to include anisoles,[43] gave exceptionally clean transformation of all three crown ethers, **2–4**, into their respective phenoxides from which phenols **6**, **7**, and **8** were isolated after acidification. The experimental conditions necessary to bring about these demethylations deserve some comment. Whereas Harrison found that demethylation of oestrone methyl ether with lithium iodide in boiling collidine (174 °C) required 48 h to reach completion, our preliminary attempts to demethylate the crown ether anisoles under similar conditions quickly revealed that much shorter times and lower temperatures sufficed. In preparative scale experiments, collidine was replaced by pyridine (bp 115 °C), and demethylation was found to be complete within a few hours. Neither anisole nor 2,6-dimethylanisole gave detectible amounts of demethylation product when similarly treated, even with exposure times extended to 72 h. The relative ease of demethylation of the crown ether anisoles suggests that macrocycle provides a particularly favorable environment for attack by iodide ion on the methyl group, possibly via coordination of Li^+ to both the crown and aryl ethereal oxygen atoms.

Crown phenols **6** and **7** were obtained as crystalline solids, mp 66.0–66.5 and 48–49 °C, respectively; the 21-membered ring phenol was a liquid which solidified near 0 °C. Unlike its anisyl precursor, phenol **6** exhibited an NMR singlet for the benzylic hydrogen atoms, implying that an intra-annular hydroxy group has greater freedom of movement vis-ā-vis the macroring than a methoxy group in the same environment. On the other hand, acetylation of phenol **6** to produce acetate **12** caused the reappearance of the AB system in the NMR spectra as did similar derivatization of the 18-membered phenol, emphasizing that the degree of intramolecular overcrowding and mobility of these 15- and 18-crown systems are closely dependent on the nature and size of the intra-annular substituent.

The spatial relationship between the intraannular hydroxy group and the polyoxygenated ring in these phenols is central to the theme of this investigation, and while infrared studies in solution did indicate that the substituent was within intramolecular hydrogen-bonding distance of at least some of the ethereal oxygen atoms in all three compounds, we sought more detailed and precise information concerning the total molecular geometry and topology. Of the two crystalline compounds, the 18-crown-5 homologue **7** was potentially the more interesting vis-ā-vis receptor activity. Accordingly, it was chosen for X-ray analysis. And since we also wished to explore the effect of para substitution on the chemical activity of the phenolic group, the 18-crown phenol was nitrated ($NaNO_2/HNO_3$), and the crystal structure of the resulting *p*-nitro derivative **10** was also determined.

Although crystals of **7** were satisfactory, on optical examination they did not diffract well. The paucity of the data for **7** is a consequence of its loose molecular packing and partial disorder of the macrocyclic ring (details are discussed below and in the Experimental Section). Crystals of **10** behaved normally and gave a good intensity data set. Both **7** and **10** contain discrete molecules separated by normal van der Waals distances; stereoviews of the structures with our labeling scheme are given in Figures 1 and 2. Selected molecular dimensions and torsion angles are in Table I.

There are considerable variations in the observed C–C distances in **7** ranging between 1.24 and 1.52 (2) Å, and many of the ring atoms have large temperature factors. This is entirely consistent with the scarcity of diffraction data noted above and may be ascribed to positional disorder, or large vibrations, or both. Although individual bond lengths are not well defined, the overall conformation of **7** is clear. Molecule **10**, which diffracted normally, has molecular dimensions comparable with those observed in other 18-membered macrocycles, with a mean ring C–C bond length of 1.485 (4) Å, e.g., $C_{12}H_{24}O_5S$ (mean 1.493 (9) Å),[44] $C_{12}H_{24}O_5S$·NaSCN (mean 1.495 (6) Å),[45] $C_{12}H_{24}O_5S$·KSCN

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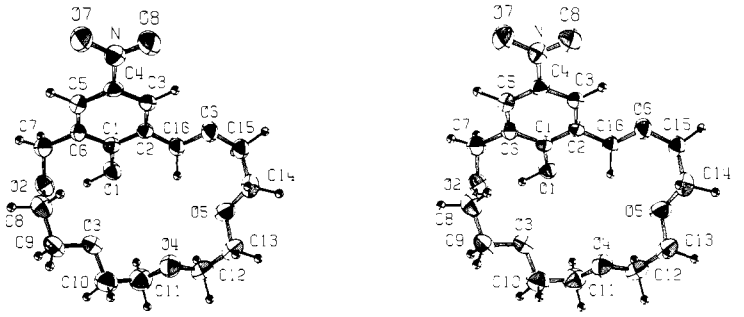

Figure 2. Stereoview of a molecule of **10** with the crystallographic numbering scheme.

(mean 1.496 (13) Å).[46] The macroring C–O distances in **7** and **10** (means 1.412 (13) and 1.417 (3) Å, respectively) are normal.

In 18-crown-6 complexes where the six heteroatoms are coordinated to a central atom, gauche C–C and anti C–O torsion angles have been observed;[45-51] any deviation from six coordination results in considerable change in these torsion angles.[45-48,52] Absence of a central coordinating atom also results in variations in the macrocycle ring conformation which will then be at the mercy of crystal packing forces and any other conformation determining forces such as hydrogen bonding. This is the situation with both **7** and **10**. Although both molecules share the significant general feature of having an intraannular relationship between the aromatic ring substituent and the macrocycle cavity, it is also apparent that the precise orientation of the phenolic OH group is different in **7** and **10**. Whether this is a consequence of the additional *p*-nitro group in **10** or is soley due to crystal packing effects and differences in hydrogen bonding is a moot point. In the unsubstituted compound **7** the macrocycle has an "opened out" conformation (Figure 3a) with an angle of 28° between the aromatic ring plane and the mean plane of the macrocyclic ring atoms; in the *p*-nitro derivative **10** the corresponding angle is larger (47°), and the macrocyclic ring has a somewhat "oval" conformation (Figure 3b). In **7** the transannular hydrogen bond is to ether oxygen O(5) (O(1)···O(5) 2.856 (15) Å and H(O1)···O(5) 2.05 Å) leading to a nine-membered hydrogen-bonded ring and resulting in ring torsion angles for C–C and C–O bonds which are far removed from the usual gauche and anti values, respectively. Thus the O(4)–C(12)–C(13)–O(5) angle is anti (178°), and O(5)–C(14)–C(15)–O(6) is fully eclipsed (1°); the C(10)–C(11)–O(4)–C(12) (−80°), C(15)–C(14)–O(5)–C(13) (−113°), and C(14)–C(15)–O(6)–C(16) (−101°) torsion angles are closer to gauche than anti values. In **10** the C(6)–C(7)–O(2)–C(8) (70°) and C(14)–C(15)–O(6)–C(16) (−76°) angles are considerably removed from anti values, as a consequence of the intramolecular O—H···O hydrogen bond to benzylic oxygen atom O(2) (O(1)···O(2) 2.707(4) and H(O1)···O(2) 1.91 Å).

