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# Macrocyclic receptor molecules with a pendant carboxylic acid group for the complexation of urea

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**Abstract.** The synthesis of 5,5′-di-*tert*-butyl-3-(carboxymethyl)biphenyl† crown ethers and several lariat ethers with pendant carboxylic acid groups, together with the determinations of the p$K_a$ values of these crown ether carboxylic acids, are described. In addition, the complexation of urea by these crown ethers has been investigated. Both the larger-ring biphenyl crown ethers ($\geqslant$29 ring atoms) and lariat ethers ($\geqslant$27 ring atoms) solubilized urea in chloroform. The data for urea complexation by the lariat ethers show that, for assistance in urea complexation, it is important for the carboxylic acid group to be located close to the macrocyclic ring. When the carboxylic acid group of the lariat ethers is located in an appropriate position, urea is complexed by 21–27% of these macrocyclic ligands, as is also the case with the biphenyl crown-ether carboxylic acids. These results demonstrate that a pendant carboxylic acid group can assist in the complexation of a neutral molecule.

Previously we have described the complexation of urea and uronium salts with different crown ethers[1,2]. The crystal structure of the benzo-27-crown-9-uronium perchlorate complex showed that the cation is completely encapsulated in the cavity of the host and coordinated via all the hydrogen atoms of the guest. In this paper, we describe the effect of attaching a carboxylic acid group to the host molecule as an "internal" proton-donating group in order to investigate if such a group is able to participate in the complexation of a neutral guest. If proton transfer occurs within such a complex, the thermodynamic stability of the complex would be enhanced due to the charge separation which would increase the electrostatic interactions between host and guest.

A few examples of such proton transfer to other basic guest molecules have been reported[3-5]. *Cram* et al.[3] and *McKervey* et al.[4] have shown that a proton-donating group attached at the 2-position of 1,3-xylyl crown ethers is able to transfer a proton to a guest molecule, such as *tert*-butylamine or ammonia. Proton transfer from host to guest was also demonstrated by *Bauer* and *Gutsche*[5] for an "*endo*-calix" complex between *p*-allylcalix[4]arene and *tert*-butylamine, in which the proton of a phenolic group of the calixarene was transferred to the amine.

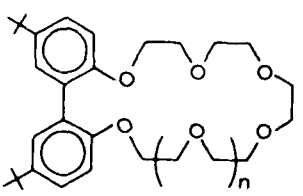
*Cram* and coworkers[6] have found that substituents at the 3- and 3′-positions of a binaphthyl crown ether interact with a complexed amino acid. Lariat ethers* offer an alternative approach to bring a functional group close to the crown ether cavity[7].

In the present study, we have used biphenyl crown ethers with one rather rigid side-chain attached at the 3-position of the biphenyl unit to situate a functional group close to the crown ether cavity. Consequently, we have studied several synthetic routes to mono-substituted biphenyl crown ethers. Hitherto, only *Cram* and coworkers have reported a mono-substituted binaphthyl crown ether as a side-product in the synthesis of 3,3′-disubstituted binaphthyl crown ethers[8]. We have also used crown ethers with a functionalized group attached to a flexible chain. The structures of all crown ethers used in this study are shown in Chart 1.

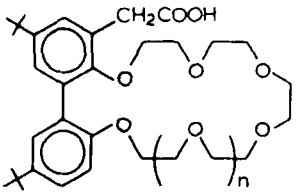
Two types of liquid–liquid phase transfer experiments were carried out with these crown ethers. Firstly, with the crown ethers **1** and crown ether carboxylic acids **3–6** we have studied the liquid–liquid phase transfer of urea from acidic aqueous solutions to chloroform as described for (di)benzo crown ethers[2]. Secondly, a different series of experiments was carried out without the addition of perchloric acid to the aqueous phase for crown ethers **3** and **4** and for crown

† *Chem. Abstr.* name: 5,5′-bis(1,1-dimethylethyl)biphenyl-3-acetic acid.

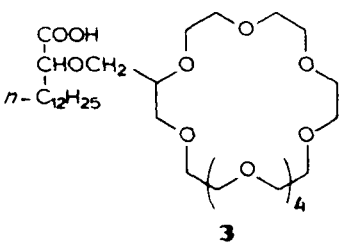
* Lariat ethers are macrocycles that carry one or more pendant arms in which one or more ligating sides are incorporated. These may or may not be involved in the complexation.



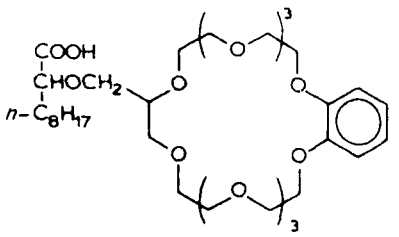
**1a**, $n = 2$
b, $n = 3$
c, $n = 4$
d, $n = 5$



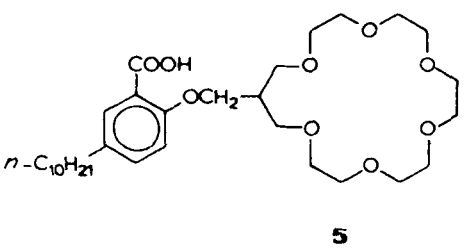
**2a**, $n = 3$
b, $n = 4$
c, $n = 5$



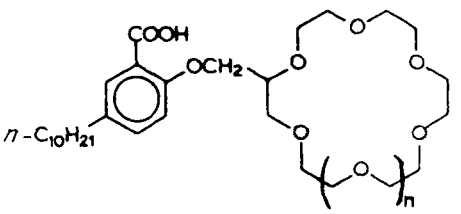
**3**



**4**



**5**



**6a**, $n = 1$
b, $n = 3$
c, $n = 4$
d, $n = 5$

ethers **2** and **6** with ring sizes of $\geqslant 27$. In this way, the influence of the ring size as well as the assistance of the carboxylic acid group of the crown ether on the complexation of urea have been evaluated.

In a third series of experiments we studied the solubilization (solid–liquid phase transfer) of urea in an apolar solvent by means of the crown ether carboxylic acids **2–4**, **6c** and **6d**.

In this paper, the syntheses of the crown ethers which appear in Chart 1, the dissociation constants for the crown ether carboxylic acids in methanol/water mixtures and the results of two-phase transfer of urea with these crown ethers are reported.

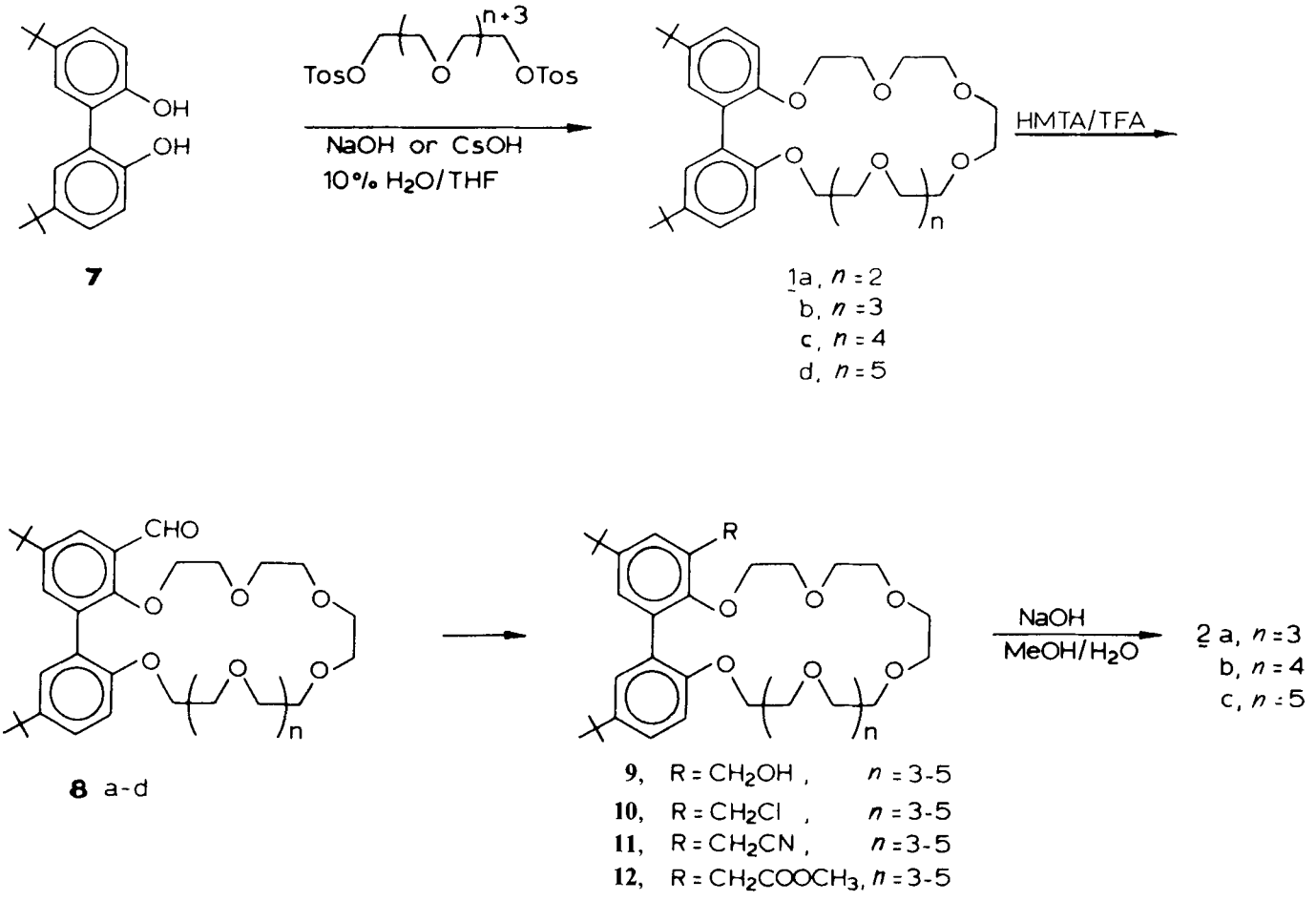
## Results and discussion

A convenient route to the preparation of 3-formyl biphenyl* crown ethers is the direct aromatic substitution of the corresponding unsubstituted biphenyl crown ethers. In the literature, the formylation of benzo crown ethers with hexamethylenetetramine (HMTA) in trifluoroacetic acid (TFA) has been described by *Wada* and coworkers[9]. This seemed to be a suitable reaction for the formylation of biphenyl crown ethers. Since such a formylation reaction would be expected to occur at positions *ortho* and *para* to an alkoxy substituent, it was necessary to block the 5-position of the biphenyl crown ethers.

