Correlation between the reactivities and the computed conformational and electronic properties of N,S,O-mixed-donor crown ethers†

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The nucleophilic coupling of the secondary nitrogen atoms of the mixed-donor crown ethers [16]aneS_4N, [15]aneS_4N, [15]aneO_4N, [15]aneO_2S_2N and [12]aneS_3N to an epoxide proceeds in an unexpected manner. The degree of coupling appears to be inversely related to the number of thioethers in the crown ether. Two possible explanations were considered: (*i*) steric factors affecting the accessibility of the lone pair on the secondary nitrogen and (*ii*) electronic factors affecting the nucleophilicity of the nitrogen. In order to discriminate between these possibilities, molecular modeling was applied. Firstly, suitable conformers of the mixed-donor crown ethers were generated by a conformational search on a molecular mechanics level (MM3). Next, these conformers underwent a (semi-empirical) PM3 geometry optimisation to obtain information on the electronic properties. Results of the molecular-modeling study indicate that both steric and electronic factors work hand-in-hand, rendering a plausible explanation for the observed phenomena: with an increasing number of thioethers in the crown ether, the orientation of the nitrogen lone pair becomes directed more towards the inside of the macrocycle so that the accessibility for reaction is decreased. Apart from this, the nucleophilicity of the secondary nitrogen is also reduced seriously with increasing number of thioethers, as can be deduced from the location, size and level of the HOMOs. These are located mainly on the sulfur atoms in the (oxa)azathia crown ethers, thereby lowering the reactivity of the nitrogen atom. In the case of [15]aneO_4N, the HOMO is located on the nitrogen lone pair only, which provides an explanation for the observed higher reactivity of this macrocycle.

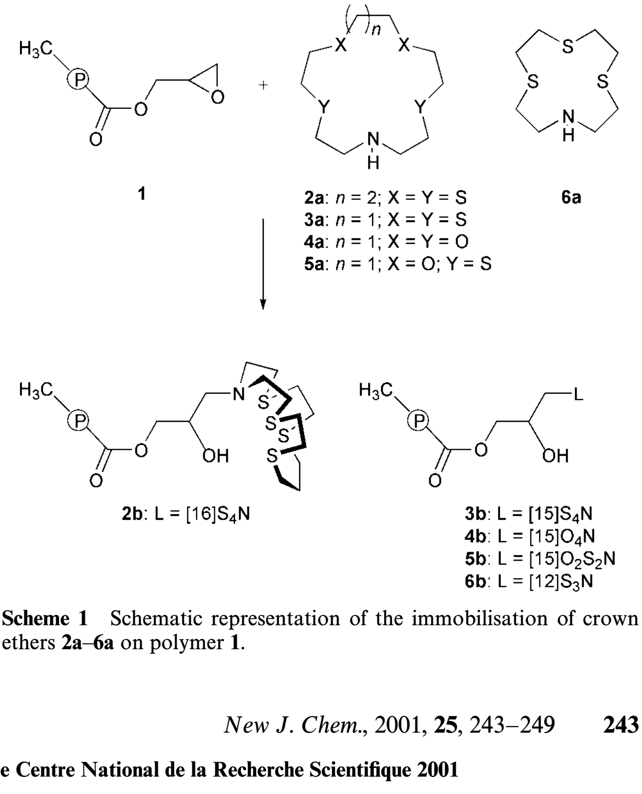
The ability of oxygen crown ethers to co-ordinate specifically to cations has been extensively exploited to bind and separate alkali and alkaline earth metal ions from solution.[1,2] Crown ethers containing nitrogen and/or sulfur donor atoms are of interest as their affinity is directed more towards (heavy) transition metal ions. This affinity can be fine-tuned by altering the composition of the donor-atom set.[3] Our research is focused on the immobilisation of mixed-donor crown ethers on highly cross-linked glycidyl methacrylate copolymers in order to obtain selectively chelating ion exchangers for the complexation and subsequent separation of heavy metal ions.

A common approach to immobilise ligands onto polymers is to connect a ligand to a spacer molecule and subsequently anchor this spacer-ligand adduct onto, for example, silica.[4,5] A spacer is not required for a glycidyl methacrylate copolymer, poly(GMA-O), as the epoxide groups originating from the monomers act as such after ring-opening by nucleophiles.[6]

In this paper, the reactivity of five mixed-donor crown ethers, with the common formula [X]aneO_mS_nN (with ring size X being 16, 15 or 12; m being 0, 2, or 4; and n being 0, 2, 3 or 4) towards a glycidyl methacrylate copolymer is discussed. In the ring-opening reaction of the epoxide groups, the secondary nitrogen atom of the macrocycles acts as the nucleophile.

The mixed-donor crown ethers [16]aneS_4N (**2a**), [15]aneS_4N (**3a**), [15]aneO_4N (**4a**), [15]aneO_2S_2N (**5a**) and [12]aneS_3N (**6a**) (see Scheme 1) appear to behave differently towards copolymer poly(GMA-O) (**1**). In order to gain insight into the factors that determine these differences, a molecular-modeling study was undertaken. Two possible factors have been considered, namely the orientation of the reacting lone pair on the nitrogen atom, and the electronic effects that the other donor atoms in the macrocycles have on the reactivity of the nitrogen atom.