Properties. One of the most important reactions of a phenol is its chemical ionization in aqueous solution. The question arose, therefore, as to how the crown ether environment might affect the acidity of these crown ether phenols. The pK_a's of **6**, **7**, and **8** and their corresponding nitro derivatives **9**, **10**, and **11**, and for comparison with literature data, 2,6-dimethylphenol and *p*-nitrophenol, were measured by spectrophotometric estimation of the phenoxide produced with variation of pH brought about by titration with sodium hydroxide. Comparison of the pK_a values

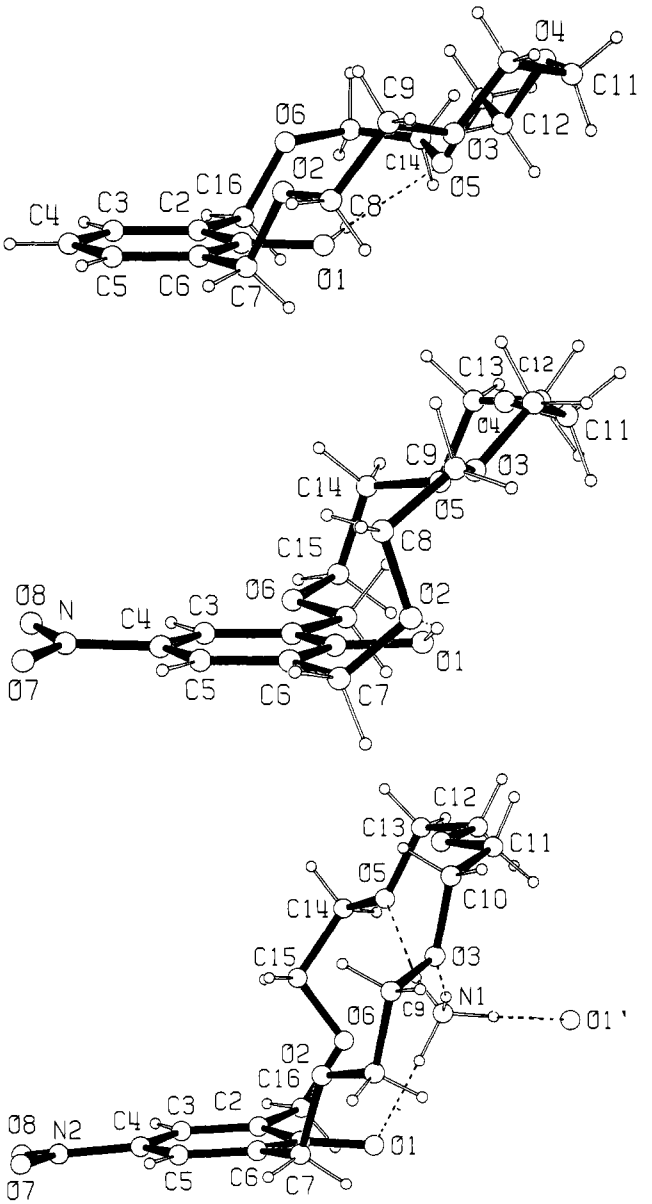

Figure 3. Side view of the structures of (a, top) **7**, (b, middle) **10**, and (c, bottom) **16**. In all drawings, arbitrary spheres have been assigned to all the atoms.

in Table II provides little evidence that there is a significant crown ether effect on the acidity of these compounds in aqueous solution. Thus the 15-, 18-, and 21-crown phenols have pK_a's essentially equal to that of 2,6-dimethylphenol; the trend to lower pK_a with increasing ring size is small and may be insignificant. Similarly, there is a small trend in the same direction toward greater acidity among the three crown nitrophenols. The absence of significant crown effects on the acidities of these phenols notwithstanding, their behavior and properties as phenoxides were revealing, leading

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Table I. Selected Dimensions for **7**, **10**, and **16** (Full Details Are in the Supplementary Material)

	7	**10**	**16**
	A. Bond Lengths (Å)		
macrocyclic ring:			
C–O (range)	1.381–1.442 (12)	1.410–1.425 (4)	1.392–1.450 (3)
(mean)	1.412 (13)	1.417 (3)	1.417 (3)
C–C (range)	1.238–1.523 (17)	1.477–1.498 (4)	1.473–1.498 (3)
mean	1.412 (16)	1.485 (4)	1.489 (4)
aromatic ring:			
C(1)–O(1)	1.333 (7)	1.359 (3)	1.287 (3)
C(1)–C(2)	1.395[a]	1.392 (4)	1.435 (3)
C(1)–C(6)	1.395[a]	1.407 (4)	1.428 (3)
C(2)–C(3)	1.395[a]	1.379 (3)	1.367 (3)
C(3)–C(4)	1.395[a]	1.384 (4)	1.392 (3)
C(4)–C(5)	1.395[a]	1.377 (4)	1.390 (4)
C(5)–C(6)	1.395[a]	1.376 (4)	1.367 (4)
C(2)–C(16)	1.493 (12)	1.499 (4)	1.506 (3)
C(6)–C(7)	1.518 (14)	1.506 (4)	1.487 (4)
	B. Bond Angles (deg)		
macrocyclic ring:			
C–C–O (range)	106.0–122.5 (10)	108.4–113.3 (3)	107.8–113.5 (2)
(mean)	112.0 (10)	110.8 (3)	109.8 (2)
C–O–C (range)	110.0–117.4 (10)	111.2–114.0 (2)	112.1–113.4 (2)
(mean)	113.6 (10)	112.6 (2)	112.8 (2)

C. Short Intramolecular Hydrogen-Bonded Distances (Å) and Angles (deg)

7 O(1)···O(5) 2.856 (15), H(O1)···O(5) 2.05
O(1)—H(O1)···O(5) 141.3

10 O(1)···O(5) 2.707 (4), H(O1)···O(2) 1.91
O(1)—H(O1)···O(2) 141.6

16 N(1)···O(1) 2.690 (4), H(1)···O(1) 1.86
N(1)···O(3) 2.884 (4), H(2)···O(3) 1.95
N(1)···O(5) 2.883 (4), H(3)···O(5) 1.95
N(1)···O(1)′ 2.781 (4), H(4)···O(1)′ 1.76
N(1)—H(1)···O(1) 159.6
N(1)—H(2)···O(3) 170.4
N(1)—H(4)···O(5) 166.5
N(1)—H(3)···O(1)′ 166.6

The primed atoms are related to the unprimed atoms by the following symmetry operation:
$^1/_2 - x, ^1/_2 - y, ^1/_2 - z$

	7	**10**	**16**
	D. cis Torsion Angles in the Macrocyclic Rings[b]		
(i) C–C–O–C			
C(6)–C(7)–O(2)C(8)	−179.6	70.2	−170.6
C(9)C(8)–O(2)C(7)	165.2	−163.3	−176.4
C(8)C(9)–O(3)C(10)	176.1	171.9	177.7
C(11)C(10)–O(3)C(9)	−178.4	168.5	−177.8
C(10)C(11)–O(4)C(12)	−80.2	171.3	−170.4
C(13)C(12)–O(4)C(11)	−178.6	169.6	176.7
C(12)C(13)–O(5)C(14)	177.8	169.6	−176.3
C(15)C(14)–O(5)C(13)	−112.8	177.8	−171.0
C(14)C(15)–O(6)C(16)	−100.6	−75.6	−174.6
C(2)C(16)–O(6)C(15)	−60.6	171.7	−69.5
(ii) O–C–C–O			
O(2)C(8)–C(9)O(3)	−14.8	64.4	−68.9
O(3)C(10)–C(11)O(4)	78.7	70.1	72.4
O(4)C(12)–C(13)O(5)	178.1	−75.0	−59.7
O(5)C(14)–C(15)O(6)	0.6	79.5	−68.9
(iii) C–C–C–O			
C(1)C(6)–C(7)O(2)	70.2	45.2	78.1
C(1)C(2)–C(14)O(6)	−66.2	−175.0	−63.0

[a] Constrained during refinement. [b] Average esd's on torsion angles are 1.4, 0.4, and 0.3° for **7**, **10**, and **16**, respectively.

ultimately to the isolation of stable crystalline salts. A measure of the looseness or tightness of ion pairing in simple phenoxides can be obtained from the position of λ_{max} of the long-wavelength absorption in the electronic spectrum. Smid and his co-workers have used this effect to determine the amount of loosening of ion pairs brought about by addition of a crown ether.[53] Tight ion pairs of alkali metal picrates were found to absorb at 360 nm while crown ether separated ion pairs absorbed at 380 nm in tetrahydrofuran. The parent phenoxide ion has been found by Zaugg and Schaefer to exhibit a long-wavelength λ_{max} in the UV in water or methanol which is unaffected by a change in counterion (Table III).[54] This invariance in λ_{max} for the alkali metal phenoxides in hydroxylic solvents is attributed to strong solvation of both ions. However, in aprotic solvents such as dimethyoxyethane, and to

(53) Bourgoin, M.; Wong, K. H.; Hui, J. Y.; Smid, J. *J. Am. Chem. Soc.* **1975**, *97*, 3462–3467.