The 5,5′-di-*tert*-butylbiphenyl crown ethers **1** were prepared from biphenyldiol **7** and an appropriate polyethylene glycol ditosylate (Scheme 1). The subsequent reaction with 1.5 equivalents of HMTA in TFA gave 3-formyl-5,5′-di-(*tert*-butyl)biphenyl crown ethers **8** in 33–96% yields. The $^{13}C$ NMR spectrum showed that twelve different aryl carbon atoms were present, at δ 112.0, 123.0–128.9, 132.1, 136.2, 143.4, 145.9, 153.6 and 158.2 (all ±0.2), with only one absorption below δ 120 which corresponds to an unsubstituted carbon atom in an *ortho* position relative to an alkoxy substituent. This establishes that only one aromatic ring was formylated at the 3-position[10]. In the unsubstituted biphenyl crown ethers **1**, only six different aryl-carbon atom absorptions were present, at δ 112.3, 124.7, 128.0, 129.0, 142.8 and 154.1 (±0.2). For the formylated biphenyl crown ethers **8**, two quaternary carbon absorptions at δ 34.2 and δ 34.5 (±0.2) and an absorption for a CHO-carbon atom at δ 191.5 ± 0.3 were observed. In the mass spectra of **8**, the molecular ion peaks were found. Thus, steric crowding at the 3-position, as we have previously found in the case of a chloromethylation reaction[10], does not seem to play a role in this formylation reaction. This is probably due to the less bulky reagents compared with the reactive intermediate in the chloromethylation reaction with chloromethyl methyl ether and $SnCl_4$ as catalyst. Very recently, *Lindsten* et al.[11] also reported that acetylation at the 3-position of a biphenyl crown ether is possible.

Further reactions to produce the biphenyl crown-ether carboxylic acids (Scheme 1) were carried out with three 3-formyl-5,5′-di(*tert*-butyl)biphenyl crown ethers **8** ($n$ = 3–5). Crown ether aldehydes **8** were reduced by

* *C.A.* name: biphenyl-3-carboxaldehyde.




*Scheme 1*

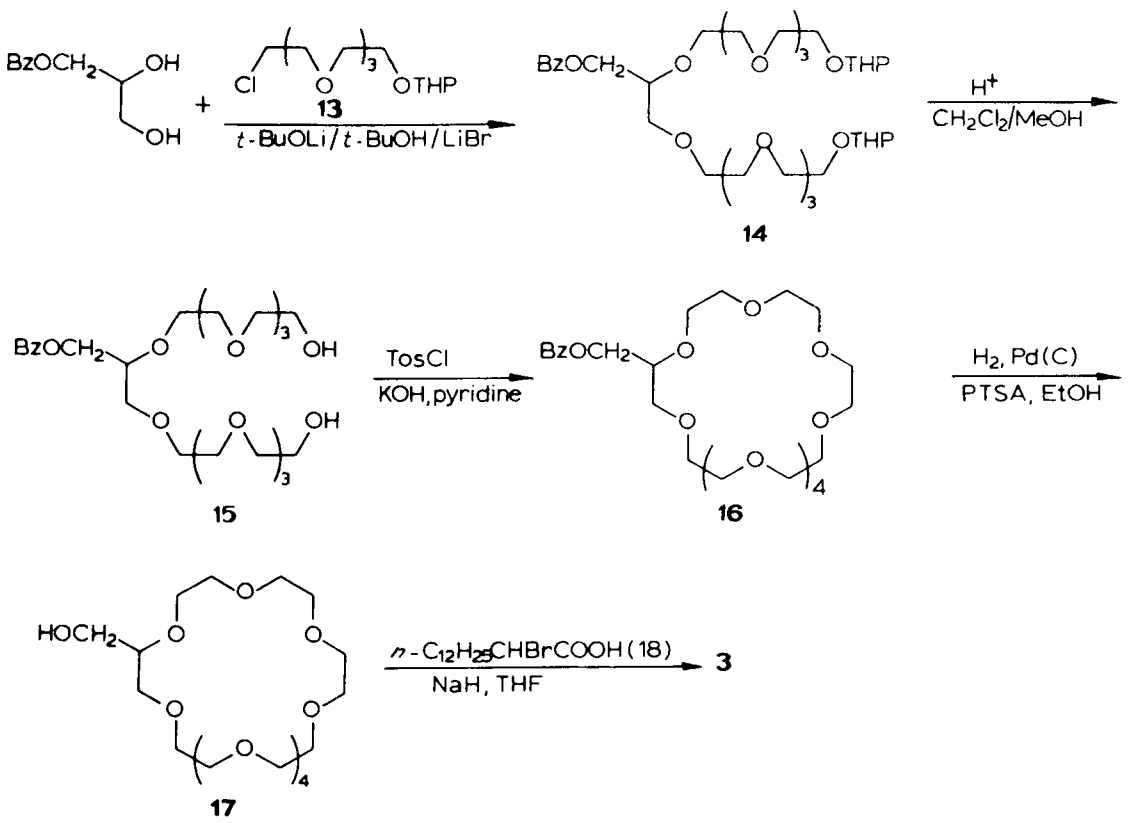
lithium aluminum hydride to the corresponding alcohols **9**, in yields of 67–80%. Absorptions for the CHO groups in both $^1$H NMR and $^{13}$C NMR spectra disappeared, while in the $^{13}$C NMR, spectral absorptions for the benzylic carbon atom appeared at δ 62.0. The signals for the benzylic protons in the $^1$H NMR spectra show that these protons are not equivalent, probably due to hydrogen bonding of the OH-hydrogen atom with a crown-ether oxygen atom, which is in agreement with the reported non-equivalency of the benzylic protons in 3,3′-bis(hydroxymethyl)biphenyl crown ethers[10]. In the IR spectra, OH absorptions were present between 3420 and 3470 cm$^{-1}$ and in the mass spectra molecular ion peaks were observed.

These 3-(hydroxymethyl)biphenyl crown ethers **9** were converted with thionyl chloride into the 3-chloromethyl crown ethers **10** in 54–87% yields. In the $^{13}$C NMR spectra, the benzylic carbon atom absorptions had shifted to δ 42.1, while in the $^1$H NMR spectra, singlets appeared for the benzylic protons. The mass spectra of these 3-(chloromethyl)biphenyl crown ethers **10** exhibited molecular ion peaks.

Upon reaction with KCN in acetonitrile, the 3-(chloromethyl)biphenyl crown ethers **10** were converted into 3-(cyanomethyl)biphenyl crown ethers **11**. The benzylic carbon atoms gave rise to absorptions in the $^{13}$C NMR spectra at δ 18.8 and, in the IR spectra, cyano group absorptions were observed between 2230 and 2260 cm$^{-1}$. In the mass spectra of **11**, molecular ion peaks were observed. These reactions which occurred in 83–90% yields can only take place due to the presence of the macrocyclic ring in compounds **10**, since KCN is virtually insoluble in acetonitrile[12]. The 3-(cyanomethyl)biphenyl crown ethers **11** were converted by the *Pinner* reaction[13] into 3-(methoxycarbonylmethyl)biphenyl crown ethers **12** in 55–86% yields.

While the cyano group absorptions in the IR spectra had disappeared, carbonyl-group absorptions appeared at 1740 cm$^{-1}$ for the crown ether esters **12**. Carbonyl-carbon absorptions were also observed in the $^{13}$C NMR spectra at δ 172.6 and, at δ 35.7, the benzylic carbon atoms exhibit an absorption. In the $^1$H NMR spectra, the absorptions due to the benzylic protons were complex. In the mass spectra, the molecular ion peaks of these crown ethers were observed. The 3-(methoxycarbonylmethyl)biphenyl crown ethers **12** were hydrolyzed with NaOH in 20% water/methanol to yield the biphenyl crown ether carboxylic acids **2**. Purification was accomplished by an acid–base extraction procedure. In the IR spectra, carbonyl-group absorptions at 1730 cm$^{-1}$ were present and, in the $^{13}$C NMR spectra, carbonyl-carbon atom absorptions at δ 173.2 ± 0.1 were found. The benzylic carbon atoms in the $^{13}$C NMR spectra absorbed at δ 36.9 ± 0.2. In the $^1$H NMR spectra, the line broadening observed for the benzylic protons indicates hydrogen bonding between carboxylic acid protons and crown-ether ring oxygen atoms of crown ethers **2**, analogous to the hydrogen bonding in the 3-(hydroxymethyl)biphenyl crown ethers **9**[10]. The hydroxymethyl crown ethers, which were used as starting materials for the synthesis of the lariat ether carboxylic acids **3–6**, were obtained from the corresponding benzyloxymethyl crown ethers by debenzylation with 10% Pd/C and a catalytic amount of *p*-toluenesulfonic acid (PTSA) in ethanol under 3.4 atmospheres of hydrogen at room temperature[14].