Molecular modeling is commonly used in conformational analyses of (thia)crown ethers[7] and in calculations of the structure and stability of crown ethers with alkali[8] and alkaline earth metal ions.[9] Theoretically different conformers of crown ethers can be obtained through a conformational



Scheme 1 Schematic representation of the immobilisation of crown ethers **2a**–**6a** on polymer **1**.

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† *Non-SI units employed*: 1 kcal = 4.184 kJ; 1 eV ≈ 1.6 × 10^{-19} J ≈ 96.5 kJ mol^{-1}.

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search with molecular dynamics (MD) or molecular mechanics (MM) techniques,[7] while the actual conformer(s) may be retrieved from the Cambridge Structural Database (CSD) when their X-ray structure is known.[10] The latter provides a good starting point for a conformational search.

The aim of this paper is not to present a detailed conformational study of mixed-donor crown ethers, but to investigate steric and electronic properties of this type of macrocycle that may correlate with some observed experimental findings. A conformational search using molecular mechanics (MM3) has been conducted for each of the above-mentioned crown ethers in order to establish the conformational flexibility of the macrocycles. Subsequently, the semi-empirical method PM3 has been applied to check the MM3 results and to obtain qualitative insight into the electronic properties of these mixed-donor crown ethers.

Experimental results

The immobilisation reactions of crown ethers **2a**–**6a** on polymer **1** were analysed as a function of time by determining the nitrogen content of the polymers **2b**–**6b** by microanalysis. The results are shown in Table 1 and Fig. 1 (ligand concentration *vs.* time). Azathia crowns **2a**, **3a** and **6a** exhibit the lowest reactivity (0.7 mmol crown ether per gram polymer for **2a** and **3a** after 118 h), while oxaaza crown **4a** shows the highest reactivity (1.1 mmol per gram polymer after 118 hours). Oxaazathia crown **5a** shows an intermediate reactivity (0.9 mmol per gram polymer after 118 hours). These striking differences are already apparent after a reaction time of 1 h and are still present after prolonged reaction times.

The influence of the donor set of the crown ethers on the reactivity of the nitrogen atom towards epoxide groups is evident from these results: the degree of epoxide conversion decreases with increasing number of sulfur atoms in the macrocycles.

Several possible explanations for these observations can be given. Firstly, the orientation of the reacting lone pair on the nitrogen atom may not be the same for all macrocycles. Secondly, the different behaviour may be explained in terms of differences in nucleophilicity of the secondary nitrogens in the macrocycles.

The work described in this paper deals with the nucleophilic ring-opening of epoxides by the secondary amines of (oxa)azathia crown ethers, while unwanted competing ring-opening reactions of thioethers in the macrocycles with the epoxide groups of **1** should also be considered, as thioethers are known to be nucleophilic. To investigate whether or not the sulfur atoms of the crown ethers interfere with the nitrogen atom in the ring-opening reaction of the epoxide groups of **1**, **2a** was reacted with propylene oxide in a toluene–methanol mixture (v/v = 1 : 1). After a reaction time of 2 days, an additional C–N peak was observed in the ^{13}C NMR spectrum, arising from the addition of propylene oxide to the secondary nitrogen of **2a**. No signal arising from an additional C–S bond could be detected.

The reaction of dihexylamine with styrene oxide, in the presence of 4 equiv. of thioanisole, was conducted in order to mimic the immobilisation of an azathia crown ether where both a secondary amine and four thioether functionalities are present.[11] After a reaction time of 4 days, only traces of the dihexylamine adduct of styrene oxide was formed, and again there was no evidence of coupling of thioethers to the epoxide. On the other hand, styrene oxide is known to react easily with secondary amines when thioethers are absent.[12]

These test reactions illustrate that (*i*) the presence of thioethers decreases the reactivity of the secondary nitrogen of dihexylamine and (*ii*) interfering ring-opening reactions by the sulfur atoms of the (oxa)azathia crown ethers are unlikely to occur.

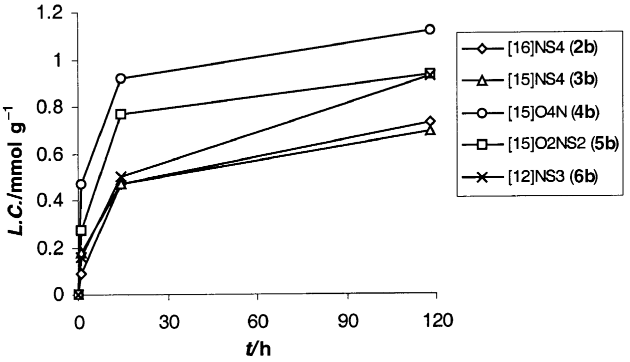

Fig. 1 Ligand concentrations, (L.C.), calculated from the nitrogen content (Table 1), on modified polymers **2b**–**6b** as a function of time.

