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Molecular Structures Department

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MOLECULAR STRUCTURES DEPARTMENT

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Introduction

This year we had our first experience of welcoming a Visiting Group who saw individually all the post-doctoral members of the Department and some, but not all, of the sites housing our equipment. Some time has been devoted to planning our portion of the new South Building to be shared with the Entomology Department.

Work has continued on the main themes of coordination chemistry of the alkali and alkaline earth metals, now with greater emphasis on the latter. This has included studies on solutions, on two-phase systems and on rat liver mitochondria in collaboration with University College London.

Crystal structure analysis is still hampered by the unreliability of our own diffractometer; we have managed to collect observations for four crystals on it and have been fortunate in being able to use those in other laboratories, Queen Mary College, London, the Polytechnic of North London and Sheffield Polytechnic. We also have set up equipment for taking measurements photographically on crystals held at the temperature of liquid nitrogen. We have determined the crystal structures of two pyrethroid insecticides (in collaboration with the Insecticides and Fungicides Department), a fungicide which is also a cation transporting compound, a derivative of a stress metabolite from blighted potatoes (in collaboration with the Food Research Institute), as well as several compounds in the coordination chemistry programme.

Coordination chemistry

Alkaline earth metal cations. Alkaline earth cations, M^{2+} , might be expected to form compounds with macrocyclic crown ethers similar to those of the alkali metal cations, M^+ , of approximately the same radius. (To preserve electroneutrality, however, the number of anions would not be the same.) Experiments with the molecules of Fig. 1 showed this expectation to be largely justified so the differences will be emphasised below.

The small ring compound, benzo-15-crown-5, gives 1:2 sandwich compounds with Sr^{2+} and Ba^{2+} just as with the larger alkali metal cations K^+ , Rb^+ and Cs^+ . With Ca^{2+} , as with Na^+ , the usual ratio is 1:1 with some solvation but there are two main differences. One is that nitrogen base adducts can be formed for the calcium compound, e.g. $Ca(NCS)_2$, benzo-15-crown-5, pyridine, and the other is that the infra-red spectrum indicates a different conformation for crown molecule from either of those in the sodium or the potassium complexes. This new conformation was determined by the crystal structure analyses, described later. Yet another conformation is suggested by the infra-red spectrum of $Mg(NCS)_2$, benzo-15-crown-5.

ROTHAMSTED REPORT FOR 1975, PART 1

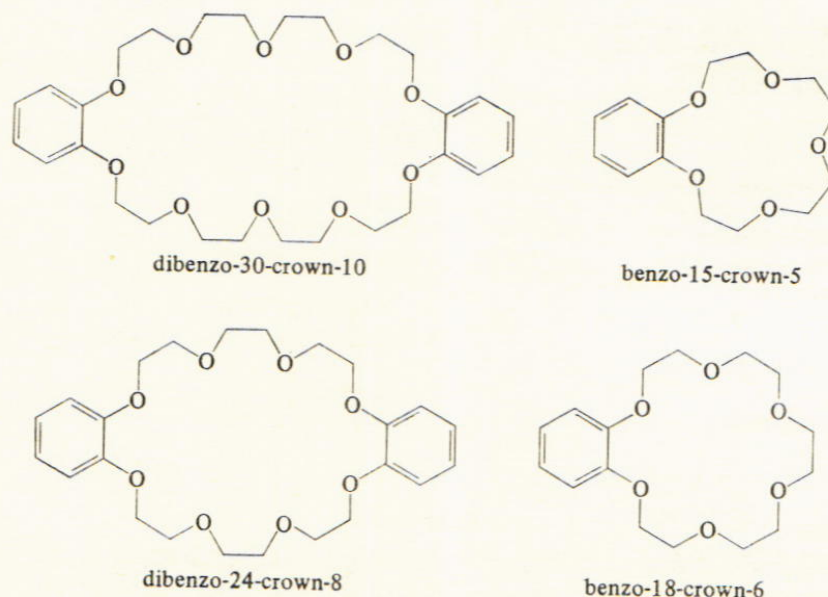


FIG. 1.