The synthesis of (benzyloxymethyl)-27-crown-9 (**16**) started from 3-*O*-benzylglycerol and the tetrahydropyranyl ether of 11-chloro-3,6,9-trioxa-1-undecanol (**13**), followed by deprotection and cyclization of the resulting benzyloxymethyl nonaethylene glycol (Scheme 2). This method gave a better cyclization yield (45%) than did a published procedure[14] in




*Scheme 2*

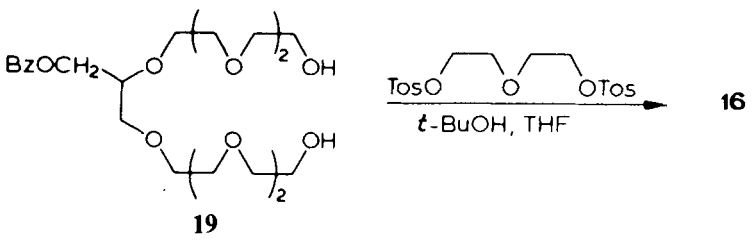
which a benzyloxymethyl pentaethylene glycol and tetraethylene glycol ditosylate were reacted with potassium *tert*-butoxide in THF to give this macrocyclic ligand in 38% yield. In Scheme 3, a second alternative procedure for the synthesis of compound **16** is given, also with a better yield (47%) than that reported in the previously published procedure[14]. Apparently, the yield of the macrocyclization reaction is enhanced by using a larger polyethylene glycol as starting material, which is probably better templated by potassium than the shorter polyethylene glycols. (Carboxymethoxy)methyl crown ether **3** was prepared from hydroxymethyl crown ether **17** and 2-bromotetradecanoic acid **18**. In Scheme 4, the synthetic route to (carboxymethoxy)-methyl benzo crown ether **4** is depicted. Benzyloxymethyl nonaethylene glycol ditosylate **20** was reacted with the cesium salt of catechol in acetonitrile[15] to give the benzyloxymethyl crown ether **21**. After debenzylation of crown ether **21**, as described for compound **16**, the hydroxymethyl crown ether **22** was reacted with sodium hydride and bromodecanoic acid (**23**) to give the (carboxymethoxy)-methyl benzo crown ether **4** in 56% yield.

(2-Carboxy-4-*n*-decylphenyloxy)methyl crown ethers **5** and **6** were prepared using a reported procedure[16].

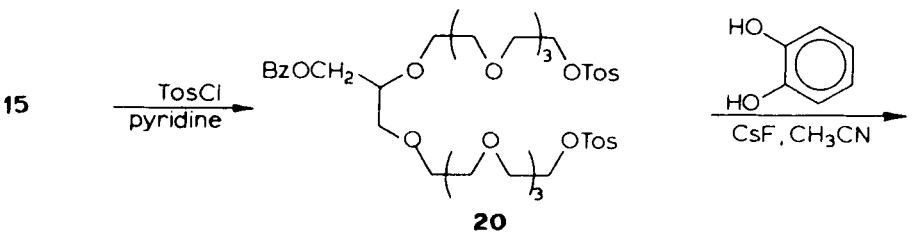
Dissociation constants for the crown ether carboxylic acids **2–6** were determined potentiometrically in 52.1 wt% MeOH/$H_2O$ at 25.0°C (Table I). Based on their acidities, the ligands **2–6** may be divided roughly into three classes: phenylacetic acids **2**, acetic acids **3** and **4** and benzoic acids **5** and **6**. Acidities of these classes of acids generally decrease in the following order (in $H_2O$): acetic acids > benzoic acids > phenylacetic acids[17]. The same order is observed for the carboxylic acid ligands under study in MeOH/$H_2O$.

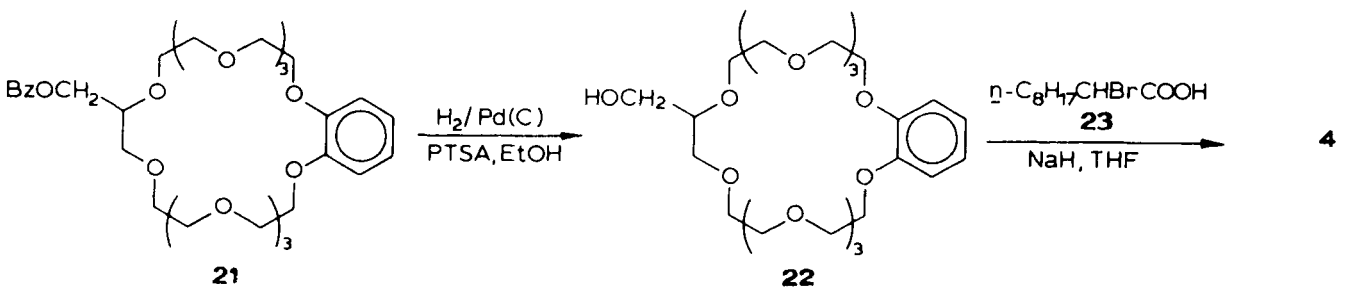
The p$K_a$ values of the three classes of the crown ether carboxylic acids do not show significant differences as a function of the ring size. For crown ethers bearing an intraannular acidic group, such as the 2,6-pyridinium[18], 2-carboxyl-1,3-xylyl[19] and 2-sulphinyl-1,3-xylyl crown ethers[20], we have observed acidities which depend strongly on the ring size of the ligands. This ring-size dependence is explained in terms of intraannular hydrogen bonding and macro-ring-assisted solvation *(vide infra)*. In order to further examine the presence of intramolecular stabilizing interactions between the carboxylic group and the (solvated) ligand, we determined the p$K_a$ values of a simple model compound for each class of acid. The p$K_a$ values of phenylacetic acid, 2-methoxybenzoic acid and methoxyacetic acid are 5.55, 5.46 and 4.61, respectively, in 52.1 wt% MeOH/$H_2O$ (in $H_2O$: 4.31[17a], 4.08[17a] and 3.47[17b], respectively). These values are all 0.5–0.6 p$K_a$ units lower than those for the corresponding crown ether carboxylic acids. Apparently, the structures of the model compounds do not sufficiently resemble the ligand structures, but indications of specific stabilizing hydrogen-bonding interactions seem to be absent in the ligands. For structurally somewhat related crown ethers with a pendant carboxylic acid group, transannular hydrogen bonding was found[21], but in these compounds the carboxylic acid group was in a sterically much more favourable position for intramolecular interaction.

Although the absolute values of the p$K_a$ data in 52.1 wt% MeOH and $CHCl_3$ would be different, we assume that the




*Scheme 3*




*Scheme 4*

relative order for the $pK_a$ values of the crown ether carboxylic acids will remain the same in the two solvents.

*Table I* $pK_a$ *values*[a] *of the crown ether carboxylic acids* **2–6** *and extraction efficiencies*[b] *of crown ethers* **1–6** *for urea in two-phase transfer experiments.*

| Crown ether | Ring size | $pK_a$ | L–L(H⁺)[c] | L–L[d] | S–L[e] |
|---|---|---|---|---|---|
| **1a** | 23 | –[f] | 0.09 | –[g] | –[g] |
| **1b** | 26 | –[f] | 0.27 | –[g] | –[g] |
| **1c** | 29 | –[f] | 0.55 | –[g] | –[g] |
| **1d** | 32 | –[f] | 0.43 | –[g] | –[g] |
| **2a** | 26 | 6.10 | –[g] | –[g] | 0.11 |
| **2b** | 29 | 6.07 | –[g] | 0.06 | 0.23 |
| **2c** | 32 | 6.17 | –[g] | 0.05 | 0.27 |
| **3** | 27 | 5.24 | 0.47 | 0.09 | 0.24 |
| **4** | 30 | 5.34 | 0.42 | 0.13 | 0.21 |
| **5** | 19 | 5.87 | 0.09 | –[g] | –[g] |
| **6a** | 18 | 5.93 | 0.05 | –[g] | –[g] |
| **6b** | 24 | 5.89 | 0.08 | –[g] | –[g] |
| **6c** | 27 | 5.89 | 0.47 | 0.04 | 0.08 |
| **6d** | 30 | 5.86 | 0.48 | 0.04 | 0.23 |

[a] $pK_a$ values ±0.05 (52.1 wt% $MeOH/H_2O$, 25.0°C). [b] Ratio of the (protonated) urea concentration and the crown ether concentration (±15%) in the organic phase. [c] Liquid–liquid phase transfer of uronium perchlorate (no crown ether was transferred to the aqueous phase). [d] Liquid–liquid phase transfer of urea (no crown ether was transferred to the aqueous phase). [e] Solid–liquid phase transfer of urea. [f] Not measured. [g] Not tested.

Two-phase liquid–liquid extraction experiments, using a chloroform layer containing 0.1 M crown ether and an aqueous layer containing 2.0 M urea in 28% $HClO_4$, were carried out as described previously with crown ethers **1** and **3–6**. The results, which are summarized in Table I, show that for the biphenyl crown ethers **1** a macrocycle with a ring size ⩾29 is required for the complexation of urea, while for crown ethers **3–6** the 27-membered ring is sufficient, as would be expected from the results of similar experiments conducted with benzo crown ethers[2]. The amount of urea transferred to the chloroform layer in the absence of crown ether was negligible. The amount of crown ether transferred to the aqueous layer, as determined by $^1H$ NMR spectroscopy with 1,2,4,5-tetramethylbenzene as internal standard, was found to be negligible.

Two-phase liquid–liquid extraction experiments with a chloroform layer containing 0.1 M crown ether and a neutral aqueous layer containing 2.0 M urea were carried out with crown ethers **3** and **4** and the larger rings of **2** and **6**. The results, summarized in Table I, demonstrate assistance of the crown-ether carboxylic acid in the complexation of urea. Acid strengths of the crown ethers appear to parallel the complexation ability. A relatively high value for the extraction efficiency (*i.e.* the ratio of urea and crown-ether concentrations in the organic phase) is observed for the most acidic crown ethers **3** and **4**.

