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Chiral Diaza-18-crown-6 Derivatives

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Summary The chiral diaza-18-crown-6 derivatives (**7**) and (**8**), which are readily synthesised from the corresponding optically active α-amino-acids or derived amino-alcohols (**1**), form complexes with primary alkylammonium salts in non-polar solvents; enantiomer recognition in complex formation depends upon the substituents R^3 on the ring nitrogen atoms.

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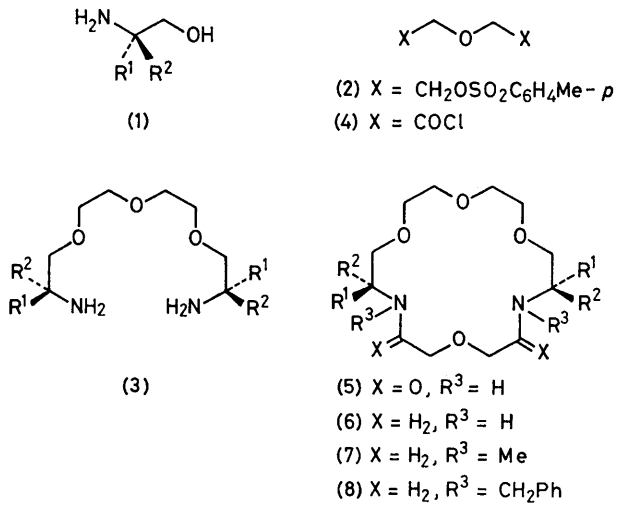
Optically active crown ethers based upon a resolved 1,1′-binaphthyl system[1] have been extensively and successfully developed as hosts that show enantiomer selection in complex formation with chiral guest alkylammonium salts. Other optically active crown ether systems[2] have been investigated in which the chirality is derived from natural sources such as sugars and tartaric acid. α-Amino-acids are potentially a useful source of chirality for the synthesis of chiral aza-crown ethers and a few reports of their utilisation have appeared,[3] but the macrocycles that have been prepared are not those that are most effective for the complexation of alkylammonium salts. We report in this communication a general synthesis of optically active diaza-18-crown-6 derivatives, based upon α-amino-acids as the starting materials, and we provide preliminary evidence for enantiomer recognition by these new crown ether systems.

The amino-alcohols (**1**), readily available by reduction of α-amino-acids, react as their mono-anions (NaH, tetrahydrofuran) with the bis-toluene-*p*-sulphonate (**2**) to give moderate yields (60—80%) of the diamines (**3**). These diamines react with the bis-acid chloride (**4**) to give acceptable yields (20—30%) of the diamides (**5**). Reduction of (**5**) with lithium aluminium hydride to give the amines (**6**), followed by alkylation [CH_2O, HCO_2H for (**7**) and $PhCH_2Cl$ for (**8**)] affords the optically active diaza-18-crown-6 derivatives (**7**) and (**8**). These crown ether systems are designed to present two identical faces to a guest ammonium cation as is the case for most of the other chiral crown ether systems that have been reported.[1,2]

The N–Me derivatives (**7a**—**c**) form strong complexes with primary alkylammonium thiocyanates in non-polar solvents ($CDCl_3$ or CD_2Cl_2) which may be examined using the n.m.r. methods that have been developed by ourselves[4] and others.[5] Extraction experiments, with (*R*,*S*)-1-phenylethylammonium thiocyanate as guest, indicate only slightly selective extraction of the (*S*)-guest salt by the (*S*,*S*)-hosts (**7a**) and (**7b**) and of the (*R*)-guest salt by the (*R*,*R*)-host (**7c**). In the presence of water the hosts (**7a**—**c**) form two types of complex (two sets of signals in the n.m.r. spectrum) with the (*R*)- or (*S*)-guest salt; the major species is identical to that formed in a single-phase ($CDCl_3$ or CD_2Cl_2) system and the minor species is probably the hydrated complex [(**7**), H_2O, RNH_3^+ ^-SCN]. As expected the complexes of these chiral hosts (**7a**—**c**) with the (*R*)- or (*S*)-enantiomers of the guest salt give distinctive and different spectra.