Complexes may be neutral, the anions being in direct contact with the cations, or cationic with the anions not coordinated. For the perchlorate anion, ClO_4^- , the infra-red spectrum at about 600 cm^{-1} is clearly diagnostic, showing several bands if the anion is coordinated and only one if not. The crystalline $[\text{M}^{n+}(\text{benzo-15-crown-5})_2]$ complexes all show only one such band. For benzo-18-crown-6 and other 18-crown-6 rings forming complexes with one cation, the behaviour of the anion cannot be deduced from geometrical considerations. The reliability of the diagnosis from the infra-red spectrum has been indicated by the crystal structure analysis of $[\text{Ba}(\text{ClO}_4)_2\text{benzo-18-crown-6} \cdot 2\text{H}_2\text{O}]$, see below.

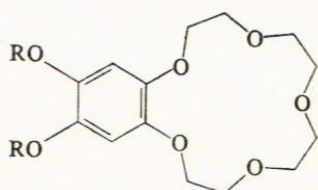
With the larger rings, dibenzo-24-crown-8 and dibenzo-30-crown-10, calcium, strontium and barium salts give 1:1 complexes but, in contrast to the alkali metals, do not yield complexes having two cations per crown ether even with anions, such as thiocyanate, which tend to coordinate to the metal. This probably results from the greater repulsion between more highly charged cations. (Wingfield)

Synthesis. A number of routes have been investigated for the synthesis of the molecule, designed to be selective for potassium shown as Fig. 1, IV, in the *Rothamsted Report for 1974*, Part 1, 166. The most successful has produced 300 mg of the penultimate stage having a benzene ring instead of cyclohexane; larger quantities will be needed to allow hydrogenation and separation of isomers to proceed.

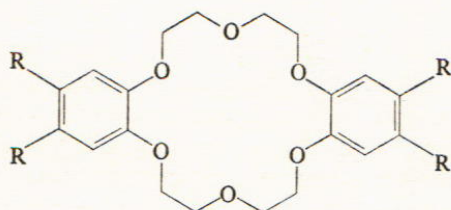
Some of the compounds in Fig. 2 were originally obtained as intermediates in these syntheses and found to have complexing ability, dictated by the macrocyclic ring, and solubilities in aqueous and non-aqueous media dependent upon substitution in the benzene ring(s). The methoxy group, OCH_3 , leads to greater solubility in water while longer chains give greater lipid solubility. The remaining compounds in Fig. 2 were synthesised to exploit these systematic variations and give tools for studying the transport of the salts of the cations. (Parsons)

The four isomeric compounds of Fig. 3 have been synthesised and their stability constants in methanol with sodium and with potassium determined; values for both

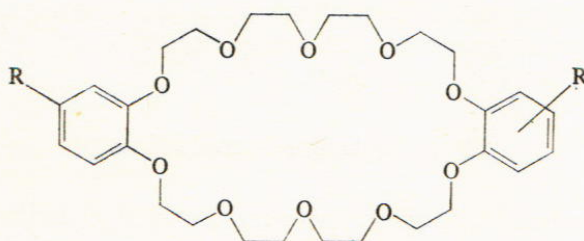
MOLECULAR STRUCTURES DEPARTMENT



- R = CH₂C₆H₅ 4,5-dibenzoyloxy benzo-15-crown-5
 R = CH₃ 4,5-dimethoxy benzo-15-crown-5
 R = C₆H₁₃ 4,5-dihexyloxy benzo-15-crown-5
 R = C₈H₁₇ 4,5-dioctyloxy benzo-15-crown-5



- R = CH₃ 4,5:4',5'-tetramethyl dibenzo-18-crown-6
 R = OCH₃ 4,5:4',5'-tetramethoxydibenzo-18-crown-6