A better method of investigating urea complexation by crown-ether carboxylic acids and participation of the covalently bound carboxylic acid group was found to be two-phase solid–liquid phase transfer. A 0.1 M solution of the crown-ether carboxylic acid in chloroform was shaken for 17 h with solid urea. The amount of urea solubilized in the chloroform layer was determined as before and the

results are summarized in Table I. In the absence of crown ethers, no urea was solubilized in chloroform. Participation of the carboxylic acid group in the complexation of urea is demonstrated by the different behaviour of crown ethers **6c** and **6d**. Since the cavity of the 27-membered crown ether **6c** is large enough to encapsulate urea, this crown ether should solubilize an approximately equal amount of urea as the corresponding 30-membered ring compound. The observation that crown ether **6c** solubilizes only a very small amount of urea, while crown ether **3** which, with the same ring size, solubilizes a relatively large amount could be ascribed either to a difference in acid strength or to the rigidity of the crown ethers. The latter explanation seems more likely since the larger biphenyl crown ethers with higher $pK_a$ values also solubilize a relatively large amount of urea. CPK models show that, for interaction between the carboxylic acid hydrogen atom of a (2-carboxyphenyloxy)-methyl crown ether and the urea oxygen atom, together with the encapsulation of urea in an almost planar conformation, a 30-membered ring is required. In the 27-membered macrocycle, such complexation is only possible when at least one oxygen atom of the macrocyclic ring is in close proximity to the urea-oxygen atom which probably produces a disfavoured oxygen–oxygen repulsion.

The results of these solid–liquid phase-transfer experiments indicate that the position of the acidic group plays an important role in the complexation of urea. In biphenyl crown ethers, a functionality attached to the 3-position of the biphenyl moiety is situated close to the crown-ether cavity and is able to interact with a complexed guest molecule. The carboxylic groups of (2-carboxyphenyloxy)-methyl and (carboxymethoxy)methyl crown ethers are also able to approach the cavity and participate in the complexation of a neutral guest.

## Conclusions

The assistance of a covalently bound carboxylic acid group in the complexation of urea by crown ethers was confirmed in the solid–liquid phase-transfer experiments. A (potential) location close to the crown-ether cavity seemed to enhance this assistance. Acid strengths appear to have a lesser influence on the assistance in urea complexation. The results of two-phase liquid–liquid extraction experiments provide a less clear picture concerning the factors which control participation in the complexation by a carboxylic acid group which is covalently bound to the crown ether, probably due to strong solvation of urea in the aqueous phase compared with the crown-ether encapsulation in chloroform.

## Experimental

Melting points were determined using a Reichert melting point apparatus and are uncorrected. The $^1$H NMR spectra were recorded on Bruker WP-80 and Varian EM 360A spectrometers and $^{13}$C NMR spectra on a Nicolet NT-200-WB spectrometer in $CDCl_3$ with $Me_4Si$ (δ 0 ppm) as the internal standard. Mass spectra were obtained using a Varian Mat 311A spectrometer and IR spectra using Perkin Elmer 257 and Nicolet MX-S spectrophotometers. Elemental analyses were carried out by the Department of Chemical Analysis of the University of Twente, Enschede, or by Galbraith Laboratories, Inc., Knoxville, Tennessee.

### *Materials*

Unless specified otherwise, reagent-grade reactants and solvents were used as received. THF was purified by distillation from $LiAlH_4$ or sodium and benzophenone. Pyridine was dried over KOH pellets. DMSO, acetonitrile and acetone were dried over molecular sieves (4 Å). Dioxane was stored over NaOH pellets and distilled prior to use. The starting materials 11-chloro-3,6,9-trioxa-1-undecanol[22,23], 3-(benzyloxy)-1,2-propanediol[24,25], 2-bromodecanoic acid[26], 10-(benzyloxymethyl)-3,6,9,12,15,18-hexaoxa-1,20-eicosanediol (**33**)[27] and polyethylene glycols[28] were prepared using reported methods. Polyethylene glycol ditosylates were prepared by adding dropwise at 0 °C 2.1 equivalents of *p*-toluenesulfonyl chloride to a solution of a polyethylene glycol and 2 equivalents of triethylamine in $CH_2Cl_2$. The resulting mixture was allowed to warm to room temperature and stirred for 17 h. Subsequently, the mixture was washed with an aqueous HCl solution and water. After drying ($MgSO_4$) and concentrating *in vacuo*, ditosylates were obtained which gave spectral data in accord with the literature[29].

### *General procedure for the synthesis of biphenyl crown ethers* **1**

Biphenyldiol **7** (20 mmol, 6.0 g) was dissolved in 700 ml of THF containing 2% $H_2O$ and 3 eq. of base. To this mixture,20 mmol of the appropriate polyethylene glycol ditosylate in 50 ml of THF was added at reflux temperature at a rate of 1 ml/h. After 70 h, the reaction mixture was cooled to room temperature, filtered and concentrated *in vacuo*. To the residue, 100 ml of water was added and the basic aqueous phase was extracted with $CHCl_3$ (3 × 100 ml). The combined chloroform layers were washed with water until the aqueous layer was neutral and then once with a saturated NaCl solution. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude crown ether.

*5,5'-Di*-tert-*butyl-1,1'-biphenyl-23-crown-7* (**1a**). Crown ether **1a** was prepared from biphenyldiol **7** and hexaethylene glycol ditosylate using NaOH as the base in 37% yield. The crude product was purified by trituration with diisopropyl ether. M.p. 96–99 °C. $^1$H NMR: δ 1.32 (s, 18H, $CH_3$), 3.5–4.1 (m, 24H, $OCH_2CH_2$), 6.9–7.0 and 7.2–7.3 (m, 6H, ArH). $^{13}$C NMR: δ 31.6 ($CH_3$), 34.1 (Ar–C), 69.0–70.9 ($OCH_2CH_2$), 112.4 (Ar C-3), 124.7 and 129.0 (Ar C-4 and C-6), 128.1 (Ar C-1), 142.9 (Ar C-5), 154.1 (Ar C-2). MS: *m/e* 544.340 (calcd. for $C_{32}H_{48}O_7$: *m/e* 544.340). Anal. calcd. for $C_{32}H_{48}O_7$: C 70.55, H 8.88; found: C 70.33, H 8.77%.

*5,5'-Di*-tert-*butyl-1,1'-biphenyl-26-crown-8* (**1b**). Crown ether **1b** was prepared from biphenyldiol **7** and heptaethylene glycol ditosylate using CsOH as the base in 60% yield. Purification of the product was accomplished by chromatography (silica gel/$CH_2Cl_2$ and 10% MeOH/$CH_2Cl_2$). $^1$H NMR: δ 1.32 (s, 18H, $CH_3$), 3.5–4.2 (m, 28H, $OCH_2CH_2$), 6.9–7.0 and 7.2–7.3 (m, 6H, ArH). $^{13}$C NMR: δ 31.6 ($CH_3$), 34.1 (Ar–C), 68.8–70.8 ($OCH_2CH_2$), 112.3 (Ar C-3), 124.7 and 129.0 (Ar C-4 and C-6), 128.0 (Ar C-1), 142.9 (Ar C-5), 154.1 (Ar C-2). MS: *m/e* 588.364 (calcd. for $C_{34}H_{52}O_8$: *m/e* 588.366).

*5,5'-Di*-tert-*butyl-1,1'-biphenyl-29-crown-9* (**1c**). Crown ether **1c** was prepared from biphenyldiol **7** and octaethylene glycol ditosylate using CsOH as the base in 76% yield. Purification of the product was accomplished by chromatography (silica gel/$CH_2Cl_2$ and 10% MeOH/$CH_2Cl_2$). $^1$H NMR: δ 1.32 (s, 18H, $CH_3$), 3.5–4.1 (m, 32H, $OCH_2CH_2$), 6.8–7.0 and 7.2–7.3 (m, 6H, ArH). $^{13}$C NMR: δ 31.5 ($CH_3$), 34.0 (Ar–C), 68.6–70.7 ($OCH_2CH_2$), 112.1 (Ar C-3), 124.7 and 128.9 (Ar C-4 and C-6), 127.9 (Ar C-1), 142.7 (Ar C-5), 154.0 (Ar C-2). MS: *m/e* 632.381 (calcd. for $C_{36}H_{56}O_9$: *m/e* 632.392).

*5,5'-Di*-tert-*butyl-1,1'-biphenyl-32-crown-10* (**1d**). Crown ether **1d** was prepared from biphenyldiol **7** and nonaethylene glycol ditosylate using CsOH as the base in 82% yield. Purification of the product was accomplished by chromatography (silica gel/$CH_2Cl_2$ and 10% MeOH/$CH_2Cl_2$). $^1$H NMR: δ 1.32 (s, 18H, $CH_3$), 3.5–4.2 (m, 36H, $OCH_2CH_2$), 6.9–7.0 and 7.2–7.3 (m, 6H, ArH). $^{13}$C NMR: δ 31.6 ($CH_3$), 34.1 (Ar–C), 68.4–70.7 ($OCH_2CH_2$), 112.2 (Ar C-3), 124.7 and 129.0 (Ar C-4 and C-6), 127.9 (Ar C-1), 142.8 (Ar C-5), 154.0 (Ar C-2). MS: *m/e* 676.424 (calcd. for $C_{38}H_{60}O_{10}$: *m/e* 676.419).

### *General procedure for the synthesis of 3-(carboxymethyl)biphenyl crown ethers* **2**

The 2-(carboxymethyl)biphenyl crown ethers were obtained quantitatively from the 2-(methoxycarbonylmethyl)biphenyl crown ethers (**12**) by refluxing for 17 h with 0.3 M NaOH in 80% MeOH/$H_2O$. The methanol/water mixture was concentrated *in vacuo* and extracted with $CHCl_3$. The basic aqueous phase was acidified with

HCl and extracted with $CH_2Cl_2$. The combined organic layers were washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to give the compounds **2**.