(54) Zaugg, H. E.; Schaefer, A. D. *J. Am. Chem. Soc.* **1965**, *87*, 1857–1866.

Table II. pK_a Values of Crown Ether Phenols at 20 °C

compound	pK_a
15-crown-4-phenol (**6**)	10.8
18-crown-5-phenol (**7**)	10.6
21-crown-6-phenol (**8**)	10.5
p-nitro-15-crown-4-phenol (**9**)	6.8
p-nitro-18-crown-5-phenol (**10**)	6.6
p-nitro-21-crown-6-phenol (**11**)	6.5
phenol	10.0 (10.0)
2,6-dimethylphenol	10.7 (10.7)
p-nitrophenol	7.2

Table III. Long-Wavelength λ_{max} for Phenols and Phenoxides (nm)

	phenol		18-crown-5-phenol (7)		*p*-nitrophenol	*p*-nitro-18-crown-5-phenol (**10**)
cation	CH_3OH	DME	CH_3OH	DME	DME	DME
H^+	274	274	280	279	308	314
Li^+	290	296	302	306	397	396
Na^+	290	302	304	317	410	407
K^+	290	314	306	322	415	405
NH_4^+			303			
Cs^+		317		324	418	412
Ca^{2+}			298			

a lesser extent dimethylformamide, even at concentrations of 10^{-4} to 10^{-5} M, phenoxide salts are associated. Association between ions in dimethoxyethane is revealed by a regular bathochromic shift in going from Li^+ to Cs^+. Zaugg and Schaefer determined the degree of tightness of the ion pair by correlating the change in the long-wavelength λ_{max} of the phenoxide with cation radius. Plots of the inverse cation radius ($1/r_c$ in $Å^{-1}$) against the wavenumber ($\bar{\nu}_0$ in $Å^{-1}$) were linear, the larger the value of the slope the greater the separation of the ions within the ion pair.

The crown ether phenols under examination here are unusual in as much as the oxygenated macrocycle may be capable of providing specific intramolecular solvation of the cationic partner in a phenoxide ion pair. The X-ray structures of the 18-crown phenol **7** and its *p*-nitro derivative **10** and space-filling models of the 15- and 21-crown phenols **6** and **8** suggest that a cation of appropriate size could bind electrostatically to the phenoxide oxygen atom while simultaneously occupying the cavity of the oxygenated macrocycle, thereby enjoying additional dipolar stabilization. One can therefore envisage the macrocycle as acting to hold the cation close to the primary binding site in an invariably tight ion pair or alternatively the transannularly located oxygen atoms may tend to pull the cation away from the phenoxide oxygen atom, forming a separated, though not necessarily solvent-separated, ion pair.

The UV spectra of the alkali metal 18-crown phenoxides in methanol (Table III) reveal that a small, but measurable cation effect is operating since λ_{max} is now cation dependent, suggesting some degree of ion pairing in methanol. These cation–phenoxide interactions are resolved into clearly defined steps on changing from methanol to the more associating solvent, dimethoxyethane, suggesting a higher degree of ion pairing in the latter. This conclusion accords with the effect on λ_{max} since the spectral shift varies in the manner expected on the basis of increasing interionic distance in a tight ion pair as shown by the linear relationship of the absorption frequency with the reciprocal of the ionic radii (Figure 4). The slope of this linear plot suggests that the degree of separation in the ion pair for the 18-crown phenoxide is intermediate between the values obtained by Zaugg and Schaefer[54] for the parent phenoxide and *p*-nitrophenoxide systems. The inference is that there is specific solvation of the cation by the crown ether in dimethoxyethane, though the distinction between a loose and a tight ion pair in this solvent is small in terms of the spatial separation of the ions, irrespective of whether the cation lies in the center of the cavity or just above it. Similar effects were observed with the alkali metal salts of the *p*-nitro-18-crown-5-phenol (**10**) in dimethoxyethane, though here the linear relationship (Figure 5) had a slope of 11.2×10^{-4}, suggesting a much less tight ion pair (an infinite slope indicates the absence of any cation effect).

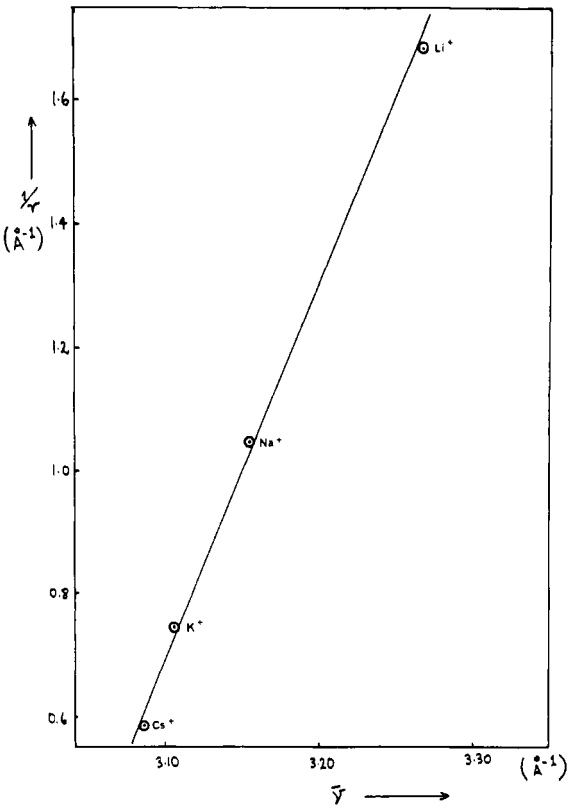

Figure 4. Plot of $1/r$ ($Å^{-1}$) against $\bar{\nu}$ ($Å^{-1}$) ($\times 10^4$) for salts of 18-crown phenol **7**.

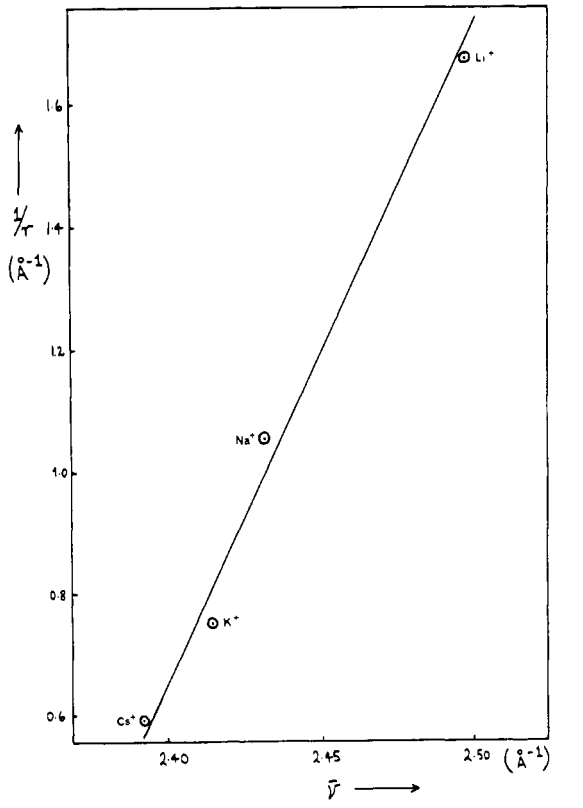

Figure 5. Plot of $1/r$ ($Å^{-1}$) against $\bar{\nu}$ ($Å^{-1}$) ($\times 10^4$) for salts of 18-crown nitrophenol **10**.