Table 1 Nitrogen content (wt.%) of **2b**–**6b** as a function of time as a measure of the reactivity of crown ethers **2a**–**6a** towards **1**

t/h	**2b**	**3b**	**4b**	**5b**	**6b**
1	0.12	0.25	0.66	0.38	0.09
14.5	0.66	0.66	1.29	1.08	0.70
118	1.02	0.97	1.57	1.31	1.30

Theoretical results

General findings

The results of conformational searches based on MM3 for all crown ethers **2a**–**6a** are summarised in Table 2. For each crown ether, the strain energies and frequencies of the first ten conformers with the lowest strain energy are listed. Table 2 suggests high conformational flexibility for **2a**, **3a** and **5a**, and a slightly lower flexibility for **4a** and **6a**, since the strain energy difference between the lowest and the highest energy conformer is about 1 kcal mol^{-1} only for **2a**, **3a** and **5a**, and 2 kcal mol^{-1} for **4a** and **6a**.

Cumulative amounts for the first ten conformers of **2a**, **3a** and **5a** are 45.7, 42.0, and 46.3%, and for **4a** and **6a** 83.5 and 85.0%, respectively. This is also a reflection of the difference in flexibility between **2a**, **3a** and **5a** *vs.* **4a** and **6a**.

Table 2 The ten conformers of **2a**–**6a** with the lowest strain energies (in kcal mol^{-1}) and their relative frequencies (in %) in parentheses. The sum of the relative frequencies gives the percentage of all conformers accounted for by these 10 conformers

Conformer	2a	3a	4a	5a	6a
1	15.287 (15.26)	15.634 (10.61)	16.194 (30.36)	19.062 (10.35)	16.171 (20.99)
2	15.616 (8.75)	15.835 (7.56)	16.708 (12.75)	19.161 (8.76)	16.252 (18.33)
3	16.151 (3.55)	16.168 (4.30)	16.727 (12.34)	19.461 (5.28)	16.347 (15.59)
4	16.285 (2.83)	16.274 (3.60)	16.811 (10.70)	19.493 (5.01)	16.587 (10.40)
5	16.320 (2.67)	16.315 (3.36)	17.020 (7.52)	19.624 (4.01)	16.742 (8.00)
6	16.330 (2.62)	16.340 (3.22)	17.460 (3.58)	19.774 (3.11)	17.148 (4.04)
7	16.332 (2.61)	16.413 (2.85)	17.653 (2.58)	19.852 (2.73)	17.306 (3.09)
8	16.340 (2.58)	16.419 (2.82)	17.988 (1.47)	19.864 (2.68)	17.636 (1.77)
9	16.381 (2.41)	16.625 (1.99)	18.045 (1.33)	19.925 (2.41)	17.756 (1.44)
10	16.381 (2.41)	16.707 (1.73)	18.286 (0.89)	20.057 (1.93)	17.776 (1.40)
Sum	45.67	42.04	83.54	46.26	85.04

Table 3 PM3 geometry-optimisation (C.C.-conformer check) and heats of formation (ΔH_f in kcal mol^{-1}) of each conformer. The + signs in the conformer check columns indicate agreement of the PM3-optimised geometry with the conformation found in the MM3 conformational search

	2a		**3a**		**4a**		**5a**		**6a**	
Conformer	C.C.	ΔH_f	C.C.	ΔH_f	C.C.	ΔH_f	C.C.	ΔH_f	C.C.	ΔH_f
1	+	−7.5	+	−1.2	+	−160.9	−	−78.8	+	−3.0
2	+	−7.9	+	0.7	+	−158.0	+	−78.2	+	−2.2
3	+	−5.7	+	−3.4	−	−158.8	+	−76.0	+	−0.8
4	+	−6.3	+	−1.7	+	−158.4	−	−81.3	+	−0.6
5	+	−6.8	+	−0.1	+	−161.1	+	−78.1	+	−2.0
6	+	−6.6	+	1.0	+	−160.0	−	−79.6	+	5.1
7	+	−5.8	+	−1.7	−	−161.5	+	−76.2	−	−0.2
8	+	−5.7	+	0.9	+	−157.9	+	−76.2	+	4.6
9	+	−8.1	+	−3.0	+	−161.0	+	−80.2	+	−1.1
10	+	−5.9	+	−2.7	+	−159.3	+	−75.8	+	−0.2

Evidence for rapid interconversion of crown ether conformers has been reported for [12]aneO$_4$.[13] Hay *et al.* reported that [12]aneO$_4$ predominantly exists as a mixture of four conformers, as the cumulative population of these conformers is more than 90%. In comparison, the cumulative amount of the first four conformers of **6a** is about 65% according to the MM3 conformational search.

In Table 3 some results of the PM3 geometry-optimised crown ether conformers obtained from MM3 are compared to the original MM3 conformers.[14] For **2a** and **3a** identical conformers were obtained in all cases. **4a** shows differences between the MM3 and the PM3 structures for conformers 3 and 7 while **5a** shows differences for conformers 1, 4 and 6. **6a** shows a difference for conformer 7 only.