*3-(Carboxymethyl)-5,5'-di*-tert-*butyl-1,1'-biphenyl-26-crown-8* (**2a**). IR (neat) 1730 $cm^{-1}$ (C=O). $^1H$ NMR: δ 1.31 (s, 18H, $CH_3$), 3.3–4.2 (m, 30H, $OCH_2CH_2$ and $ArCH_2$), 6.8–7.4 (m, 5H, ArH). MS: *m/e* 646.375 (calcd. for $C_{36}H_{54}O_{10}$: *m/e* 646.372).

*3-(Carboxymethyl)-5,5'-di*-tert-*butyl-1,1'-biphenyl-29-crown-9* (**2b**). IR (neat) 1730 $cm^{-1}$ (C=O). $^1H$ NMR: δ 1.31 (s, 18H, $CH_3$), 3.3–4.3 (m, 34H, $OCH_2CH_2$ and $ArCH_2$), 6.8–7.4 (m, 5H, ArH), 9.5 (bs, 1H, OH). $^{13}C$ NMR: δ 31.5 ($CH_3$), 34.2 and 34.3 (Ar–C), 37.0 ($ArCH_2$), 69.5–71.4 ($OCH_2CH_2$), 111.4 (Ar C-3'), 125.1, 126.8 and 128.7 (Ar C-4, C-4', C-6 and C-6'), 127.4, 127.6 and 130.9 (Ar C-3, C-1 and C-1'), 143.3 and 145.4 (Ar C-5 and C-5'), 152.5 and 153.7 (Ar C-2 and C-2'), 173.1 (CO). MS: *m/e* 690.397 (calcd. for $C_{38}H_{58}O_{11}$: *m/e* 690.398).

*3-(Carboxymethyl)-5,5'-di*-tert-*butyl-1,1'-biphenyl-32-crown-10* (**2c**). IR (neat): 1730 $cm^{-1}$ (C=O). $^1H$ NMR: δ 1.31 (s, 18H, $CH_3$), 3.4–4.3 (m, 38H, $OCH_2CH_2$ and $ArCH_2$), 6.8–7.4 (m, 5H, ArH). $^{13}C$ NMR δ 31.5 ($CH_3$), 34.1 and 34.3 (Ar–C), 36.7 ($ArCH_2$), 69.3–71.5 ($OCH_2CH_2$), 111.6 (Ar C-3'), 125.1, 126.9 and 128.6 (Ar C-4, C-4', C-6 and C-6'), 127.2, 127.7 and 130.8 (Ar C-3, C-1 and C-1'), 143.2 and 145.3 (Ar C-5 and C-5'), 152.6 and 153.7 (Ar C-2 and C-2'), 173.3 (CO). MS: *m/e* 734.425 (calcd. for $C_{40}H_{62}O_{12}$: *m/e* 734.424).

*(Carbomethoxy)methyl crown ether* **3**

After removal of the protecting mineral oil from 0.82 g (20.5 mmol) of 60% NaH by washing with *n*-pentane under nitrogen, 15 ml of THF was added followed by 1.75 g (4.1 mmol) of **17**. The mixture was then stirred at room temperature for 2 h. A solution of 2-bromotetradecanoic acid (**18**) (1.64 g, 5.4 mmol) in THF (15 ml) was added dropwise over 3 h and the mixture was stirred at room temperature for 48 h. The solvent was evaporated *in vacuo* and water (40 ml) was added to the residue. The mixture was acidified to pH 1 with 6 M HCl and extracted with $CH_2Cl_2$ (3 × 20 ml). The combined extracts were dried ($MgSO_4$) and, after evaporation of the solvent *in vacuo*, pure **3** was isolated by chromatography on silica gel with EtOAc/$CH_2Cl_2$ (1:1) as the eluent to remove unreacted substrates and then with MeOH to elute the product. The combined methanolic fractions were evaporated *in vacuo* and the residue was dissolved in $CHCl_3$, washed with 6 M HCl and water, dried ($MgSO_4$) and evaporated *in vacuo* to afford crown ether **3** (1.10 g, 41%) as a pale yellow, hygroscopic oil. IR: 3650–2300 $cm^{-1}$ (COOH), 1747 $cm^{-1}$ (C=O), 1116 $cm^{-1}$ (C–O). $^1H$ NMR: δ 0.65 – 2.0 (m, 25H, *n*-$C_{12}H_{25}$), 3.70 (bs, 38H, $OCH_2$), 8.00 (bs, 1H, COOH). Anal. calcd. for $C_{33}H_{64}O_{12} \cdot 2.5H_2O$: C 58.30, H 10.23; found: C 58.07, H 10.15%.

*(Carboxymethoxy)methyl benzo crown ether* **4**

Under the conditions described for the synthesis of **3**, hydroxymethyl crown ether **22** (2.00 g, 3.9 mmol) was reacted with NaH (0.78 g, 19.5 mmol) and 2-bromodecanoic acid (**23**)[25] (1.28 g, 5.1 mmol). The crude reaction product was chromatographed on alumina eluting sequentially with $CH_2Cl_2$, EtOAc and EtOAc/MeOH (20:1) to remove unreacted starting materials and then with MeOH/HCl (100:3) to elute the product. After the solvent was removed *in vacuo*, the residue was acidified with concentrated HCl and extracted with $CH_2Cl_2$ (2 × 20 ml). The combined extracts were washed several times with water, dried ($MgSO_4$) and then evaporated to afford 1.50 g (56%) of **4** as a hydroscopic, colourless, viscous oil. IR: 3491 $cm^{-1}$ (COOH), 1744 $cm^{-1}$ (C=O), 1126 $cm^{-1}$ (C–O). $^1H$ NMR: δ 0.65–1.9 (m, 17H, *n*-$C_8H_{17}$), 3.3–4.35 (m, 38H, $OCH_2$), 6.92 (s, 4H, ArH). Anal. calcd. for $C_{35}H_{60}O_{13} \cdot H_2O$: C 59.47, H 8.84; found: C 59.41, H 8.70%.

*2,2'-Dihydroxy-5,5'-di*-tert-*butyl-1,1'-biphenyl** (**7**)[30]

To 770 g (5.13 mol) of *p*-(*tert*-butyl)phenol at 120°C was added dropwise 63 ml (0.35 mol) of di-*tert*-butyl peroxide. The reaction mixture was refluxed for 17 h and then steam distilled. The residue was separated, concentrated *in vacuo* and subsequently crystallized from hot benzene. The crude product was recrystallized from ethanol/water (95:5) with a yield of 50 g. From the distillate, about 50% of the starting material could be recovered, pure enough to be used again. M.p. 203–205°C. IR (KBr): 3280 $cm^{-1}$ (OH). $^1H$ NMR: δ 1.33 (s, 18H, $CH_3$), 6.9–7.4 (m, 6H, ArH). $^{13}C$ NMR: δ 31.6 ($CCH_3$), 34.2 (Ar–C), 116.4 (Ar C-3), 125.7 (Ar C-1), 126.0 and 128.6 (Ar C-4 and C-6), 143.7 (Ar C-5), 151.0 (Ar C-2). MS: *m/e* 298.193 (calcd. for $C_{20}H_{26}O_2$ 298.193). Anal. calcd. for $C_{20}H_{26}O_2$: C 80.50, H 8.78; found: C 80.90, H 8.75%.

*General procedure for the synthesis of 3-formyl-5,5'-di*-tert-*butyl-1,1'-biphenyl crown ethers* **8**

A mixture of 10 mmol of a 5,5'-di-*tert*-butyl-1,1'-biphenyl crown ether (**1**), 2.1 g (15 mmol) of hexamethylenetetramine and 50 ml of trifluoroacetic acid was heated for 48 h at reflux temperature. After cooling, the mixture was poured out into 200 ml of ice and water (2:1), stirred for 15 min and subsequently extracted with $CH_2Cl_2$. The combined organic layers were washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The crude aldehyde was chromatographed on a silica gel column using 2% MeOH/$CH_2Cl_2$ as eluent.

*3-Formyl-5,5'-di*-tert-*butyl-1,1'-biphenyl-23-crown-7* (**8a**). Yield 33%. IR (neat): 1680 $cm^{-1}$ (C=O). $^1H$ NMR: δ 1.33 (s, 9H, $CH_3$), 1.34 (s, 9H, $CH_3$), 3.4–4.0 (m, 24H, $OCH_2CH_2$), 6.9–7.0 and 7.3–7.4 (m, 3H, Ar'H), 7.62 en 7.84 (dd, 2H, ArH), 10.50 (s, 1H, CHO). $^{13}C$ NMR: δ 31.4 and 31.5 ($CH_3$), 34.2 and 34.6 (Ar–C), 69.0–71.1 and 73.6 ($OCH_2CH_2$), 111.9 (Ar C-3'), 123.1, 125.6 and 128.7 (Ar C-4, C-4' and C-6'), 126.3 (Ar C-3) 128.9 and 132.0 (Ar C-1 and C-1'), 136.3 (Ar C-6), 143.5 and 145.9 (Ar C-5 and C-5'), 153.6 and 158.4 (Ar C-2 and C-2'), 191.8 (CHO). MS: *m/e* 572.336 (calcd. for $C_{33}H_{48}O_8$: *m/e* 572.335).

*3-Formyl-5,5'-di*-tert-*butyl-1,1'-biphenyl-26-crown-8* (**8b**). Yield 96%. IR (neat): 1680 $cm^{-1}$ (C=O). $^1H$ NMR: δ 1.33 (s, 9H, $CH_3$), 1.34 (s, 9H, $CH_3$), 3.5–4.3 (m, 28H, $OCH_2CH_2$), 6.9–7.0 and 7.3–7.4 (m, 3H, Ar'H), 7.61 and 7.83 (dd, 2H, ArH), 10.55 (s, 1H, CHO). $^{13}C$ NMR: δ 31.3 and 31.5 ($CH_3$), 34.1 and 34.4 (Ar–C), 68.8–70.9 and 73.2 ($OCH_2CH_2$), 112.0 (Ar C-3'), 123.0, 125.6 and 128.5 (Ar C-4, C-4' and C-6'), 126.1 (Ar C-3) 128.8 and 132.1 (Ar C-1 and C-1'), 136.2 (Ar C-6), 143.3 and 145.8 (Ar C-5 and C-5'), 153.6 and 158.1 (Ar C-2 and C-2'), 191.3 (CHO). MS: *m/e* 616.361 (calcd. for $C_{35}H_{52}O_9$: *m/e* 616.361).

