# Chiral Diaza-18-crown-6 Derivatives

By DEREK J. CHADWICK, IAN A. CLIFFE, and IAN O. SUTHERLAND*
(*Department of Organic Chemistry, The Robert Robinson Laboratories, University of Liverpool, P.O. Box* 147, *Liverpool* L69 3BX)
and ROGER F. NEWTON
(*Glaxo Group Research Ltd., Ware, Herts.* SG12 0DJ)

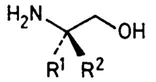
*Summary* The chiral diaza-18-crown-6 derivatives (**7**) and (**8**), which are readily synthesised from the corresponding optically active α-amino-acids or derived amino-alcohols (**1**), form complexes with primary alkylammonium salts in non-polar solvents; enantiomer recognition in complex formation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

---

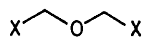
OPTICALLY active crown ethers based upon a resolved 1,1′-binaphthyl system[1] have been extensively and successfully developed as hosts that show enantiomer selection in complex formation with chiral guest alkylammonium salts. Other optically active crown ether systems[2] have been investigated in which 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]

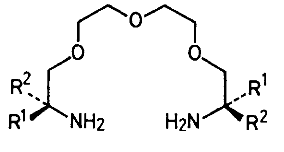
The N–Me derivatives (**7a**—**c**) form strong complexes with primary alkylammonium thiocyanates in non-polar solvents ($CDCl_3$ or $CD_2Cl_2$) which may be examined using the n.m.r. methods that have been developed by ourselves[4] and others.[5] Extraction experiments, with (*R*,*S*)-1-phenylethylammonium 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.



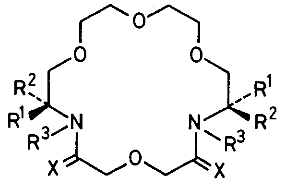
(**1**)



(**2**) X = $CH_2OSO_2C_6H_4Me$-*p*
(**4**) X = COCl



(**3**)



(**5**) X = O, $R^3$ = H
(**6**) X = $H_2$, $R^3$ = H
(**7**) X = $H_2$, $R^3$ = Me
(**8**) X = $H_2$, $R^3$ = $CH_2Ph$

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-

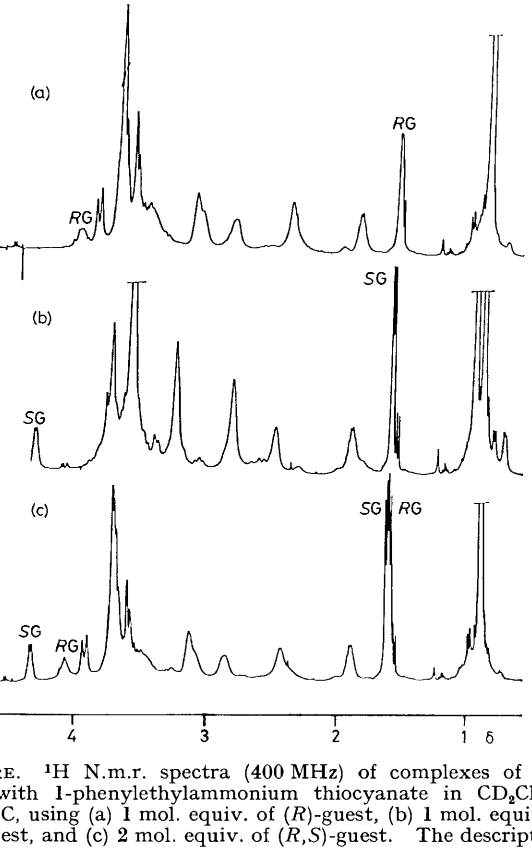


FIGURE. $^1H$ N.m.r. spectra (400 MHz) of complexes of host (**8a**) with 1-phenylethylammonium thiocyanate in $CD_2Cl_2$ at −20 °C, using (a) 1 mol. equiv. of (*R*)-guest, (b) 1 mol. equiv. of (*S*)-guest, and (c) 2 mol. equiv. of (*R*,*S*)-guest. The descriptions *RG* and *SG* refer to signals from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

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.)

[1] D. J. Cram and J. M. Cram, *Acc. Chem. Res.*, 1978, **11**, 8; J. M. Timko, R. C. Helgeson, and D. J. Cram, *J. Am. Chem. Soc.*, 1978, **100**, 2828; S. C. Peacock, L. A. Domeier, F. C. A. Gaeta, R. C. Helgeson, J. M. Timko, and D. J. Cram, *ibid.*, p. 8190; S. C. Peacock, D. M. Walba, F. C. A. Gaeta, R. C. Helgeson, and D. J. Cram, *ibid.*, 1980, **102**, 2043.

[2] W. Hain, R. Lehnert, H. Röttele, and G. Schröder, *Tetrahedron Lett.*, 1978, 625; J. F. Stoddart, *Chem. Soc. Rev.*, 1979, **8**, 85; T. Matsui and K. Koga, *Tetrahedron Lett.*, 1978, 1115; N. Ando, Y. Yamatoto, J. Oda, and Y. Inouye, *Synthesis*, 1978, 688; J. P. Behr, J. M. Lehn, D. Moras, and J. C. Thierry, *J. Am. Chem. Soc.*, 1981, **103**, 701.

[3] F. Wudl and F. Gaeta, *J. Chem. Soc., Chem. Commun.*, 1972, 107; J. G. de Vries and R. M. Kellogg, *J. Am. Chem. Soc.*, 1979, **101**, 2759; M. Zinic, B. Bosnic-Kasnar, and D. Kolbah, *Tetrahedron Lett.*, 1980, **21**, 1365; A. Shanzer and E. Berman, *J. Chem. Soc., Chem. Commun.*, 1980, 259.

[4] L. C. Hodgkinson, S. J. Leigh, and I. O. Sutherland, *J. Chem. Soc., Chem. Commun.*, 1976, 639, 640; M. R. Johnson, I. O. Sutherland, and R. F. Newton, *J. Chem. Soc., Perkin Trans.* 1, 1979, 357; L. C. Hodgkinson, M. R. Johnson, S. J. Leigh, N. Spencer, I. O. Sutherland, and R. F. Newton, *ibid.*, p. 2193.

[5] F. de Jong, D. N. Reinhoudt, and C. J. Smit, *Tetrahedron Lett.*, 1976, 1371, 1375; F. de Jong, D. N. Reinhoudt, and G. J. Torny, *ibid.*, 1979, 911.

[6] D. P. J. Pearson, S. J. Leigh, and I. O. Sutherland, *J. Chem. Soc., Perkin Trans.* 1, 1979, 3113.