That these crown ether macrocycles can act as intramolecular solvation shells for alkali metal phenoxides was also apparent from their bulk physical properties which revealed a distinctly covalent

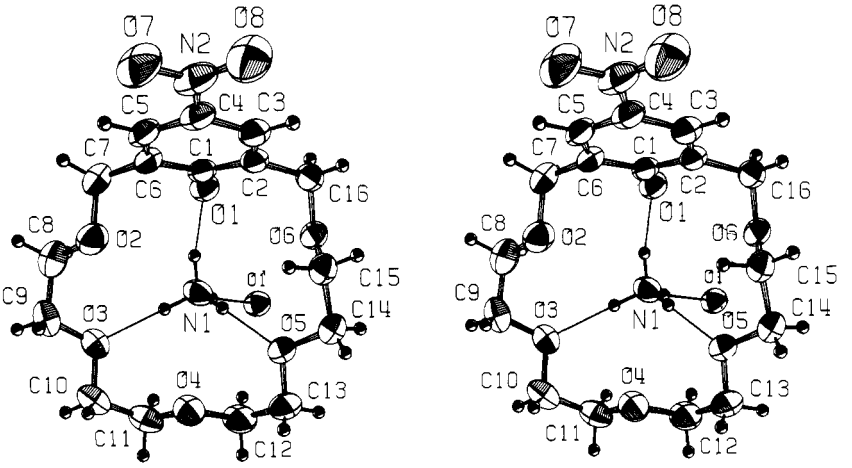

Figure 6. Stereoview of **16** with the crystallographic numbering system.

character. The sodium salt of the *p*-nitro-18-crown phenol **10** was prepared in water and then extracted into chloroform. Concentration of the solution followed by addition of hexane gave the crystalline phenoxide **14**, mp 97.0–97.5 °C. This salt eluted readily on a TLC plate in chloroform, and its mass spectrum showed a base peak at *m/e* 294 corresponding to loss of $NaNO_3$ from the molecular ion. The potassium salt of the *p*-nitro-21-crown-6-phenol (**11**), prepared in a similar way, exhibited a parent ion in the mass spectrum at *m/e* 439. Furthermore, preliminary liquid membrane–transport studies indicate that all of these crown phenols are efficient carriers (CH_2Cl_2 membrane) of alkali metal cations from a basic aqueous source (pH 12–13) to a receiving acid phase (0.1 M, HCl). 18-Crown-6-phenol (**7**) is a nonselective carrier for lithium sodium and potassium ions under these conditions.

The reactivity of these crown ether phenols toward ammonia and selected amines was next considered. There are now numerous studies to support the view that binding of ammonium ions to neutral crown ethers takes place via hydrogen bonding to the ethereal oxygen atoms. Were proton transfer to occur between a crown ether phenol and ammonia, the resulting ammonium phenoxide might enjoy crown ether stabilization through solvation of the ammonium ion in the cavity, with the phenoxide oxygen atom acting electrostatically as the primary binding site. The existence of such stabilization obviously depends on the various geometric and topological factors discussed earlier. In fact, when a methanolic solution of the 18-crown-5-phenol was saturated with ammonia, complete conversion to the phenoxide **15** (λ_{max} 302 nm) was observed. This observation became significant when it was subsequently found that neither phenol nor 2,6-dimethylphenol was converted to phenoxide ion when similarly treated. This contrasting behavior is clearly not due to pK_a differences for as we have seen the 18-crown-5-phenol and 2,6-dimethylphenol have identical pK_a values, but it can be interpreted as resulting from enhanced stabilization of the crown ether phenoxide (**15**) through hydrogen-bonding solvation of the ammonium ion by the crown ether oxygen atoms. However, the crown size is also important: when the smaller 15-crown-4-phenol was exposed to ammonia in methanol only slight (ca. 5%) conversion to the phenoxide was detected, but the larger 21-crown-6-phenol showed complete conversion to phenoxide. In cycles **7** and **8**, with 18- and 21-membered rings, respectively, the ammonium ion can lie close to the phenoxide oxygen atom while simultaneously accommodated by the encircling oxygen atoms. Ammonium 2,6-dimethylphenoxide is not capable of this kind of additional stabilization. Phenoxide generation was also observed by UV spectroscopy with the 18-crown-5-phenol and methylamine, ethylamine, *tert*-butylamine, 1-phenylethylamine, and ethanolamine in methanol. No conversion was observed with secondary or tertiary amines in methanol. Addition of *tert*-butylamine, methylamine, or 1-phenylethylamine to a carbon tetrachloride solution of the 18-crown-5-phenol led to the slow formation of large colorless crystals, but these reverted to their components on isolation.

The stability of crystalline crown phenol–amine salts was increased significantly when the *p*-nitro group was added to the aromatic ring. The *p*-nitro-18-crown-5-phenol (**10**) was found to give the greatest range of crystalline salts: **16**, mp 155–159 °C; **17**, mp 135–137.5 °C; **18** mp 144–145 °C; and **19**, mp 172–175 °C. The *p*-nitro-21-crown-6-phenol (**11**) also gave crystalline salts with amines, though under more limited conditions, the salts tending to oil out of solution rather than crystallise. The *p*-nitro-15-crown-4-phenol (**9**) formed a salt with ammonia which was thermally unstable, revering to the free phenol on melting. The *p*-nitro-18-crown-5-phenol also gave 2:1 salts with diamines; 1,2-diaminoethane gave **20**, mp 164–167 °C, while 1,3-propanediamine gave **21**, mp 184.0–186.5 °C.

The *p*-nitro-18-crown-5-ammonium phenoxide (**16**) was chosen for X-ray crystallographic analysis to probe the relationship between the primary binding site (the phenoxide oxygen atom), the secondary binding sites (the ethereal oxygen atoms), and the overall receptor–guest topology. A stereoview of **16** is shown in Figure 6. The torsion angle pattern in the macrocycle is close to gauche about C–C bonds and close to anti about C–O bonds with the exception of C(2)–C(16)–O(6)–C(15) (−70°). The conformation adopted by **16** is undoubtedly a consequence of the incorporation of the $^+NH_4$ ion into the cavity via the formation of three N—H···O hydrogen bonds, one to the phenoxide oxygen (N···O(1) 2.690 (4) Å) and two to ethereal oxygens (N···O(3) 2.884 (4) Å, and N···O(5) 2.883 (4) Å). Space for the ammonium ion is achieved by increasing the dihedral angle between the aromatic and macrocyclic ring planes to 58° (cf. 28° in **7** and 47° in **10**) as shown in Figure 3c. The remaining hydrogen atom of the $^+NH_4$ ion points away from the ring cavity and is involved in an intermolecular N—H···O hydrogen bond (N···O 2.781 (4) Å) to the phenoxy oxygen of an adjacent molecule. In this way, centrosymmetric hydrogen-bonded dimers are formed.