*3-Formyl-5,5'-di*-tert-*butyl-1,1'-biphenyl-29-crown-9* (**8c**). Yield 50%. IR (neat): 1680 $cm^{-1}$ (C=O). $^1H$ NMR: δ 1.33 (s, 9H, $CH_3$), 1.34 (s, 9H, $CH_3$), 3.4–4.2 (m, 32H, $OCH_2CH_2$), 6.85–7.0 and 7.3–7.4 (m, 3H, Ar'H), 7.61 and 7.83 (dd, 2H, ArH), 10.54 (s, 1H, CHO). $^{13}C$ NMR: δ 31.3 and 31.5 ($CH_3$), 34.1 and 34.4 (Ar–C), 68.3–70.8 and 73.1 ($OCH_2CH_2$), 112.0 (Ar C-3'), 123.0, 125.6 and 128.9 (Ar C-4, C-4' and C-6'), 126.1 (Ar C-3), 128.5 and 132.1 (Ar C-1 and C-1'), 136.2 (Ar C-6), 143.3 and 145.8 (Ar C-5 and C-5'), 153.6 and 158.0 (Ar C-2 and C-2'), 191.2 (CHO). MS: *m/e* 660.390 (calcd. for $C_{37}H_{56}O_{10}$: *m/e* 660.387).

*3-Formyl-5,5'-di*-tert-*butyl-1,1'-biphenyl-32-crown-10* (**8d**). Yield 62%. IR (neat): 1680 $cm^{-1}$ (C=O). $^1H$ NMR: δ 1.33 (s, 9H, $CH_3$), 1.34 (s, 9H, $CH_3$), 3.5–4.3 (m, 36H, $OCH_2CH_2$), 6.9–7.8 (m, 5H, ArH), 10.54 (s, 1H, CHO). $^{13}C$ NMR: δ 31.3 and 31.5 ($CH_3$), 34.1 and 34.5 (Ar–C), 68.5–70.8 and 73.2 ($OCH_2CH_2$), 112.0 (Ar C-3'), 123.0, 125.6 and 128.9 (Ar C-4, C-4' and C-6'), 126.1 (Ar C-3), 128.6 and 132.1 (Ar C-1 and C-1'), 136.2 (Ar C-6), 143.4 and 145.9 (Ar C-5 and C-5'), 153.6 and 158.0 (Ar C-2 and C-2'), 191.2 (CHO). MS: *m/e* 704.411 (calcd. for $C_{39}H_{60}O_{11}$: *m/e* 704.414).

*General procedure for the synthesis of 3-(hydroxymethyl)biphenyl crown ethers* **9**

A solution of 5 mmol of the 3-formylbiphenyl crown ether **8** in 25 ml of THF was added dropwise to a suspension of 0.09 g (2.5 mmol) of $LiAlH_4$ in 25 ml of THF at 0°C. The mixture was stirred for 24 h at room temperature. The excess hydride was then destroyed by the addition of 1 ml of EtOAc and 1 ml of water and stirring was continued for 17 h. The solids were filtered and the filtrate was concentrated *in vacuo* after drying over $MgSO_4$.

*3-(Hydroxymethyl)-5,5'-di*-tert-*butyl-1,1'-biphenyl-26-crown-8* (**9a**). Yield 80%. IR (neat): 3420 $cm^{-1}$ (OH). $^1H$ NMR: δ 1.31 (s, 18H,

* *Chem. Abstr.* name: 5,5'-bis(1,1-dimethylethyl)biphenyl-2,2'-diol.

$CH_3$), 3.4–4.9 (m, 30H, $OCH_2CH_2$ and $ArCH_2$), 6.8–7.4 (m, 5H, ArH). $^{13}C$ NMR: δ 31.5 ($CH_3$), 34.1 and 34.3 (Ar–C), 62.0 ($ArCH_2$), 68.9–69.8 ($OCH_2CH_2$), 111.8 (Ar C-3'), 125.0, 125.7, 128.8 and 128.9 (Ar C-4, C-4', C-6 and C-6'), 127.9 (Ar C-3) 130.4 and 133.6 (Ar C-1 and C-1'), 143.4 and 145.0 (Ar C-5 and C-5'), 153.1 and 153.8 (Ar C-2 and C-2'). MS: *m/e* 618.381 (calcd. for $C_{35}H_{54}O_9$: *m/e* 618.377).

*3-(Hydroxymethyl)-5,5'-di-*tert*-butyl-1,1'-biphenyl-29-crown-9* (**9b**). Yield 80%. IR (neat): 3470 $cm^{-1}$ (OH). $^1H$ NMR: δ 1.31 (s, 18H, $CH_3$), 3.4–4.9 (m, 34H, $OCH_2CH_2$ and $ArCH_2$), 6.8–7.4 (m, 5H, ArH). $^{13}C$ NMR: δ 31.5 ($CH_3$), 34.2 and 34.3 (Ar–C), 62.0 ($ArCH_2$), 69.0–71.6 ($OCH_2CH_2$), 111.9 (Ar C-3'), 125.1, 125.7, 128.8 and 129.0 (Ar C-4, C-4', C-6 and C-6'), 127.9 (Ar C-3) 130.4 and 133.6 (Ar C-1 and C-1'), 143.5 and 145.2 (Ar C-5 and C-5'), 153.0 and 153.8 (Ar C-2 and C-2'). MS: *m/e* 662.405 (calcd. for $C_{37}H_{58}O_{10}$: *m/e* 662.403).

*3-(Hydroxymethyl)-5,5'-di-*tert*-butyl-1,1'-biphenyl-32-crown-10* (**9c**). Yield 67%. IR: (neat) 3460 $cm^{-1}$ (OH). $^1H$ NMR: δ 1.31 (s, 18H, $CH_3$), 3.5–4.7 (m, 38H, $OCH_2CH_2$ and $ArCH_2$), 6.9–7.4 (m, 5H, ArH). $^{13}C$ NMR: δ 31.5 ($CH_3$), 34.1 and 34.2 (Ar–C), 62.0 ($ArCH_2$), 69.5–71.4 ($OCH_2CH_2$), 111.9 (Ar C-3'), 125.0, 125.5, 128.7 and 128.8 (Ar C-4, C-4', C-6 and C-6'), 127.7 (Ar C-3), 130.3 and 133.6 (Ar C-1 and C-1'), 143.3 and 145.1 (Ar C-5 and C-5'), 152.9 and 153.6 (Ar C-2 and C-2'). MS: *m/e* 706.431 (calcd. for $C_{39}H_{62}O_{11}$: *m/e* 706.429).

*General procedure for the synthesis of 3-(chloromethyl)biphenyl crown ethers* **10**

To a solution of 2.5 mmol of the 3-(hydroxymethyl)biphenyl crown ether **9** dissolved in 50 ml of toluene, two equivalents of $SOCl_2$ were added dropwise. The mixture was stirred for 7 h at room temperature and then 50 ml of water was added slowly. The organic layer was separated, washed with water and dried over $K_2CO_3$. The solvent was evaporated *in vacuo* and the residue was purified by chromatography ($Al_2O_3$/THF).

*3-(Chloromethyl)-5,5'-di-*tert*-butyl-1,1'-biphenyl-26-crown-8* (**10a**). Yield 73%. $^1H$ NMR: δ 1.32 (s, 18H, $CH_3$), 3.5–4.3 (m, 28H, $OCH_2CH_2$), 4.81 (s, 2H, $ArCH_2$), 6.8–7.4 (m, 5H, ArH). $^{13}C$ NMR: δ 31.5 ($CH_3$), 34.1 and 34.4 (Ar–C), 42.1 ($ArCH_2$), 69.0–72.3 ($OCH_2CH_2$), 112.1 (Ar C-3'), 125.3, 126.4, 128.7 and 130.1 (Ar C-4, C-4', C-6 and C-6'), 127.4 (Ar C-3), 130.0 and 131.4 (Ar C-1 and C-1'), 143.4 and 145.8 (Ar C-5 and C-5'), 152.9 and 153.8 (Ar C-2 and C-2'). MS: *m/e* 636.346 (calcd. for $C_{35}H_{53}ClO_8$: *m/e* 636.343).

*3-(Chloromethyl)-5,5'-di-*tert*-butyl-1,1'-biphenyl-29-crown-9* (**10b**). Yield 87%. $^1H$ NMR: δ 1.32 (s, 18H, $CH_3$), 3.5–4.3 (m, 32H, $OCH_2CH_2$), 4.80 (s, 2H, $ArCH_2$), 6.9–7.4 (m, 5H, ArH). $^{13}C$ NMR: δ 31.4 and 31.5 ($CH_3$), 34.1 and 34.3 (Ar–C), 42.1 ($ArCH_2$), 67.9–72.2 ($OCH_2CH_2$), 112.1 (Ar C-3'), 125.2, 126.3, 128.6 and 130.1 (Ar C-4, C-4', C-6 and C-6'), 127.4 (Ar C-3), 130.0 and 131.4 (Ar C-1 and C-1'), 143.3 and 145.7 (Ar C-5 and C-5'), 152.8 and 153.7 (Ar C-2 and C-2'). MS: *m/e* 680.372 (calcd. for $C_{37}H_{57}ClO_9$: *m/e* 680.369).