- R = C(CH₃)₃ 4,4' (or 4,5') ditertiarybutyl dibenzo-30-crown-10

FIG. 2.

cations are lower than those for the molecule without methyl groups, the preference for potassium ν sodium remaining at about 8:1. (Wingfield)

Transport through organic phases. Experiments on the effect of macrocyclic ethers on the uptake of potassium by respiring mitochondria have shown that ditert. butyldibenzo-30-crown-10, see Fig. 2, produced the largest effect. Benzo-15-crown-5, Fig. 1, gives no effect but the variants on dibenzo-15-crown-5 described last year (III of Fig. 1, *Rothamsted Report for 1974*, Part 1, 166-167) as having lower affinities for potassium, as measured by the change in emf of this cation in methanol, do have effects on uptake by mitochondria. Quantitative measurements indicate an optimum affinity for maximum uptake.

The compounds of Fig. 3, nearly inactive for potassium, produce rapid release of calcium by the mitochondria. These results, obtained by Dr. E. J. Harris, Biophysics Department, University College London, have encouraged us to try to distinguish the effects of affinity for the crown compound in competition with polar solvents (water or methanol) from those of lipophilicity in the extraction of the metal complex into an organic solvent. We have therefore set up some test systems in which alkali metal and alkaline earth metal salts may travel from an aqueous medium of higher concentration to one of lower concentration through an organic phase; i.e. the organic phase is sand-

ROTHAMSTED REPORT FOR 1975, PART 1

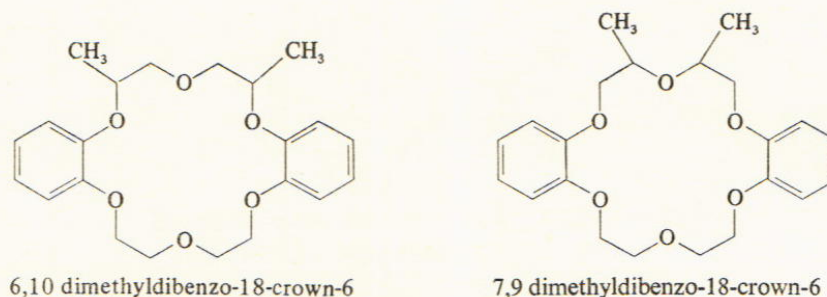


FIG. 3. Each methyl group may be above or below the plane of the paper giving two isomers for each molecule.

wiched between the aqueous ones. Transport takes place only when the macrocyclic ether under test is present in the organic phase; there is an optimum crown concentration for transport to take place and to avoid accumulation in the organic phase. Other variables, including the anion, temperature, and organic phase have been investigated and a standard procedure for comparative purposes has been evolved.

Two-phase systems, water/organic medium, also have been investigated and the number of molecules of benzo-15-crown-5 per cation in the organic phase at equilibrium determined. For example, in nitrobenzene for each sodium ion extracted there are about 20 molecules of crown compound and for each potassium ion between three and four such molecules; the results are quite different from the cation:crown ratios, 1:1 for sodium and 1:2 for potassium, obtained by emf measurements in, and isolation from, polar solvents. (Bola, Mathur, Parsons, Truter and Wingfield)

Crystal structure determinations

Natural products

From blighted potatoes. The molecular structure of one derivative of phytuberin, a stress metabolite accumulated in blighted potatoes, was reported last year (*Rothamsted Report for 1974*, Part 1, 169). It was shown to be compact having a rigid skeleton of three fused rings. This conformational information, in conjunction with direct methods, enabled us to solve the phase problem and hence determine the crystal structure of another derivative, hydroxyphytuberin, Fig. 4, which posed a very difficult technical

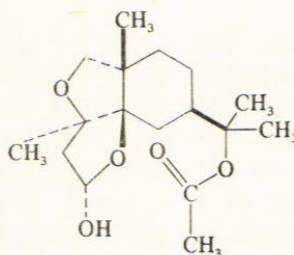


FIG. 4.