The principal dimensions for **16** are in Table I. The mean C_{sp^3}–C_{sp^3} bond length in the macrocyclic ring is 1.489 (4) Å, and the mean C–O bond length is 1.417 (3) Å, in accord with values found in **7** and **10** and other molecules.[44-50] The dimensions of the phenoxide moiety deserve comment; the bond lengths (Table I) are consistent with a significant contribution from a form such as **16a** with the formal negative charge on the phenoxide oxygen delocalized into the nitrophenyl ring and significant quinoid character. This is exactly the situation with many picrate salts where the phenoxide C–O distances indicate substantial double bond character and the adjacent C–C bonds in the aromatic ring are lengthened.[55,56] The similarity to picrate structures even extends to the packing of **16**, thus pairs of phenoxide rings are packed around crystallographic twofold axes with a characteristic plane-to-plane overlap and a mean interplane spacing of 3.39 Å. Stereoviews of the packing diagrams of **7**, **10**, and **16** have been

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(56) Ferguson, G.; Kaitner, B.; Lloyd, D.; McNab, J. C. *J. Chem. Res. (s)*, **1984**, 182–185.

deposited. Neither **7** nor **10** has plane-to-plane stacking of aromatic rings as found in **16**.

In summary, we have devised structures with convergence between a phenolic group acting as a primary binding site and a macrocyclic oxygenated array acting as a secondary binding site and have shown how the two types of binding can be employed synergistically for the reception of ammonia and primary amines. This study should assist in the design of more elaborate and structured receptors with several primary binding sites for host–guest reception.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra were recorded on an Hitachi Perkin-Elmer R20-A spectrometer at 60 MHz with tetramethylsilane as internal standard. IR spectra were obtained on a Perkin-Elmer 257 grating spectrophotometer. Mass spectra were measured at 70 eV on an AEI MS-30 spectrometer. Ultraviolet spectra were recorded on a Perkin-Elmer 124 spectrophotometer. Combustion analyses were performed by the Microanalysis Laboratory, University College, Cork.

2,6-Bis(bromomethyl)anisole (1). 2,6-Dimethylanisole (Aldrich) in ether was shaken with 2 N NaOH to remove traces of 2,6-dimethylphenol and then distilled and brominated with freshly recrystallised *N*-bromosuccinimide in carbon tetrachloride to afford the dibromide, mp 79.0–81.5 °C (from ether) (lit.[41] mp 75 °C).

2-Methoxy-1,3-xylyl-15-crown-4 (2). To a suspension of sodium hydride (6.0 g, 0.25 mol) in dry tetrahydrofuran (25 mL) was added dropwise over 3 h with stirring a solution of dibromide **1** (18.0 g, 0.06 mol) and triethylene glycol (9.0 g, 0.06 mol) in tetrahydrofuran (100 mL). The mixture was heated with stirring under reflux for 12 h and then cooled and water was added dropwise until gas evolution ceased. Inorganic salts were removed by filtration, and the filtrate was concentrated to an oil. The crude product was distilled to afford 7.2 g (45%) of crown anisole **2**: bp 115–116 °C (0.001 torr); ^{1}H NMR ($CDCl_3$) δ (at 40 °C), 7.30–6.80 (3 H, *m*, aromatic), 5.04–3.99 (4 H, AB q, benzylic), 3.89 (3 H, s, OMe), 3.70–2.90 (12 H, m, $-OCH_2CH_2O-$); IR (film) 2890, 1590, 1470, 1080 cm^{-1}; *m/e* (%) 282 (M^+, 68), 133 (92), 91 (56), 89 (100). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.83; H, 7.80. Found: C, 63.75; H, 7.98.

2-Methoxy-1,3-xylyl-18-crown-5 (3). Dibromide **1** (45.0 g, 0.15 mol) and tetraethylene glycol (32.0 g, 0.17 mol) were cyclized in tetrahydrofuran containing sodium hydride following the procedure described above for **2**. The crude product was distilled to afford 28.7 g (58%) of **3**: bp 150–151 °C (0.005 torr); mp 50.0–50.5 °C (from heptane); ^{1}H NMR ($CDCl_3$) δ 7.30–6.80 (3 H, m, aromatic), 4.69 (4 H, s, benzylic), 4.21 (3 H, s, –OMe), 3.54–3.67 (16 H, m, $-OCH_2CH_2O-$); IR (KBr) 2860, 1100 cm^{-1}; *m/e* (%) 326 (M^+, 21), 123 (83), 91 (100), 86 (62). Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.57; H, 7.98. Found: C, 62.80; H, 8.61.

2-Methoxy-1,3-xylyl-21-crown-6 (4). Dibromide **1** (20.0 g, 0.07 mol) and pentaethylene glycol (16.2 g, 0.07 mol) were cyclized in tetrahydrofuran containing sodium hydride following the procedure described above for **2**. The crude product was distilled to afford 12.8 g (51%) of **4**: bp 200 °C (0.005 torr); mp 82.0–82.5 °C (from heptane); ^{1}H NMR ($CDCl_3$) δ 7.50–6.90 (3 H, m, aromatic), 4.61 (4 H, s, benzylic), 4.04 (3 H, s, –OMe), 3.70–3.56 (20 H, m, $-OCH_2CH_2O-$); IR (KBr) 2870, 1080 cm^{-1}; *m/e* (%) 370 (M^+, 25), 149 (37), 133 (100), 119 (37), 91 (69), 89 (87). Anal. Calcd for $C_{19}H_{30}O_7$: C, 61.62; H, 8.11. Found C, 61.93; H, 8.03.

2-Hydroxy-1,3-xylyl-15-crown-4 (6). Anhydrous lithium iodide (Alpha) (14.0 g, 0.10 mol) and crown ether anisole **2** (14.1 g, 0.05 mol) were dissolved in dry pyridine (100 mL) under dry nitrogen, and the solution was heated under reflux with stirring for ca. 8 h. Pyridine was removed at reduced pressure, and water (50 mL) was added. The solution was again concentrated at reduced pressure and more water added and the process repeated. The residue was redissolved in water (50 mL), and the solution was acidified with dilute hydrochloric acid. Extraction with chloroform (5 × 100 mL) followed by removal of the solvent gave a tarry residue which on trituration with hot carbon tetrachloride or heptane (5 × 100 mL) gave **6** as a colorless oil which slowly crystallized on standing. Alternatively, the crude product could be purified by chromatography on silica gel (600 g) with a 80:20 chloroform:hexane, chloroform, chloroform:metahnol gradient to give 12.2 g (91%) of **6** which crystallized on standing. Recrystallization from hot heptane gave colorless needles: mp 66.0–66.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.70 (1 H, s, OH), 7.25–6.65 (3 H, m, aromatic), 4.62 (4 H, s, benzylic), 3.62 (12 H, s, $-OCH_2CH_2O-$); IR (KBr) 3400, 1090 cm^{-1}; *m/e* (%) 268 (78, M^+), 120 (70), 91 (68), 89 (100). Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.69; H, 7.46. Found: C, 62.86; H, 7.33.

2-Hydroxy-1,3-xylyl-18-crown-5 (7). Crown ether anisole **3** (16.3 g, 0.05 mol) was subjected to the procedure above for demethylation of **2** with a reaction time of 10 h, to give, after purification of the product by column chromatography on silica gel, the phenol **7**: 14.4 g (92%); mp 49.0–51.0 °C (from heptane); ^{1}H NMR ($CDCl_3$) δ 7.90 (1 H, 6 s, OH), 7.25–6.55 (3 H, m, aromatic), 4.60 (4 H, s, benzylic), 3.63 (16 H, s, $-OCH_2CH_2O-$); IR (KBr) 3360, 1080 cm^{-1}; *m/e* (%) 312 (M^+, 87), 177 (51), 141 (13), 136 (32), 134 (15), 133 (72), 132 (18), 121 (71), 120 (78), 92 (65), 91 (77), 90 (100). Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.54; H, 7.69. Found: C, 61.49; H, 7.74.