Orientation of the nitrogen lone pair

Table 4 shows the orientation of the nitrogen lone pair for all PM3-optimised conformers of **2a–6a**. The oxygen-containing crown ethers **4a** and **5a** almost exclusively show an outside orientation of the lone pair, while the sulfur-containing crown ethers **3a** and **6a** show a certain preference for an inside orientation. On the other hand, the sulfur-containing crown ether **2a** shows an almost equal distribution between outside and inside orientations. Fig. 2 shows typical examples of an outside and an inside orientation of a nitrogen lone pair. Furthermore, the lone pairs on sulfur and oxygen can be easily distinguished. The conformers depicted in Fig. 2 are illustrative examples; other conformers with inside or outside orientations of the nitrogen lone pair give similar pictures.

Effective nucleophilicity

All calculations were performed at the PM3 level. Similar eigenvalues of MOs were obtained for all conformers. The eigenvalues of the HOMO, HOMO-1, . . ., HOMO-($n-1$) (n = number of heteroatoms in the ring) of the most stable conformer of **2a–6a** (conformer 1 from the conformational search) are listed in Table 5. The eigenvalues of the MOs of the other conformers of **2a–6a** are similar to those calculated for the first conformer and are therefore not presented in Table 5.

Table 4 Orientation of the nitrogen lone pair, derived from PM3 calculations, for the first 10 conformers of **2a–6a**. Orientation inside the ring: in; outside the ring: out

Conformer	**2a**	**3a**	**4a**	**5a**	**6a**
1	out	in	out	out	out
2	in	in	out	out	in
3	in	in	out	out	in
4	in	in	out	out	in
5	out	out	out	out	in
6	out	in	out	out	in
7	out	in	out	out	in
8	in	in	out	in	out
9	in	out	out	out	in
10	in	in	out	out	in

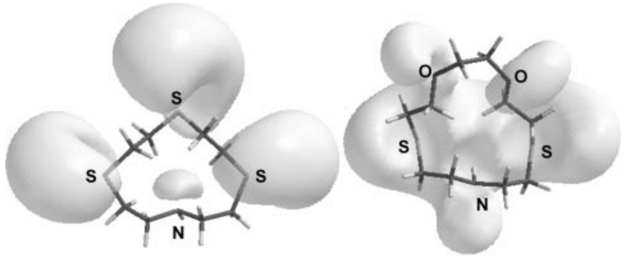

Fig. 2 PM3-calculated electronic structure of conformer 3 of [12]aneS$_3$N and conformer 1 of [15]aneO$_2$S$_2$N. The electrostatic potential (light grey) shows the size and location of the lone pairs of S, O, and N. The N lone pair of [12]aneS$_3$N is directed inside the ring, while the N lone pair of [15]aneO$_2$S$_2$N is directed outside the macrocycle.

Fig. 3 shows the HOMO, HOMO-1, HOMO-2, HOMO-3, and HOMO-4 of **2a** (conformer 1). Both the HOMO and the HOMO-4 exhibit density on the nitrogen and on the two adjacent sulfurs, albeit in the case of the HOMO the major density is on the sulfurs and in the case of the HOMO-4 the major density is on the nitrogen. The HOMO-1 shows density on the adjacent sulfurs only, while the HOMO-2 and HOMO-3 show density on the most remote sulfurs. The location of these molecular orbitals is similar for all other conformers of **2a** that have been investigated.

Crown ethers **3a** and **6a** show a very similar electronic structure to **2a**: the MOs located on the sulfur atoms are highest in energy. The MO on the nitrogen atom is the HOMO-4 in the case of **3a** and the HOMO-3 in the case of **6a**.

Fig. 4 shows the HOMO, HOMO-1, HOMO-2, HOMO-3, and HOMO-4 of **4a** (conformer 5). In this case, the HOMO is an orbital related to the nitrogen only, while the HOMO-1 and HOMO-2 are located on at least three oxygens and HOMO-3 and HOMO-4 show, apart from density on three oxygens, some density on nitrogen as well. Again, the location of the MOs on **4a** is the same for all ten conformers that have been investigated.

Table 5 Molecular orbital eigenvalues (in eV) for conformer 1 of **2a–6a**. The bold entries are the MOs located on nitrogen atoms. All calculations were performed using PM3

MO	**2a**	**3a**	**4a**	**5a**	**6a**
HOMO	−9.18	−9.17	**−9.20**	−9.11	−9.30
HOMO-1	−9.22	−9.24	−10.40	−9.22	−9.41
HOMO-2	−9.33	−9.35	−10.54	**−9.51**	−9.53
HOMO-3	−9.43	−9.54	−10.75	−10.67	**−10.03**
HOMO-4	**−9.63**	**−9.72**	−10.95	−10.93	