problem because there are two independent (i.e. not related by symmetry) molecules in a triclinic unit cell. There are negligible differences in conformation between the two molecules, and only in the rings adjoining the hydroxyl groups do these molecules differ from dihydrophytuberin. The crystal packing of the derivatives is quite different because the hydroxy groups give rise to hydrogen bonding holding the molecules together in

MOLECULAR STRUCTURES DEPARTMENT

helices through the crystal while in the other compound, no such interactions are possible and all intermolecular contacts are van der Waals'. Although the relative arrangement of atoms in Fig. 4 is correct, we have not been able to distinguish between the molecule shown and its mirror image. This awaits the isolation of a suitable derivative. (Hughes, with Dr. D. Coxon, Food Research Institute)

Fungicide. 1-Avenaciolide, found in *Aspergillus avenaceus*, has the chemical constitution (Brookes, Tidd & Turner, *Journal of the Chemical Society* (1963), 5385-5391) shown in Fig. 5. It is fungicidal and causes release of calcium and of magnesium from rat liver

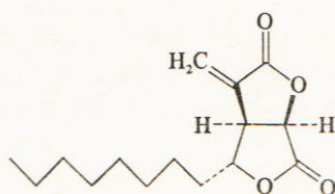
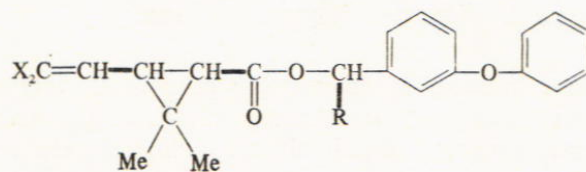


FIG. 5.

mitochondria (Harris & Wimhurst, *Archives of Biochemistry and Biophysics* (1974), **162**, 426-435). It facilitates the transfer of Mg²⁺, Ca²⁺ and K⁺ from water to an organic phase (Harris & Wimhurst, *Nature (New Biology)* (1973), **245**, 271-273) but no crystalline complexes have yet been isolated with these cations. We have determined the crystal structure of the compound and find that the paraffinic tails of the avenaciolide molecules lie parallel and the lactone head groups are in distinct bands. In this respect, the packing resembles that of long chain fatty acids. The fused five-membered rings result in a rigid arrangement of the four oxygen atoms which does not favour the attachment of more than one oxygen atom to a given cation. In the absence of a suitable derivative we have not been able to determine the absolute stereochemistry, that shown in Fig. 5 is based on a recent synthesis (Anderson & Fraser-Reid, *Journal of the American Chemical Society* (1975), **97**, 3870-3871); the mirror image was formerly accepted as correct. (Hughes)

Synthetic compounds

Insecticides. As part of our collaboration with M. Elliott and N. F. Janes of the Insecticides and Fungicides Department we have determined the crystal structures of two active pyrethroids, 'NRDC 157 and 167' of Fig. 6, for comparison with the more potent 'NRDC 161', reported last year (*Rothamsted Report for 1974*, Part 1, 139, 169, and Owen, paper 6. Observations were collected on a diffractometer for 'NRDC 157'



NRDC 157	X = Br, R = H
NRDC 167	X = Cl, R = H
NRDC 161	X = Br, R = CN

FIG. 6.

ROTHAMSTED REPORT FOR 1975, PART 1

and by automatic scanning of films for 'NRDC 167'; the former are more precise, random errors in the observations being in the ratio 1:1.5.