2-Hydroxy-1,3-xylyl-21-crown-6 (8). Crown ether anisole **4** (6.0 g, 0.16 mol) was demethylated by using the procedure described above for **2** with a reaction time of 6 h to give, after purification by column chromatography on silica gel, the phenol **8** (4.1 g, 70%) as a viscous liquid which crystallized at 0 °C: ^{1}H NMR ($CDCl_3$) δ 8.00 (1 H, 6 s, OH), 7.40–6.65 (3 H, m, aromatic), 4.74 (4 H, s, benzylic), 3.77–3.72 (20 H, m, $-OCH_2CH_2O-$); IR (film) 3380 and 1080 cm^{-1}; *m/e* (%) 356 (M^+, 19), 281 (69), 135 (51), 108 (50), 95 (65), 91 (00). Anal. Calcd for $C_{18}H_{28}O_7$: C, 60.67; H, 7.87. Found: C, 60.79; H, 7.82.

2-Acetoxy-1,3-xylyl-15-crown-4 (12). A mixture of sodium hydride (0.5 g) and 15-crown-4-phenol (**6**) (0.75 g) in dimethoxyethane (40 mL) under dry nitrogen was heated under reflux for 1 h and then acetic anhydride (5 mL) was added dropwise. After a further 1 h the mixture was cooled and water (50 mL) was added. The aqueous mixture was heated at 60 °C for 30 min and then extracted with chloroform (3 × 25 mL). The combined extracts were washed with aqueous sodium bicarbonate and water and dried. Removal of the solvent followed by distillation at 150 °C (0.005 mmHg) gave the acetate **12** as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 7.40–7.00 (3 H, m, aromatic), 4.76, 4.55, 4.32, 4.02 (4 H, AB q, benzylic), 3.70–3.00 (12 H, m, $-OCH_2CH_2O-$), 2.31 (3 H, s, CH_3); IR (film) 1755 cm^{-1}; M/*e* (%) 310 (M^+, 28), 282 (12), 268 (26), 276 (18), 133 (60), 120 (58), 119 (40), 91 (100).

2-Acetoxy-1,3-xylyl-18-crown-5 (13). A sample of phenol **7** (0.9 g) was acetylated with acetic anhydride following the procedure just described for phenol **6** to give **13** as a colorless oil: bp 170 °C (0.005 mmHg) (0.4 g); ^{1}H NMR ($CDCl_3$) δ 7.40–6.30 (3 H, m, aromatic)8 4.65, 4.47, 4.26, 4.16 (4 H, AB q, benzylic), 3.70–3.00 (16 H, m, $-OCH_2CH_2O-$), 2.31 (3 H, s, CH); IR (film) 1750 cm^{-1}; *m/e* (%) 354 (M^+, 15), 311 (15), 177 (19), 135 (23), 133 (35), 120 (42), 119 (42), 91 (58), 89 (100).

5-Nitro-2-hydroxy-1,3-xylyl-15-crown-4 (9). Phenol **6** (2.0 g) in water (500 mL) at 20 °C was nitrated by adding sodium nitrite (6.0 g) followed by concentrated nitric acid (5 mL). After the mixture was stirred at 20 °C for 30 min, TLC with methanol–chloroform (2:98) showed the absence of starting material. The aqueous solution was extracted with chloroform (6 × 75 mL), and the combined extracts were washed with water and dried. Removal of solvent left a brown oil (2.4 g) which on trituration with hot heptane (5 × 50 mL) gave **9** (2.1 g, 92%): mp 105.5–106.0 °C after recrystallization from carbon tetrachloride; ^{1}H NMR ($CDCl_3$) δ 8.80 (1 H, br s, OH), 8.12 (2 H, s, aromatic), 4.72 (4 H, s, benzylic), 4.00–3.50 (12 H, *m*, $-OCH_2CH_2O-$); *m/e* (%) 313 (M^+, 87), 296 (7), 180 (7), 166 (14), 165 (70), 164 (46), 149 (13), 133 (100), 119 (16), 91 (47), 90 (45), 89 (97). Anal. Calcd for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.06; N, 4.47. Found: C, 53.54; H, 5.97; N, 4.47.

5-Nitro-2-hydroxy-1,3-xylyl-18-crown-5 (10). Application of the above nitration procedure to crown phenol **7** gave **10** (93%), mp 91.0–91.5 °C, after recrystallization from carbon tetrachloride; ^{1}H NMR ($CDCl_3$) δ 9.10 (1H, br s, OH), 8.20 (2 H, s, aromatic), 4.79 (4 H, s, benzylic), 3.96–3.50 (16 H, m, $-OCH_2CH_2O-$); *m/e* (%) 357 (M^+, 15), 313 (38), 165 (28), 164 (20), 133 (46), 89 (100). Anal. Calcd for $C_{16}H_{23}NO_8$: C, 53.78; H, 6.45; N, 3.92. Found: C, 53.78; 6.50; N, 3.85.

5-Nitro-2-hydroxy-1,3-xylyl-21-crown-6 (11). Application of the above procedure to crown phenol , gave **11** (92%), mp 73.0–73.5 °C, after recrystallization from benzene–heptane: ^{1}H NMR ($CDCl_3$) δ 8.22 (2 H, s, aromatic), 4.81 (4 H, s, benzylic), 3.90–3.40 (20 H, m, $-OCH_2CH_2O-$); *m/e* (%) 401 (M^+, 95), 384 (100), 180 (15), 118 (20), 177 (22), 165 (54), 164 (92), 149 (15), 148 (14), 134 (20), 133 (91), 131 (15), 91 (39), 90 (39), 89 (100). Anal. Calcd for $C_{18}H_{27}NO_9 \cdot H_2O$: C, 51.55; H, 6.92; N, 3.34. Found: C, 51.78; H, 6.88; N, 3.50.

Salt Formation with Crown Phenols. Salts were prepared by adding gaseous ammonia or the liquid amine in slight excess to a solution of the phenol in the solvent indicated.

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Table IV. Crystal Data and Data Collection Summary for **7**, **10**, **16**

	7	10	16
formula	$C_{16}H_{24}O_6$	$C_{16}H_{23}NO_8$	$C_{16}H_{26}N_2O_8$
M_r	312.4	357.4	374.4
space group[a]	$Pc2_1b$	$P2_1/c$	$I2/a$
crystal system	orthorhombic	monoclinic	monoclinic
cell dimensions			
a, Å	9.779 (2)	10.503 (1)	20.476 (2)
b, Å	18.943 (3)	9.003 (3)	9.092 (3)
c, Å	8.915 (2)	18.924 (3)	21.211 (2)
β, deg		101.98 (1)	108.92 (1)
V, Å^3	1651.4	1750.5	3733.8
Z	4	4	8
density calcd, g cm^{-3}	1.26	1.36	1.33
crystal dimensions, mm	0.40 × 0.25 × 0.20	0.45 × 0.18 × 0.15	0.40 × 0.30 × 0.20
λ, Å	0.70926	0.70926	0.70926
μ, cm^{-1}	1.03	1.02	1.00
θ_{max}, deg	25	20	27
scan type	$\omega/2\theta$	$\omega/2\theta$	$\omega/2\theta$
ω-scan width, deg	all (0.60 + 0.35 tan θ)		
unique data measured	1506	1627	4186
data used ($I > 3\sigma(I)$)	759[b]	1189	2635[b]
final no. least-squares parameters	190	230	248
R	0.053	0.032	0.053
R_w, $(\sum w\Delta^2/\sum wF_o^2)^{1/2}$	0.061	0.034	0.061