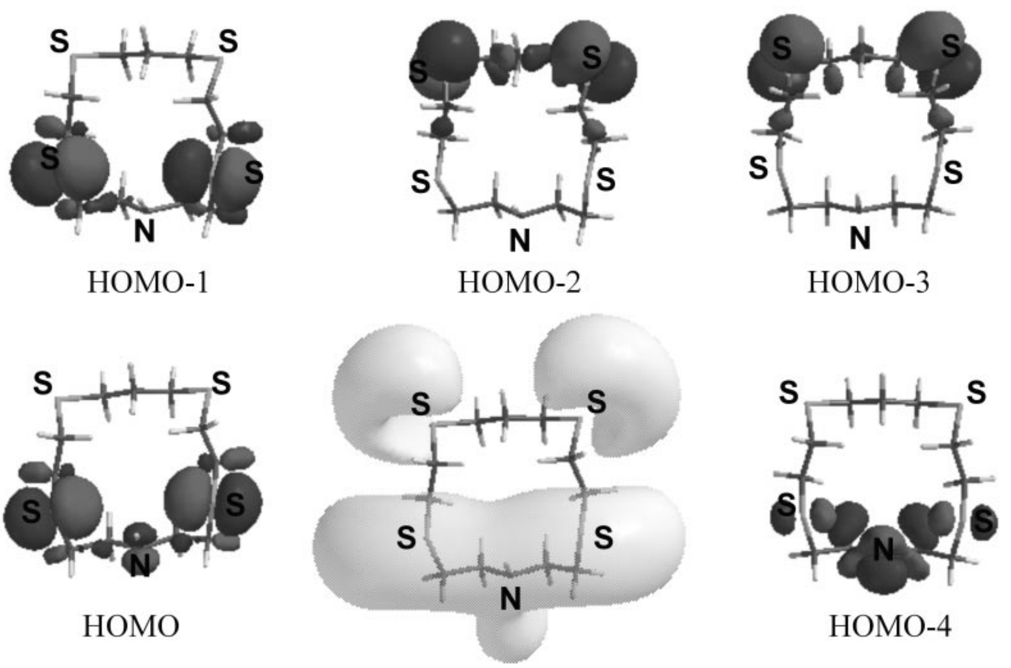

Fig. 3 PM3-calculated electronic structure of conformer 1 of [16]aneS_4N. The electrostatic potential (light grey) shows the size and location of the lone pairs of S and N. The 5 highest HOMOs are shown in dark grey.

In the case of **5a**, the HOMO, HOMO-1 and HOMO-2 are located on the sulfur atoms and/or the nitrogen, with the HOMO-2 showing the major density on the nitrogen. The HOMO-3 and HOMO-4 are located on the oxygen atoms.

Generally, sulfur-centred molecular orbitals are highest in energy, followed by those that are nitrogen-centred. The oxygen-centred molecular orbitals were found to be lowest in energy. All HOMOs of the crown ethers show very similar eigenvalues of about −9.2 eV. The eigenvalues of the nitrogen-centred orbitals are −9.63 (**2a**), −9.72 (**3a**), −9.20 (**4a**), −9.51 (**5a**), and −10.03 (**6a**) eV.

Ring strain

The possible role of ring strain in the explanation of the experimental findings was checked for **2a**–**6a** with MM3 *via* the isodesmic reaction (1), described below in the Theoretical methods section. Linear analogues of the crown ethers **2a**–**6a** were built by virtually breaking the carbon–carbon bond of the ethylene fragment most remote from the secondary amine, and adding two hydrogens. Generally all *anti* conformations were used for the strain energy calculation of the linear analogues. Table 6 lists the results of the calculated ring-strain energies, which vary from 2.3 to 6.7 kcal mol^{-1}.

Discussion and conclusions

The observed differences in reactivity of crown ethers **2a**–**6a** towards polymer **1** will be discussed in terms of the factors that have been mentioned previously. It should be noted that

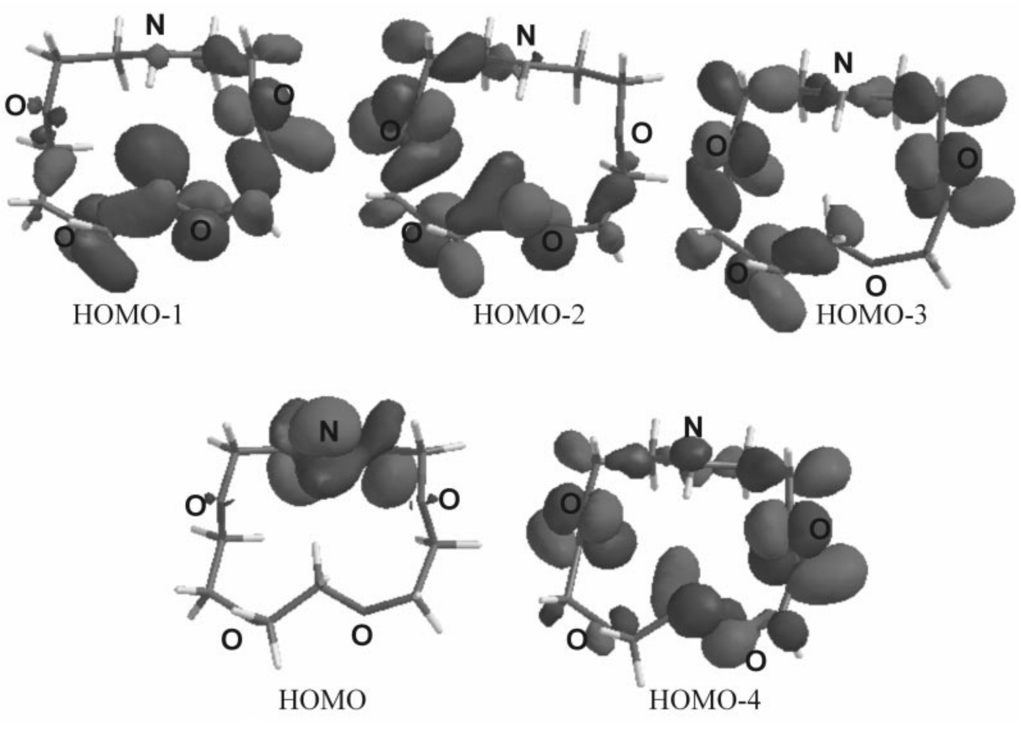

Fig. 4 PM3-calculated electronic structure of conformer 5 of [15]aneO_4N. The 5 highest HOMOs are shown.