In (**1**), (**3**), and (**5**)—(**8**): **a**; R^1 = $CHMe_2$, R^2 = H
b; R^1 = CH_2Ph, R^2 = H
c; R^1 = H, R^2 = Ph

The *N*-benzyl derivative (**8a**) forms weak complexes with (*R*)- and (*S*)-1-phenylethylammonium thiocyanate in CD_2Cl_2 and the n.m.r. spectra of the two diastereoisomeric complexes are very different (Figure, a and b). The spectrum of host (**8a**) complexed with 1 mol. equiv. of (*R*,*S*)-guest represents a time-averaged spectrum for the host signals in the two diastereoisomeric species,[6] consistent with rapid exchange of the (*R*)- and (*S*)-guest cations; however, the signals for the enantiomeric guests show the expected chemical-shift differences in the presence of the chiral host (**8a**). The n.m.r. spectrum (Figure, c) of host (**8a**) in the presence of 2 mol. equiv. of the (*R*,*S*)-guest is virtually identical with that of the host (**8a**) in the complex with the (*R*)-guest (Figure, a) indicating that under these conditions the host (**8a**) selectively complexes with the (*R*)-guest rather than the (*S*)-guest. This pronounced enantiomer selectivity is lost in the presence of water since under these conditions hydrated complexes are formed; it is not therefore possible to check this apparent enantiomer selectivity by extraction experiments. The host (**8b**), in which the substituent R^1 is sterically less demanding, shows similar behaviour in dry CD_2Cl_2 or $CDCl_3$ but the apparent enantio-

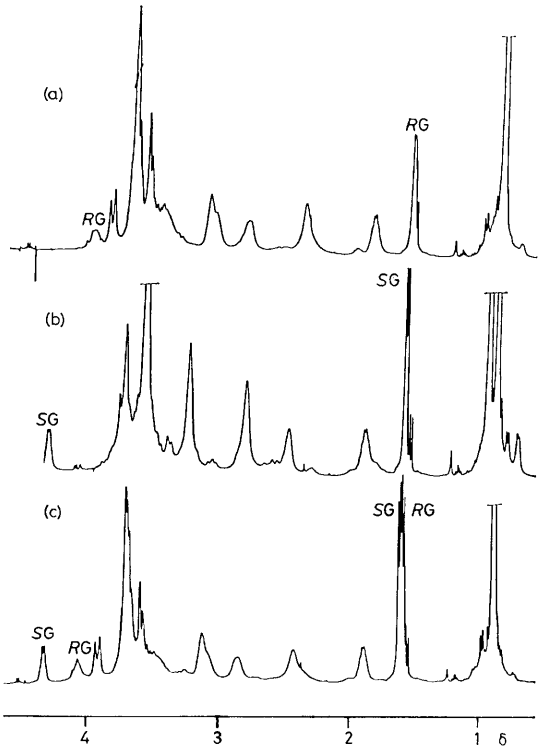


Figure. ^1H N.m.r. spectra (400 MHz) of complexes of host (**8a**) with 1-phenylethylammonium thiocyanate in CD_2Cl_2 at −20 °C, using (a) 1 mol. equiv. of (*R*)-guest, (b) 1 mol. equiv. of (*S*)-guest, and (c) 2 mol. equiv. of (*R*,*S*)-guest. The descriptions *RG* and *SG* refer to signals from the (*R*)-guest and (*S*)-guest, respectively.

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mer selectivity in favour of the (*R*)-guest is qualitatively less than that shown by the host (**8a**).

These preliminary results indicate that the chiral aza-crown systems (**7**) and (**8**) show enantiomer selectivity in the formation of complexes with 1-phenylethylammonium thiocyanate, in the absence of water, to an extent that depends upon the groups R^1 (or R^2) and R^3. This selectivity is difficult to rationalise but we note that the complexes of (**7**) with benzylammonium thiocyanate or with a single enantiomer of 1-phenylethylammonium thiocyanate do not show the diastereoisomerism, associated with *syn*- and *anti*-relationships between the guest and the side chains on the nitrogen atoms of the macrocycle, found for other diaza-18-crown-6 systems that we have examined.[4] Thus the n.m.r. spectra of these complexes, at temperatures where guest–host exchange processes are slow on the n.m.r. time-scale, are consistent with the presence of largely a single species of diastereoisomer. The analogous complexes of (**8**) are too weakly bound for the detection of diastereoisomerism of this type.

We thank Glaxo Group Research for a grant to I. A. C., and the S.R.C. 400 MHz n.m.r. service at Sheffield for running the n.m.r. spectra.

(*Received*, 23*rd June* 1981; *Com.* 737.)

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