[a] For **7** systematic absences are as follows: $hk0$ absent if k is odd and $0kl$ if l is odd, consistent with either $Pc2_1b$ or $Pcmb$. $Pc2_1b$ chosen and confirmed by analysis. $Pc2_1b$ is a nonstandard setting of $Pca2_1$ with equivalent positions x, y, z; $-x, {}^1/_2 + y, -z$; $x, {}^1/_2 + y, {}^1/_2 - z$; and $-x, y, {}^1/_2 + z$. For **10** systematic absences are $h0l$ absent if l is odd and $0k0$ if k is odd. Space group determined unequivocally. For **16** systematic absences are hkl absent if $h + k + l$ is odd and $h0l$ if h and l are both odd, consistent with either $I2/a$ or Ia. $I2/a$ chosen and confirmed by analysis. $I2/a$ is a nonstandard setting of $C2/c$ with equivalent positions $[(\pm)({}^1/_2,{}^1/_2,{}^1/_2)][(x,y,z)$ and $({}^1/_2 + x, -y, z)]$. [b] The crystals did not diffract at all well beyond θ Mo Kα of 20°, hence the relatively small total of observed reflections for **7** and **16**.

18-Crown-6-nitrophenol (**7**) and (a) ammonia gave yellow rhombic crystals of **16**, mp 155.0–159.0 °C, from methanol. Anal. Calcd for $C_{16}H_{30}N_2O_8$: C, 51.34; H, 6.95; N, 7.48. Found: C, 51.16; H, 7.02; N, 7.39. (b) Ethanolamine gave brown rhombic crystals, mp 172.0–175.0 °C, from methanol. Anal. Calcd for $C_{18}H_{30}N_2O_9$: C, 51.67; H, 7.18; N, 6.70. Found: C, 51.63; H, 7.30; N, 6.66. (c) And *tert*-butylamine gave yellow rhombic crystals, mp 135.5–137.5 °C, from benzene–heptane. Anal. Calcd for $C_{20}H_{34}N_2O_8$: C, 55.80; H, 7.81; N, 6.51. Found: C, 55.80; H, 7.81; N, 6.51. (d) (±)-1-Phenylethylamine gave yellow rhombic crystals, mp 144.0–145.0 °C, from carbon tetrachloride. Anal. Calcd for $C_{24}H_{34}N_2O_8$: C, 60.25; H, 7.11; N, 5.85. Found: C, 60.56; H, 7.06, N, 5.99. (e) 1,2-Diaminoethane gave crystals, mp 164–167 °C, from methanol. Anal. Calcd for $C_{34}H_{54}N_4O_{16}$: C, 52.22; H, 6.98; N, 6.91. Found: C, 52.71; H, 6.98; N, 7.23. (f) 1,3-Diaminopropane gave crystals, mp 184.0–186.5 °C, from methanol. Anal. Calcd for $C_{35}H_{56}N_4O_{16}$: C, 53.29; H, 7.10; N, 7.10. Found: C, 53.48; H, 7.35; N, 7.07. (g) Sodium hydroxide gave yellow crystals, mp 97–98 °C, from chloroform–hexane. Anal. Calcd for $C_{16}H_{22}NO_8Na$: C, 50.67; H, 5.81; N, 3.70. Found: C, 50.60; H, 5.91; N, 3.58.

The following salts of the 21-crown nitrophenol (**11**) were prepared: ammonia gave yellow prisms, mp 140–153 °C, from methanol–benzene; *tert*-butylamine gave yellow rhombic crystals, mp 130.0–132.0 °C, from methanol–benzene; potassium hydroxide gave yellow crystals from chloroform, m/e 439 (M^+).

Determination of pK_a Values. A glass cell (36-mL capacity) equipped with quartz windows was mounted in the cell compartment of a Cary 14 spectrophotometer. A Metrohm EA 1250 combined pH electrode dipped into the cell contents above the light beam. The electrode, coupled to an automatic titration apparatus, controlled the addition of base which passed through a Teflon capillary tube. The Radiometer pH-state assembly consisted of a pH meter (type PHM 26), a titrator (type TTT 116), and an auto-burette (type ABU 1C). All pH values were those measured directly from the solutions, no further corrections being applied. The electrode was standardized immediately before use with Radiometer buffer solution (pH 4.01 and 9.22 at 25 °C). Addition of 1 N sodium hydroxide from the automatic titrator was used to vary the pH of the sample solution at preset intervals. Readings of absorbance at each pH setting were taken. The pK_a values were determined by comparing the experimental titration curves with theoretical curves plotted with the equation

$$(\text{Abs})_{obsd} = (\text{Abs})_{max}K_a/(a_H + K_a)$$

where $(\text{Abs})_{obsd}$ is the observed absorobance, $(\text{Abs})_{max}$ is the absorbance maximum, K_a is the equilibrium constant for the ionization reaction, and a_H is the activity of the proton released.

Table V. Final Fractional Coordinates (×10^4) for **7** with Estimated Standard Deviations in Parentheses

atom	x	y	z
O(1)	2514 (5)	3837[a]	3112 (6)
O(2)	570 (6)	3395 (6)	5655 (8)
O(3)	1081 (7)	1907 (5)	5221 (7)
O(4)	3897 (7)	1463 (5)	4230 (9)
O(5)	4892 (7)	3036 (5)	2361 (11)
O(6)	5384 (6)	4316 (5)	3648 (7)
C(1)	2364 (7)	4442 (4)	3858 (6)
C(2)	3346 (7)	4975 (4)	3818 (6)
C(3)	3124 (7)	5605 (4)	4592 (6)
C(4)	1920 (7)	5701 (4)	5405 (6)
C(5)	938 (7)	5168 (4)	5445 (6)
C(6)	1160 (7)	4538 (4)	4672 (6)
C(7)	110 (9)	3950 (9)	4781 (13)
C(8)	−404 (10)	2826 (9)	5771 (14)
C(9)	305 (13)	2171 (8)	6386 (14)
C(10)	1877 (14)	1312 (8)	5692 (12)
C(11)	2700 (12)	1058 (6)	4488 (12)
C(12)	3717 (10)	2082 (6)	3416 (12)
C(13)	5054 (11)	2418 (7)	3229 (13)
C(14)	6168 (15)	3388 (9)	2208 (31)
C(15)	6396 (12)	3970 (10)	2784 (19)
C(16)	4629 (11)	4865 (6)	2940 (11)

[a] Held constant to define the origin.