Table 6 Calculated ring strain energies (kcal mol^{-1}) based on MM3 calculations and the isodesmic reaction: ring-X-CH_2CH_2-X + 2 $CH_4 \leftrightarrow CH_3X$-chain-$XCH_3$ + CH_3CH_3. Strain energy (MM3) of methane and ethane: 0.0 and 1.0 kcal mol^{-1}, respectively

	2a	3a	4a	5a	6a
Ring	15.3	15.6	16.2	19.1	16.2
Chain	12.0	10.8	12.8	13.8	8.5
Strain energy	2.3	3.8	2.4	4.3	6.7

this can be done on a qualitative level only, because of the relatively small size of the effect observed in terms of energy. The highest and the lowest degree of modification (of the crown ethers on the resin) differ by about a factor 2, which corresponds to an energy difference of 0.4 kcal mol^{-1} only.

Orientation of the nitrogen lone pair

As mentioned previously, the oxygen-containing crown ethers **4a** and **5a** show an almost exclusively outside orientation of the nitrogen lone pair, while the sulfur-containing crown ethers **2a**, **3a** and **6a** show either an inside orientation or a mixed inside/outside one (see Table 4). The outside orientation seems very favourable for nucleophilic coupling, while the inside orientation seems not as favourable. Indeed, the oxygen-containing crown ethers show the highest activities in the nucleophilic coupling with the epoxide, while the all-sulfur crown ether analogues show the lowest activities.

However, the difference between **4a** and **5a**, and the differences between **2a**, **3a**, and **6a**, cannot be explained by the orientation of the nitrogen lone pair alone, because within these groups the orientation is virtually the same.

From these results it can be concluded that an outside orientation of the nitrogen lone pair is a favourable reaction condition, but that one or more other factors also influence the reaction.

Effective nucleophilicity

As mentioned in the Theoretical methods section, the HOMO can be correlated with its effective nucleophilicity. In the case of the oxaaza crown ether **4a**, the HOMO is an N-centred orbital, but the HOMOs in the (oxa)azathia crown ethers all appear to be S-centred orbitals. This implies that a thioether should be able to act as a *kinetic* nucleophile. The thermodynamic preference is of course in favour of the reaction of the nitrogen nucleophile with the epoxide.

Thioethers are known to be good nucleophiles. They react easily with simple alkyl halides to produce stable sulfonium salts in excellent yields. Depending on specific reaction conditions, the process is reversible. Solvolysis of 4-chlorobutyl phenyl sulfide in refluxing methanol produces s-phenyl tetrahydrothiophenium chloride almost quantitatively.[15] The latter is slowly converted back to the starting material in chloroform. Furthermore, anchimeric assistance of thioethers in nucleophilic substitutions of 2-halogenoethyl thioethers has been described extensively: epi-sulfonium ions were suggested as the transition state or even as reactive intermediate.[15,16]

The reaction of a thioether with an epoxide is an interesting case: nucleophilic attack of the thioether leads to a sulfonium ion with an alkoxide in the β-position. This putative intermediate is structurally identical to that formed from addition of a sulfonium methylide to a carbonyl group, which is used for the synthesis of epoxides.[17] This indicates that the intermediate formed by the reaction of a thioether with an epoxide group will only result in the original thioether and epoxide. This is in agreement with the test experiments, where no addition of the thioethers in **2a** or thioanisole to propylene oxide was observed (see Experimental).

In the case of epoxide ring opening by primary or secondary amines, the situation is different: after transfer of a proton from the amine to the epoxide oxygen, a thermodynamically stable product is formed, in contrast to the thioether case. Thioethers would then be able to act as a nucleophile, competing kinetically with the thermodynamically favoured nitrogen. The more thioethers present in the crown ether, the slower the reaction with the nitrogen would be.

Accepting the above concept, an attractive explanation is offered for the observed reactivity of the macrocycles towards the epoxide. It would result in the order **4a** (no S), **5a** (2 S), **6a** (3 S), and **2a** and **3a** (both 4 S), perfectly in line with the observed order (see Fig. 1). Alternatively, the eigenvalue of the N-centred orbital, the HOMO-*n*, (with n = number of S) could be used to predict the order of reactivity because this orbital reflects both the number and reactivity of the thioethers in the macrocycles. From Table 5 it is clear that **4a** should be the most reactive in the coupling to the epoxide, to be followed by **5a**, **2a**, **3a**, and finally **6a**. This order is as expected, with the exception of **6a**, whose reactivity is underestimated.