*3-(Chloromethyl)-5,5'-di-*tert*-butyl-1,1'-biphenyl-32-crown-10* (**10c**). Yield 54%. $^1H$ NMR: δ 1.32 (s, 18H, $CH_3$), 3.5–4.2 (m, 36H, $OCH_2CH_2$), 4.80 (s, 2H, $ArCH_2$), 6.9–7.4 (m, 5H, ArH). $^{13}C$ NMR: δ 31.5 ($CH_3$), 34.2 and 34.4 (Ar–C), 42.1 ($ArCH_2$) 68.7–72.2 ($OCH_2CH_2$), 112.0 (Ar C-3'), 125.3, 126.4, 128.7 and 130.2 (Ar C-4, C-4', C-6 and C-6'), 127.3 (Ar C-3), 130.0 and 131.3 (Ar C-1 and C-1'), 143.3 and 145.8 (Ar C-5 and C-5'), 152.8 and 153.7 (Ar C-2 and C-2'). MS: *m/e* 724.390 (calcd. for $C_{39}H_{61}ClO_{10}$: *m/e* 724.395).

*General procedure for the synthesis of 3-(cyanomethyl)biphenyl crown ethers* **11**

To a solution of 1.5 mmol of the 3-(chloromethyl)biphenyl crown ether **10** dissolved in 50 ml of acetonitrile, an excess of KCN was added and the suspension was refluxed for 17 h. The mixture was filtered and concentrated *in vacuo* and the residue was taken up in chloroform. The organic layer was washed with water, dried over $MgSO_4$ and concentrated *in vacuo* to give the pure product.

*3-(Cyanomethyl)-5,5'-di-*tert*-butyl-1,1'-biphenyl-26-crown-8* (**11a**). Yield 90%. IR (neat): 2230 $cm^{-1}$ (C–N). $^1H$ NMR: δ 1.31 (s, 18H, $CH_3$), 3.4–4.1 (m, 30H, $OCH_2CH_2$ and $ArCH_2$), 6.9–7.4 (m, 5H, ArH). MS: *m/e* 627.377 (calcd. for $C_{36}H_{53}NO_8$: *m/e* 627.377).

*3-(Cyanomethyl)-5,5'-di-*tert*-butyl-1,1'-biphenyl-29-crown-9* (**11b**). Yield 83%. IR (neat): 2260 $cm^{-1}$ (C–N). $^1H$ NMR: δ 1.31 (s, 9H, $CH_3$), 1.33 (s, 9H, $CH_3$), 3.5–4.2 (m, 34H, $OCH_2CH_2$ and $ArCH_2$), 6.8–7.4 (m, 5H, ArH). $^{13}C$ NMR: δ 18.8 ($ArCH_2$), 31.5 ($CH_3$), 34.2 and 34.4 (Ar–C), 68.8–71.8 ($OCH_2CH_2$), 112.0 (Ar C-3'), 124.8, 125.4, 128.6 and 129.4 (Ar C-4, C-4', C-6 and C-6'), 123.2, 127.2 and 131.1 (Ar C-3, C-1 and C-1'), 143.5 and 145.9 (Ar C-5 and C-5'), 152.1 and 153.7 (Ar C-2 and C-2'). MS: *m/e* 671.402 (calcd. for $C_{38}H_{57}NO_9$: *m/e* 671.403).

*3-(Cyanomethyl)-5,5'-di-*tert*-butyl-1,1'-biphenyl-32-crown-10* (**11c**). Yield 86%. IR (neat): 2260 $cm^{-1}$ (C–N). $^1H$ NMR: δ 1.31 (s, 9H, $CH_3$), 1.33 (s, 9H, $CH_3$), 3.5–4.3 (m, 38H, $OCH_2CH_2$ and $ArCH_2$), 6.9–7.0 and 7.3–7.4 (m, 5H, ArH). $^{13}C$ NMR: δ 18.8 ($ArCH_2$), 31.5 ($CH_3$), 34.2 and 34.4 (Ar–C), 68.6–71.8 ($OCH_2CH_2$), 112.0 (Ar C-3'), 124.8, 125.4, 128.6 and 129.5 (Ar C-4, C-4', C-6 and C-6'), 123.1, 127.1 and 130.9 (Ar C-3, C-1 and C-1'), 143.4 and145.9 (Ar C-5 and C-5'), 152.1 and 153.6 (Ar C-2 and C-2'). MS: *m/e* 715.435 (calcd. for $C_{40}H_{61}NO_{10}$: *m/e* 715.430).

*General procedure for the synthesis of 3-(methoxycarbonylmethyl)-biphenyl crown ethers* **12**

Through a refluxing solution of 2.5 mmol of a 3-(cyanomethyl)--5,5'-di-*tert*-butyl-1,1'-biphenyl crown ether **11** in methanol, dry gaseous HCl was passed for 4 h. Subsequently, 10 ml of water was added to the reaction mixture to hydrolyse the product. The mixture was concentrated *in vacuo* and the residual water layer was extracted with $CH_2Cl_2$. The $CH_2Cl_2$ layer was washed with water, dried over $MgSO_4$ and concentrated to give the pure corresponding carboxylic ester.

*3-(Methoxycarbonylmethyl)-5,5'-di-*tert*-butyl-1,1'-biphenyl-26-crown-8* (**12a**). Yield 86%. IR (neat): 1740 $cm^{-1}$ (C=O). $^1H$ NMR: δ 1.31 (s, 18H, $CH_3$), 3.4–4.2 (m, 33H, $OCH_2CH_2$, $OCH_3$ and $ArCH_2$), 6.9–7.4 (m, 5H, ArH). MS: *m/e* 660.396 (calcd. for $C_{37}H_{56}O_{10}$: *m/e* 660.387).

*3-(Methoxycarbonylmethyl)-5,5'-di-*tert*-butyl-1,1'-biphenyl-29-crown-9* (**12b**). Yield 55%. IR (neat): 1740 $cm^{-1}$ (C=O). $^1H$ NMR: δ 1.31 (s, 18H, $CH_3$), 3.4–4.2 (m, 37H, $OCH_2CH_2$, $OCH_3$ and $ArCH_2$), 6.8–7.4 (m, 5H, ArH). $^{13}C$ NMR: δ 31.5 ($CH_3$), 34.2 and 34.3 (Ar–C), 35.7 ($ArCH_2$), 51.8 ($OCH_3$), 68.3–71.7 ($OCH_2CH_2$), 112.2 (Ar C-3'), 125.1, 126.6, 128.7 and 128.8 (Ar C-4, C-4', C-6 and C-6'), 126.7, 127.9 and 131.0 (Ar C-3, C-1 and C-1'), 143.3 and 145.3 (Ar C-5 and C-5'), 152.9 and 153.8 (Ar C-2 and C-2'), 172.6 (CO). MS: *m/e* 704.433 (calcd. for $C_{39}H_{60}O_{11}$: *m/e* 704.414).

*3-(Methoxycarbonylmethyl)-5,5'-di-*tert*-butyl-1,1'-biphenyl-32-crown-10* (**12c**). Yield 70%. IR (neat): 1740 $cm^{-1}$ (C=O). $^1H$ NMR: δ 1.31 (s, 8H, $CH_3$), 3.4–4.3 (m, 41H, $OCH_2CH_2$, $OCH_3$ and $ArCH_2$), 6.8–7.4 (m, 5H, ArH). $^{13}C$ NMR: δ 31.5 ($CH_3$), 34.1 and 34.3 (Ar–C), 35.7 ($ArCH_2$), 51.8 ($OCH_3$), 68.4–71.7 ($OCH_2CH_2$), 112.2 Ar C-3'), 125.1, 126.6, 128.7 and 128.8 (Ar C-4, C-4', C-6 and C-6'), 126.7, 127.8 and 130.9 (Ar C-3, C-1 and C-1'), 143.2 and 145.2 (Ar C-5 and C-5'), 152.9 and 153.7 (Ar C-2 and C-2'), 172.6 (CO). MS: *m/e* 748.444 (calcd. for $C_{41}H_{64}O_{12}$: *m/e* 748.440).

*Tetrahydropyranyl ether of 11-chloro-3,6,9-trioxa-1-undecanol* **13**

11-Chloro-3,6,9-trioxa-1-undecanol[22,23] (39.4 g, 0.185 mmol), dihydropyran (22.7 g, 0.27 mol) and 3 drops of concentrated HCl were stirred for 1 h at room temperature, after which tribenzylamine was added to neutralize the acidic catalyst. The precipitated hydrochloride was filtered off and the filtrate was distilled under vacuum to give 46.4 g (84%) of **13** as a viscous, colourless liquid. B.p. 120–121 °C (0.35 mmHg). IR (neat): 1124 $cm^{-1}$ (C–O). $^1H$ NMR: δ 1.3–2.0 (m, 6H, $CH_2$), 3.2–4.3 (m, 18H, $OCH_2$), 4.60 (bs, 1H, CH). Anal. calcd. for $C_{13}H_{25}ClO_5$: C 52.61, H 8.49; found: C 52.98, H 8.53%.

*Bis-tetrahydropyranyl ether of 13-(benzyloxymethyl)-3,6,9,12,15,18,-21,24-octaoxa-1,26-hexacosanediol* (**14**)

To 500 ml of *t*-BuOH, 1.90 g (0.27 mol) of lithium metal was added and the mixture was refluxed for 1 h under nitrogen. When 3-(benzyloxy)-1,2-propanediol[24,25] (15.90 g, 87.5 mmol) was added dropwise to this solution, a white precipitate formed. To this heterogeneous mixture was added 52.0 g (0.175 mol) of **13**, followed by 7.60 g (87.5 mmol) of anhydrous LiBr. The mixture was refluxed and

stirred for 15 days. The solvent was evaporated under reduced pressure and 150 ml of water was added to the residue. The mixture was extracted with $CH_2Cl_2$ (5 × 200 ml) and the combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give the crude reaction product. Chromatography on alumina using $Et_2O$ and $Et_2O$/EtOH (50:1) as eluents afforded 19.5 g (32%) of **14** as a pale yellow oil. IR (neat): 1122 $cm^{-1}$ (C–O). $^1H$ NMR: δ 1.3–2.0 (m, 12H, $CH_2$), 3.3 – 4.1 (m, 41H, $OCH_2CH_2$), 4.5–4.75 (m, 4H, $ArCH_2$ and OCHO), 7.35 (s, 5H, ArH). Anal. calcd. for $C_{36}H_{62}O_{13}$: C 61.52, H 8.89; found: C 61.36, H 8.70%.