All three compounds have similar unit cell dimensions and space group; 'NRDC 157 and 167' are isostructural and have a conformation quite different from that of 'NRDC 161' especially in the bonds near the benzene rings. The same conformational relationship between the ester group and the cyclopropane ring is found in all three compounds. For 'NRDC 157' the absolute configuration was determined by anomalous dispersion of X-rays. (Owen, with Elliott and Janes, *Insecticides and Fungicides*)

Dioxaspiro compound. Among the fungal metabolite antibiotics having cation-transporting properties are several monobasic acids of complicated constitution, one of the simplest, called A23187, has the empirical formula $C_{29}H_{37}N_3O_6$. The critical first stage in the synthesis of analogous compounds resulted in two isomers of 2,8-bis(bromomethyl)-1,7-dioxaspiro[5,5]undecane, Fig. 7, I or II. We have shown the crystalline

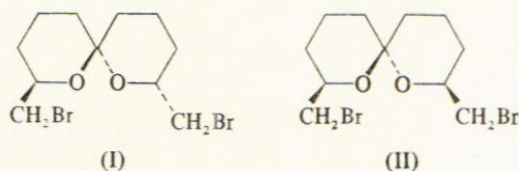


FIG. 7.

isomer to be I (the desired product). The pyran rings are in the chair conformation with the bromomethyl substituents equatorial and these will be modified during the next stages of the synthesis. (Hughes, with Prof. F. Sondheimer and Dr. T. M. Cresp, University College London)

Macrocyclic ethers. The structure analysis of the uncomplexed molecule dibenzo-24-crown-8, of Fig. 1, has been completed. It has a different conformation, with a higher conformational energy than in the complexes containing two cations $(KNCS)_2$ dibenzo-24-crown-8 (Mercer & Truter, *Journal of the Chemical Society (Dalton Transactions)* (1973), 2469-2473) or $(Na-o\text{-nitrophenolate})_2$ dibenzo-24-crown-8 (Hughes, see paper 3), and this appears to be correlated with intermolecular packing interactions.

The uncomplexed molecule, benzo-15-crown-5 (Fig. 1) is also being investigated. We are now taking photographs of a crystal held at the temperature of liquid nitrogen in a device fitted to a Weissenberg camera. The device is an improved version of an earlier design (Swallow, Ph.D. Thesis, University of Leeds, 1961) successive modifications having reduced consumption to less than 1 litre h^{-1} of liquid nitrogen. A dramatic improvement in the diffraction pattern results from reduction in the thermal vibrations of the atoms in the crystal. (Hanson, Hughes and Truter)

Alkaline earth cation complexes of macrocyclic ethers. Two complexes of calcium thiocyanate with benzo-15-crown-5, one having water and the other having methanol in the crystal, have been found to contain eight coordinated calcium. The oxygen from a solvent molecule and two nitrogen atoms from thiocyanate anions are on one side of the cation and on the other side are five oxygen atoms from the macrocyclic ether; in both compounds the conformations of this molecule are different from those found previously in sodium (Bush & Truter, *Journal of the Chemical Society (Perkin Transactions II)* (1972), 341-344) or potassium (Mallinson & Truter, *Journal of the Chemical*

MOLECULAR STRUCTURES DEPARTMENT

Society (Perkin Transactions II) (1972), 1818–1823) complexes. Differences in the Ca–N–C–S angles are correlated with the infra-red spectra. (Owen)

In the crystal of $[\text{Ba}(\text{ClO}_4)_2\text{benzo-18-crown-6} \cdot 2\text{H}_2\text{O}]$ there are discrete entities of this formula. The barium ion is 10-coordinated; the six oxygen atoms of benzo-18-crown-6 and one oxygen from a perchlorate ion are on one side of it and two water molecules and one oxygen of the second perchlorate ion are on the other side. (Mortimer and Truter)

Computing

ICL 4-70 programs. To reduce the time required for some of our work we have implemented a suite of efficient X-ray crystallographic programs, SHEL-X, written by Dr. G. M. Sheldrick of Cambridge University where he uses an IBM 370/168. For identical test runs the 4-70 takes 10–12 times as long as the IBM 370/168. For large least-squares refinement on the 4-70 the SHEL-X program takes three-quarters of the time required by our previous program so the saving is appreciable but not dramatic. (Owen)

IBM 1130 programs. Programs have been modified to process intensities obtained by the Science Research Council microdensitometer service. In particular, facilities for interlayer scaling (Hamilton, Rollett & Sparks, *Acta Crystallographica* (1965), **18**, 129–130) and for handling data in several scale groups have been added. A new structure factor calculation routine has increased the maximum number of atoms to 100.