Ring strain

The MM3 results indicate that ring-strain energies in all macrocycles are rather low, as would be expected for (oxa)azathia crown ethers. The magnitude is in the same range as cyclopentane (7.3 kcal mol^{-1}), cyclohexane (1.4 kcal mol^{-1}) and cycloheptane (7.6 kcal mol^{-1}). Therefore, it is not likely that ring strain plays a significant role in the explanation of the experimental results. The only exception to this might be **6a** (ring strain: 6.7 kcal mol^{-1}), as its reaction behaviour is initially fully comparable with **2a** and **3a**, but finally reaches the same level as **5a**.

Concluding remarks

In principle, the observed reactivity of the different crown ethers can be rationalised by the above mentioned effect of the effective nucleophilicity. However, the effect of the orientation of the nitrogen lone pair cannot be neglected. It is also a kinetic effect, because the macrocycles seem to be quite flexible. It might well work hand-in-hand with the effect of the effective nucleophilicity. The effect of (the release of) ring strain does not seem to be important for these flexible macrocycles. Only the slightly different behaviour of **6a** (compared to **2a** and **3a**) may be related to the higher ring strain of the former. Close inspection of Fig. 1 shows that **6a** initially shows a very similar reactivity to **2a** and **3a**, and that later on its reactivity increases to the level of **5a**.

Molecular modeling proved to be a useful tool to gain insight into unexpected experimental results. A conformational search with MM3 is a useful approach for large systems like those discussed in this paper. The additional PM3 results increase the insight into the phenomena discussed in this study in a qualitative way.

Experimental

Reagents and analytical methods

The copolymer poly(GMA-O) was prepared by radical-initiated suspension polymerisation using a mixture (6 : 4 v/v) of glycidyl methacrylate (GMA) and ethylene glycol dimethacrylate (EDMA) with an equal volume of cyclohexanol-1-dodecanol (9 : 1 v/v) as the porogen.[18]

DMF was stored under a dinitrogen atmosphere over molecular sieves. Toluene was distilled from sodium metal and stored under dinitrogen over molecular sieves.

The ligand concentrations of the functionalised polymers were calculated on basis of the wt.% of nitrogen. Elemental analyses (C, H, N, S) were carried out by the Microanalytical

Department of University College Dublin (Republic of Ireland). ^1H NMR and ^{13}C NMR spectra were recorded on a 200 MHz Jeol JNM FT-NMR spectrometer. Chemical shifts are quoted with respect to TMS as an internal reference. Mass spectra were recorded on a Finnigan MAT TSQ-700 equipped with a custom-made electrospray interface (ESI).

Theoretical methods

The SPARTAN package[19] was used for all calculations (SPARTAN 2.0 and PC SPARTAN Plus). Molecular mechanics (MM3) was used as the method of choice for the generation of conformers of the N,S,O-substituted macrocycles, mainly for two reasons: for large systems such as these macrocycles it is almost the only practical approach in order to avoid excessive computational times, and because these macrocycles are built up from saturated hydrocarbon fragments linked by (thio)ether moieties it might be expected that molecular mechanics will give reasonable results.

The conformers were subjected to an additional geometry optimisation using the semi-empirical method PM3, mainly to obtain information on the electronic structure of the conformers, and as an additional check on the structures obtained by MM3.

Lone pairs are visualised by an isosurface of a distinct value (-10.0 kcal mol^{-1}) of their electrostatic potential. MOs are visualised in the usual way, or alternatively as a (quantitative) projection on the isosurface (border: 0.08 electrons au^{-3}) formed by the bonding electrons.

In rather classical FMO theory,[20] nucleophilicity can be correlated with the HOMO of a molecule. Location, shape and eigenvalues were determined by the PM3 method.

PM3 calculations also yield heats of formation, but these are generally not accurate enough for the comparison of small energy differences.

The role of ring strain as a possible explanation for the observed experimental results was checked using a simple isodesmic reaction:

$$\llcorner\text{ring-XCH}_2\text{CH}_2\text{X–}\lrcorner + 2\text{CH}_4 \rightarrow$$

$$\rightarrow \text{CH}_3\text{X-chain-XCH}_3 + \text{CH}_3\text{CH}_3 \quad (1)$$

Macrocyclic compounds

[15]aneO$_4$N (**4a**) was purchased from Aldrich. [16]aneS$_4$N (**2a**) was prepared as described previously.[21]

Synthesis of 7-aza-1,4,10,13-tetrathiacyclopentadecane ([15]aneS$_4$N, 3a), 10-aza-1,4-dioxa-7,13-dithiacyclopentadecane ([15]aneO$_2$S$_2$N, 5a) and 7-aza-1,4,10-trithiacyclododecane ([12]aneS$_3$N, 6a). The dithiol 1,4,7,10-tetrathiadecane (for the synthesis of **3a**) was prepared by converting 3,6-dithia-1,8-octanediol to the dithiol according to a literature procedure.[22] The dithiols 3,6-dioxa-1,8-octanedithiol (for the preparation of **5a**) and 2,2′-thiodiethanethiol (for the preparation of **6a**) were obtained from Aldrich. The Boc-protected crown ether analogues of **3a**, **5a** and **6a** were prepared in the same manner as for **2a**,[21] by reacting *N*-Boc-bis(2-chloroethyl)amine with the corresponding dithiol, using the high-dilution method with Cs_2CO_3 in DMF.[23] The products were purified by column chromatography (silica) using 100% CH_2Cl_2, the yields being 35–40%. The Boc-protected ligands were deprotected with a 50% TFA solution in CH_2Cl_2 for 15 min at room temperature (90% yield).