*13-(Benzyloxymethyl)-3,6,9,12,15,18,21,24-octaoxa-1,26-hexacosanediol* (**15**)

To 13.80 g (0.020 mol) of **14**, dissolved in a mixture of $CH_2Cl_2$ (150 ml) and MeOH (50 ml), 4 ml of concentrated HCl was added. The solution was stirred at room temperature for 3 h and 5.0 g of solid $NaHCO_3$ was added. After the mixture had been stirred overnight, the salts were filtered, the filtrate was evaporated *in vacuo* and 50 ml of EtOAc was added. After filtration, the filtrate was evaporated *in vacuo* to afford 10.5 g (100%) of **15** as a colourless, extremely hydroscopic, viscous oil. IR: 3460 $cm^{-1}$ (OH), 1101 $cm^{-1}$ (C–O). $^1H$ NMR: δ 2.97 (bs, 2H, OH), 3.63 (bs, 37H, $OCH_2CH_2$), 4.52 (s, 2H, $ArCH_2$), 7.28 (s, 5H, ArH). Anal. calcd. for $C_{26}H_{46}O_{11} \cdot 2.5\ H_2O$: C 53.87, H 8.87; found: C 53.42, H 8.57%.

*(Benzyloxymethyl)-27-crown-9* **16**[14]

*Route A* (Scheme 2). Powdered KOH (0.86 g, 13.0 mmol) was suspended in dioxane (17 ml) and the mixture was heated to 60°C under nitrogen. A solution of **15** (1.74 g, 3.25 mmol) and *p*-toluenesulfonyl chloride (0.62 g, 3.25 mmol) in dioxane (10 ml) was added dropwise over 6 h and the reaction mixture was stirred at 60°C for 48 h. The solvent was removed *in vacuo* and the residue was purified by chromatography on alumina using EtOAc as the eluent to give 0.76 g (45%) of **16**.

*Route B* (Scheme 3). To a solution of 3,6,9,12,15,18-hexaoxa--10-(benzyloxymethyl)-1,20-eicosanediol (**19**)[27] (4.02 g, 9.0 mmol) in 250 ml of THF, *t*-BuOK (2.25 g, 20.0 mmol) was added and the mixture stirred under nitrogen for 1 h. A solution of diethylene glycol ditosylate[29] (3.94 g, 9.5 mmol) in THF (100 ml) was added dropwise and the reaction mixture was stirred for 9 days at room temperature. The solvent was removed *in vacuo* and the residue was dissolved in water (50 ml). The resulting solution was neutralized with 0.1 M HCl and extracted with $CH_2Cl_2$ (2 × 20 ml). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give a residue which was chromatographed on alumina using EtOAc as the eluent to give 2.17 g (47%) of **16**, $n = 4$.

*(Hydroxymethyl)-27-crown-9* (**17**)[14]

(Benzyloxymethyl)-27-crown-9 (**16**) (2.13 g, 4.1 mmol) was dissolved in 95% EtOH (25 ml) and Pd/C (10%, 0.20 g) was added together with a catalytic amount of *p*-toluenesulfonic acid. The mixture was shaken under 3.4 atmospheres of hydrogen at room temperature for 48 h. After filtration of the catalyst and evaporation of the solvent *in vacuo*, crude **17** (1.75 g) was obtained and used in the next step without further purification.

*Ditosylate of 13-(benzyloxymethyl)-3,6,9,12,15,18,24-octaoxa-1,26--hexacosanediol* (**20**)

A solution of *p*-toluenesulfonyl chloride (4.58 g, 24.0 mmol) in 10 ml of dry pyridine was added dropwise to a stirred solution of **15** (5.35 g, 10.0 mmol) in pyridine (10 ml) which had been cooled to – 10°C. After the addition was complete, the mixture was kept at 0°C overnight. The reaction mixture was poured onto ice, acidified with 6 M HCl and extracted with $CH_2Cl_2$ (2 × 20 ml). The combined extracts were washed with water, dried ($MgSO_4$) and evaporated *in vacuo* to provide 8.25 g (98%) of **20** as a viscous, pale yellow oil. IR (neat): 1356, 1190 and 1176 $cm^{-1}$ (S=O), 1097 $cm^{-1}$ (C–O). $^1H$ NMR: δ 2.45 (s, 6H, $CH_3$), 3.35–3.9 (m, 33H, $OCH_2$), 4.0–4.3 (m, 4H, $OCH_2$), 4.55 (s, 2H, $ArCH_2$), 7.15–7.9 (m, 13H, ArH). Anal. calcd. for $C_{40}H_{58}O_{15}S_2$: C 56.99, H 6.93; found: C 56.87, H 6.84%.

*17-(Benzyloxymethyl)-2,3-benzo-30-crown-10* (**21**)

Under nitrogen, pyrocatechol (0.72 g, 6.5 mmol) was dissolved in dry acetonitrile (110 ml) and anhydrous CsF (4.94 g, 32.5 mmol) was added in one portion. The mixture was then stirred vigorously for 1 h. A solution of **20** (95.50 g, 6.5 mmol) in acetonitrile (45 ml) was added dropwise and the reaction mixture was heated at 65°C for 48 h. After filtration, the solvent was removed *in vacuo* and the residue was chromatographed on alumina using EtOAc as eluent to give 2.28 g (58%) of **21** as a pale yellow, viscous oil. IR: (neat) 1116 $cm^{-1}$ (C–O). $^1H$ NMR: δ 3.5–4.3 (m, 37H, $OCH_2$), 4.55 (s, 2H, $ArCH_2$), 6.92 (s, 4H, ArH), 7.35 (s, 5H, ArH). Anal. calcd. for $C_{32}H_{48}O_{11}$: C 63.14, H 7.95; found: C 62.93, H 8.12%.

*17-(Hydroxymethyl)-2,3-benzo-30-crown-10* (**22**)

Hydrogenolysis of **21** (2.76 g, 4.5 mmol) was conducted in EtOH (60 ml) with 10% Pd/C (0.3 g) and a catalytic amount of *p*-toluenesulfonic acid under a pressure of 3.4 atm of hydrogen at room temperature for 48 h. The catalyst was filtered and the filtrate evaporated *in vacuo* to give a residue which was purified by column chromatography on alumina using EtOAc/MeOH (10:1) as eluent to afford **22** (2.22 g, 94%) as an extremely hygroscopic colourless oil. IR (neat): 3474 $cm^{-1}$ (OH), 1120 $cm^{-1}$ (C–O). $^1H$ NMR: δ 3.00 (bs, 1H, OH), 3.1–4.3 (m, 37H, $OCH_2CH_2$), 6.92 (s, 4H, ArH). Anal. calcd. for $C_{25}H_{42}O_{11} \cdot H_2O$: C 55.96, H 8.26; found: C 56.39, H 7.98%.

*Determination of dissociation constants*

The $pK_a$ measurements were carried out in nitrogen-flushed solvents in a thermostatted titration vessel at 25.0°C using a computerized potentiometric titration device. The titration was controlled and evaluated by a PDP 11/84 (Digital Equipment Corporation) computer equipped with a laboratory peripheral system (LPS) comprising a 12 bit ADC connected to the Knick industrial pH meter type DIM. Burette (Mettler DV11) control was provided via TTL pulses from a DR11 interface. Between every (fixed) titrant addition there was a waiting time of at least 50 s in which the pH did not vary more than 0.02 units. The concentrations of the titrands were kept low (< 0.005 mol/$dm^3$) in order to prevent homoconjugation of the carboxylic acids[31]. Titrants were 0.03–0.10 M solutions of tetrabutylammonium and tetramethylammonium hydroxide. The combined glass/silver–silver chloride electrode (Metrohm, 6.0203.000) was calibrated daily in buffer solutions, and used as described by *Bates*[32]. All measurements were carried out at least in duplicate and generally showed excellent agreement. All calculations were performed using the SUPERQUAD[33] programme on a PDP11 computer.

*Extraction experiments*

*Liquid–liquid phase transfer of uronium perchlorate.* A $CDCl_3$ solution (1 ml) of crown ether (0.1 mmol) and 0.1 mmol of 1,2,4,5-tetramethylbenzene was agitated for 17 h with 1 ml of an aqueous solution which contained 2.0 mmol of urea in 28% $HClO_4$. Subsequently, 0.5 ml of the chloroform layer was separated using a syringe, concentrated and the residue redissolved in water or methanol/water for the urea determination which was carried out as described previously[2]. The remaining 0.5 ml of the chloroform layer was used to determine, by $^1H$ NMR spectroscopy, the amount of crown ether transferred to the water phase during the equilibration from comparison of the ratios of crown ether to 1,2,4,5-tetramethylbenzene of the chloroform solution both before and after the period of equilibration.

*Liquid–liquid phase transfer of urea.* A $CDCl_3$ solution (1 ml) of crown ether (0.1 mmol) and 0.1 mmol of 1,2,4,5-tetramethylbenzene was agitated for 17 h with 1 ml of an aqueous solution which contained 2.0 mmol of urea. The amount of transferred urea was determined in the same way as described above for the phase transfer of uronium perchlorate.

*Solid–liquid phase transfer of urea.* A $CDCl_3$ solution (1 ml) of crown ether (0.1 mmol) was agitated for 17 h with an excess of solid urea. The chloroform solution was filtered, concentrated and redissolved in methanol/water for the urea analysis[2].

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