Table VI. Final Fractional Coordinates for **10** (×10^4) with Estimated Standard Deviations in Parentheses

atom	x	y	z
N	2680 (3)	1858 (3)	5313 (1)
O(1)	6121 (2)	−1233 (2)	7422 (1)
O(2)	4259 (2)	−1033 (2)	8215 (1)
O(3)	6448 (2)	736 (2)	8804 (1)
O(4)	8942 (2)	1810 (2)	8527 (1)
O(5)	9660 (2)	1454 (2)	7130 (1)
O(6)	7468 (2)	917 (2)	5813 (1)
O(7)	1515 (2)	1833 (3)	5311 (1)
O(8)	3135 (2)	2582 (3)	4875 (1)
C(1)	5238 (3)	−517 (3)	6908 (2)
C(2)	5709 (3)	160 (3)	6352 (2)
C(3)	4863 (3)	935 (3)	5826 (2)
C(4)	3560 (3)	996 (3)	5859 (2)
C(5)	3082 (3)	301 (3)	6398 (2)
C(6)	3908 (3)	−475 (3)	6930 (2)
C(7)	3443 (3)	−1283 (4)	7526 (2)
C(8)	4165 (3)	443 (4)	8471 (2)
C(9)	5287 (3)	773 (4)	9068 (2)
C(10)	7517 (4)	1245 (4)	9330 (2)
C(11)	8765 (3)	927 (4)	9114 (2)
C(12)	10216 (3)	1664 (4)	8391 (2)
C(13)	10294 (3)	2376 (4)	7698 (2)
C(14)	9467 (3)	2126 (4)	6438 (2)
C(15)	8836 (3)	1050 (4)	5868 (2)
C(16)	7143 (3)	70 (3)	6379 (2)

X-ray Crystal Structure Analyses of 7, 10, and 16. For the three structures, accurate cell parameters were obtained by least-squares refinement of the setting angles of 25 reflections (with θ in the range 10–15°) measured on an Enraf Nonius CAD4 diffractometer using graphite monochromatized Mo–Kα radiation. In each case intensities were collected by the $\omega/2\theta$ scanning procedure. The stability of each crystal was checked by measurement of three reflections at regular intervals; there was no evidence of crystal decay. All data were corrected for Lorentz and polarization effects; absorption correction was not considered necessary. Crystal data and a summary of the data collection procedure are given in Table IV.

The structures were solved by direct methods with MULTAN 80.[57] In each case, the first E-map revealed all the non-hydrogen atoms. Initial full-matrix least-suares refinement[58] allowing the atoms isotropic vibra-

Table VII. Final Fractional Coordinates ($\times 10^4$) for **16** with Estimated Standard Deviations in Parentheses

atom	x	y	z
N(1)	1636 (1)	2891 (3)	2291 (1)
N(2)	1410 (1)	-1681 (3)	4975 (1)
O(1)	2488 (1)	1937 (2)	3472 (1)
O(2)	1135 (1)	3655 (2)	3584 (1)
O(3)	582 (1)	4983 (2)	2306 (1)
O(4)	228 (1)	3014 (2)	1185 (1)
O(5)	967 (1)	412 (2)	1494 (1)
O(6)	2142 (1)	-726 (2)	2552 (1)
O(7)	1108 (1)	-1123 (3)	5338 (1)
O(8)	1511 (1)	-3017 (3)	4970 (1)
C(1)	2183 (1)	1105 (3)	3780 (1)
C(2)	2198 (1)	-465 (3)	3720 (1)
C(3)	1946 (1)	-1344 (3)	4111 (1)
C(4)	1644 (1)	-735 (3)	4552 (1)
C(5)	1570 (1)	781 (3)	4578 (1)
C(6)	1816 (1)	1691 (3)	4193 (1)
C(7)	1701 (2)	3307 (3)	4184 (1)
C(8)	1056 (2)	5164 (3)	3476 (2)
C(9)	450 (2)	5461 (3)	2887 (2)
C(10)	15 (1)	5174 (3)	1717 (1)
C(11)	210 (1)	4576 (3)	1148 (1)
C(12)	515 (2)	2364 (4)	732 (1)
C(13)	551 (2)	741 (4)	832 (1)
C(14)	1149 (2)	-1091 (3)	1590 (1)
C(15)	1489 (1)	-1401 (3)	2317 (1)
C(16)	2507 (1)	-1113 (3)	3227 (1)

tion reduced R to 0.183, 0.113, and 0.157 for **7**, **10**, and **16**, respectively; these values dropped to 0.074, 0.084, and 0.095 on allowing anisotropic thermal motion in the refinement. All of the hydrogen atoms involved in hydrogen bonding and most of the remaining hydrogen atoms were visible in difference maps and were included in subsequent refinement cycles with fixed idealized geometry (C-H, N-H 0.95 Å); only overall isotropic temperature factors U_{iso} for H atoms were allowed to refine. All the atoms of **7**, but especially the aromatic ring, showed large thermal motion and/or small disorder. For computational convenience the aromatic ring was constrained to refine as a rigid group with C-C = 1.395 Å and C-C-C = 120°. At the conclusion of the refinements, the values of R and $R_w = [\sum w\Delta^2/\sum F_o^2]^{1/2}$ were respectively 0.053 and 0.061 for **7**, 0.032 and 0.034 for **10** and 0.053 and 0.061 for **16**. Atomic scattering factors for carbon, nitrogen, and oxygen were taken from ref 59, and those for hydrogen were taken from ref 60. For the refinements, weights were derived from the counting statistics, and difference electron-density maps computed at the conclusion of refinements were essentially featureless. The final fractional coordinates for non-hydrogen atoms with estimated standard deviations for **7**, **10**, and **16** are given in Tables V-VII, respectively. Tables of thermal parameters, molecular dimensions, hydrogen atom positions, mean-plane data, crystal-packing diagrams, and structure factor listings are available as supplementary material.

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Registry No. 1, 30787-74-7; **2**, 65112-33-6; **3**, 65112-34-7; **4**, 81336-34-7; **6**, 65112-35-8; **7**, 65112-36-9; **8**, 94707-40-1; **9**, 65112-37-0; **10**, 65112-38-1; **10**·(±)-1-phenylethylamine, 94707-41-2; **10**·$^1/_2$(1,2-diaminoethane), 94731-57-4; **11**, 94707-43-4; **11**·NH_3, 94707-44-5; **11**·*t*-$BuNH_2$, 94707-45-6; **11**·K, 94707-48-9; **12**, 94707-46-7; **13**, 94707-47-8; **14**, 65198-21-2; **15**, 64975-19-5; **17**, 64975-20-8; **19**, 94707-42-3; **21**, 94731-58-5; 2,6-dimethylanisole, 1004-66-6; triethylene glycol, 112-27-6; tetraethylene glycol, 112-60-7; pentaethylene glycol, 4792-15-8; LiI, 10377-51-2.

Supplementary Material Available: Thermal parameters, calculated hydrogen coordinates, mean plane data, molecular dimensions, stereoviews of packing diagrams, and listings of observed and calculated structure amplitudes for **7**, **10**, and **16** (38 pages). Ordering information is given on any current masthead page.

Stereoselective Total Synthesis of the Complement Inhibitor K-76

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Abstract: A 21-step stereoselective total synthesis of (±)-K-76 is reported starting from 6-acetoxy-4-methyl-4-hexenal (**23**) and 3-methoxy-2-cyclohexenone (**6**). The key steps in the synthesis are the demonstration that alkylidenecyclopropanes such as **27** can serve as initiators for electrophile-induced polyene cyclizations, the development of a new method for conversion of organomercurials such as **28** into olefins, and the demonstration that phenyl boronate protecting groups can serve to moderate the basicity of 1,2-diols such as **39**.

The human complement system consists of more than 20 serum proteins that function collectively to protect the host from invading microorganisms.[1] Several cellular events, termed the inflammatory response, are closely associated with the action of complement. This response aids in the defense of the host by localizing lymphocytes (cells that mediate immunological reactions) and phagocytes (cells that ingest immune complexes) at the site of infection.

The inflammatory response can also be detrimental to the host. Persistent stimulation of the complement system can lead to chronic inflammation and local tissue damage. This self-destructive pathway is characteristic of rheumatoid arthritis and many other immune-complex diseases.[2] Although the biological factors that account for the acute hypersensitivity associated with these diseases are not completely understood, available evidence clearly implicates complement activation as a key step. Thus, some control of the inflammatory response might be possible upon development of agents that inhibit activation of the complement system.

K-76 (**5**), a fungal metabolite recently isolated[3] from *Stachybotrys complementi* nov. sp. K-76 as the result of a massive screening effort involving over 3000 strains of fungi, has been

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