[15]aneS$_4$N (**3a**). ^1H NMR (200 MHz; CDCl$_3$; Me$_4$Si): δ 1.86 (1 H, br s, NH), 2.60–2.90 (20 H, m, CH$_2$). ^{13}C NMR (50 MHz; CDCl$_3$; Me$_4$Si): δ 32.26, 32.58, 32.73 (CH$_2$–S), 48.64 (CH$_2$–N). Anal. found: C, 42.39; H, 7.27; N, 4.27; S, 45.26%. Calc. for $C_{10}H_{21}S_4N$: C, 42.36; H, 7.47; N, 4.94; S, 45.23%. ESI-MS: 284 $[M + H]^+$.

[15]aneO$_2$S$_2$N (**5a**). ^1H NMR (200 MHz; CDCl$_3$; Me$_4$Si): δ 2.19 (1 H, br s, NH), 2.71–2.89 (12 H, m, CH$_2$–S and CH$_2$–N), 3.63 (4 H, s, CH$_2$–O), 3.70 (4 H, t, CH$_2$–O). ^{13}C NMR (50 MHz; CDCl$_3$; Me$_4$Si): δ 32.11 and 33.22 (CH$_2$–S), 48.35 (CH$_2$–N), 70.75 and 72.01 (CH$_2$–O). Anal. found: C, 47.55; H, 8.45; N, 5.18%. Calc. for $C_{10}H_{21}O_2S_2N$: C, 47.76; H, 8.43; N, 5.57%. ESI-MS: 251 $[M^{\cdot}]^+$.

[12]aneS$_3$N (**6a**). ^1H NMR (200 MHz; CDCl$_3$; Me$_4$Si): δ 1.98 (1 H, br s, NH), 2.69–2.90 (16 H, m, CH$_2$). ^{13}C NMR (50 MHz; CDCl$_3$; Me$_4$Si): δ 31.15 (CH$_2$–S), 32.23 (CH$_2$–S), 49.81 (CH$_2$–N). Anal. found: C, 43.11; H, 7.62; N, 5.98; S, 43.61%. Calc. for $C_8H_{17}NS_3$: C, 43.01; H, 7.67; N, 6.27; S, 43.05%. ESI-MS: 223 $[M^{\cdot}]^+$.

Immobilisation experiments

The crown ethers were immobilised onto copolymer **1** by the following general procedure: three batches, each containing a mixture of the crown ether (0.63 mmol) and poly(GMA-O) **1** (100 mg, 0.42 mmol epoxide groups) in 5 ml dry toluene, were heated at 100 °C under a dinitrogen atmosphere for 1, 14.5 and 118 h, respectively. The resulting resins were filtered off and purified in a Soxhlet with toluene (6 h). The resins were dried *in vacuo* at 50 °C for 16 h and analysed by microanalysis.

Test reactions

Reaction of propylene oxide with 2a. A mixture of **2a** (230 mg, 0.77 mmol) and propylene oxide (0.217 ml, 3.10 mmol) was stirred in a mixture of 1 ml dry toluene and 1 ml dry methanol at room temperature in a sealed flask. After 48 h the solvents and excess propylene oxide were removed under reduced pressure.

N-(2-Hydroxypropyl)-[16]aneS$_4$N. ^1H NMR (200 MHz; CDCl$_3$; Me$_4$Si): δ 1.08 (3 H, d, CH$_3$), 1.86 (2 H, p, CH$_2$–*C*H$_2$–CH$_2$), 2.47 (2 H, m, N–*C*H$_2$–CHOH), 2.61–2.74 (20 H, m, CH$_2$–S and CH$_2$–N macrocycle), 3.70 (1 H, m, C*H*OH). ^{13}C NMR (50 MHz; CDCl$_3$; Me$_4$Si): δ 19.44 (CH$_3$) 29.89 (CH$_2$–*C*H$_2$–CH$_2$), 30.54, 30.62 and 32.32 (CH$_2$–S), 54.25 (N–CH$_2$ macrocycle), 62.54 (N–*C*H$_2$–CHOH), 63.39 (CHOH).

Reaction of styrene oxide with dihexylamine in the presence of 4 equiv. of thioanisole. A stirred mixture of dihexylamine (0.15 ml, 0.63 mmol), thioanisole (0.30 ml, 2.52 mmol) and styrene oxide (0.05 ml, 0.42 mmol) was heated in 5 ml dry toluene at 100 °C under a dinitrogen atmosphere for 4 days. The solvent was removed under reduced pressure and the ^{13}C NMR of the reaction mixture showed a mixture of starting materials. A small additional signal at 60.12 ppm was assigned to the CH$_2$(styrene oxide)–N carbon atom of the adduct of dihexylamine and styrene oxide.

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