More extensive programs for including intermolecular as well as intramolecular interactions with various energy functions have been written. Reports on the results are held over until next year. (Owen)

Staff and visiting workers

D. L. Hughes, Catherine L. Mortimer and Mary R. Truter attended the 10th International Congress of the Union of Crystallography in Amsterdam.

Two sandwich course students, T. Bola and P. D. Mathur, worked in the Department.

Publications

GENERAL PAPERS

- 1 TRUTER, M. R. (1975) Common salt and uncommon complexes. *Proceedings of the Royal Institution* **48**, 1–27.
- 2 TRUTER, M. R. (1975) Recognition of metal cations by biological systems. *Philosophical Transactions of the Royal Society B* **272**, 29–41.

RESEARCH PAPERS

- 3 HUGHES, D. L. (1975) Crystal structures of complexes between alkali-metal salts and cyclic polyethers. Part IX. Complex formed between dibenzo-24-crown-8(6,7,9,10,12,13,20,21,23,24,26,27 - dodecahydrodibenzo [*b,n*] [1,4,7,10,13,16,19,22] octaoxacyclotetra-cosin) and two molecules of sodium *o*-nitrophenolate. *Journal of the Chemical Society (Dalton Transactions)*, 2374–2378.
- 4 MALLINSON, P. R. (1975) Crystal structures of complexes between alkali metal salts and cyclic polyethers. Part VIII. Complexes formed by caesium thiocyanate with (7*R*,9*R*,18*S*,20*S*)-6,7,9,10,17,18,20,21 - octahydro-7,9,18,20-tetramethyldibenzo[*b,k*][1,4,7,10,13,16]hexaoxacyclo-octadecin (tetramethyldibenzo-18-crown-6, Isomer F) and its (18*R*,

ROTHAMSTED REPORT FOR 1975, PART 1

- 20R)-Isomer (Isomer G). *Journal of the Chemical Society (Perkin Transactions II)*, 261–266.
- 5 MALLINSON, P. R. (1975) Crystal structure of (7R,9R,18S,20S)-6,7,9,10,17,18,20,21-Octahydro - 7,9,18,20 - tetramethyldibenzo [b,k] [1,4,7,10,13,16] hexaoxacyclo - octadecin (tetramethyldibenzo-18-crown-6, Isomer F). *Journal of the Chemical Society (Perkin Transactions II)*, 266–269.
 - 6 OWEN, J. D. (1975) Absolute configuration of the most potent isomer of the pyrethroid insecticide α -cyano-3-phenoxybenzyl *cis*-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate by crystal structure analysis. *Journal of the Chemical Society (Perkin Transactions II)*, 1865–1868.
 - 7 PARSONS, D. G., TRUTER, M. R. & WINGFIELD, J. N. (1975) Alkali metal tetraphenylborate complexes with some macrocyclic, 'crown', polyethers. *Inorganica Chimica Acta* **14**, 45–48.
 - 8 PHILLIPS, S. E. V. & TRUTER, M. R. (1975) Crystal structure of a hydrated complex of sodium iodide with phenacylkojate [2-(Hydroxymethyl)-5-phenacyl-4H-pyran-4-one]. *Journal of the Chemical Society (Dalton Transactions)*, 1066–1070.
 - 9 PHILLIPS, S. E. V. & TRUTER, M. R. (1975) Crystal structure of phenacylkojate[2-(hydroxymethyl)-5-phenacyl-4H-pyran-4-one]monohydrate and comparison with some of its complexes with alkali-metal salts. *Journal of the Chemical Society (Dalton Transactions)*, 1071–1077.