

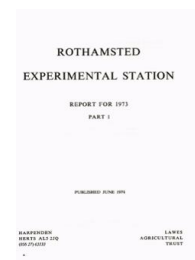
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Molecular Structures Department

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MOLECULAR STRUCTURES DEPARTMENT

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Introduction

The Molecular Structures Department is new and dates from 1 April 1973. Previously the permanent graduate staff had been employed by the Agricultural Research Council and constituted its Unit of Structural Chemistry (Hon. Director, the late Professor Sir Ronald Nyholm, F.R.S.). The department is housed temporarily in the Strand where the Unit started in October 1966, as an out-station of University College. As the present accommodation is structurally unsound, we are planning to move to Rothamsted early in 1974 into space kindly provided, temporarily, by other departments pending the provision of permanent accommodation.

The general theme of our work is the relation between molecular structure and biological activity. If new biologically active compounds are to be sought, and if those occurring naturally are to be modified or manipulated by rational and economical methods, a fundamental understanding of this relationship is essential.

In the medical field, work on enzymes and drugs is already well-supported and the department (as did the former Unit) concentrates on chemistry of major plant nutrients, particularly the co-ordination chemistry of alkali metals and alkaline earths.

A characteristic of many biological entities is that when alive they contain membranes which act as selective barriers in alkali metal transport so that on one side there is an aqueous solution containing a high concentration of potassium and a low concentration of sodium while on the other there is a low concentration of potassium and a high concentration of sodium; on death, diffusion results in concentrations of sodium or of potassium being equal on both sides of the membrane. The chemical problem is to explain this selectivity and to make compounds that simulate membranes by displaying selective ability to coordinate alkali metal ions. Because the best, and sometimes the only, method available for determining the environment of the metal in a compound is crystal structure analysis, the original Unit was set up to use this technique. The technique can be applied to the solution of structural problems in nearly any crystalline compound, as the examples of our work during the past year will show.

Classical coordination chemistry of alkali metals

We sought compounds that would confer on alkali metals the ability to pass through lipid membranes. Treatment of alkali metals by methods analogous to those used for transition metals has enabled us to obtain some compounds which can be defined unequivocally as complexes. We have studied the effect on complex formation of the nature of the donor atom (usually oxygen or nitrogen) and of the electron attracting or withdrawing powers of other groups in the molecules.

Coordinative saturation. To confer solubility in non-polar solvents it is usually necessary to neutralise the charge on the cation with one or more coordinating anions and often to complete the coordination requirement of the metal by the addition of neutral molecules. We made sodium, potassium, rubidium and caesium compounds of formula $M^+(o\text{-nitrophenolate})(1,10\text{-phenanthroline})_2$ (Layton, Nyholm, Banerjee, Fenton, Nave, & 212

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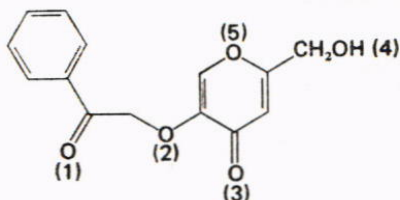
Truter, *Journal of the Chemical Society (A)* (1970) 1894–1896). Crystal structure analysis (see paper 11.6, p. 360) has now shown that the compounds are unequivocal complexes, monomeric for sodium and dimeric for the larger cations but with all donor atoms coordinated only to one metal.

Anionic complexes. Systematic investigation of the effect of change in the electro-negativity of ligand molecules led to novel complexes. If more anions are coordinated to the metal than will neutralise its charge, the metal may be found in an anionic complex. Versatile anions with one negative charge and two donor atoms are β -diketonates ($\text{RCOCHCOR}'^-$); as R and R' change from $-\text{CH}_3$ to $-\text{CF}_3$ (more electron withdrawing) so the possibility of forming complexes with more anions on the metal increases. With $(\text{CF}_3\text{COCHCOCF}_3)^-$ as the anion, compounds containing the complex anions $[\text{M}(\text{CF}_3\text{COCHCOCF}_3)_2]^-$ were obtained for Li, Na, K, Rb while uniquely for sodium the anion $[\text{Na}(\text{CF}_3\text{COCHCOCF}_3)_3]^{2-}$ was obtained and established by crystal structure analysis of its rubidium salt; the sodium is six-coordinated and established by three chelating anions which occupy the sides of a trigonal prism (see paper 11.5, p. 360). (Fenton, Nave and Truter)

Polydentate ligands

Compounds with two donor atoms attached to the same metal, i.e. chelate complexes, have higher stability constants than the analogous complexes formed from two separate ligands with the same donor atoms. Molecules with more than two donor atoms in suitable positions sterically for complex formation are likely to form still more stable complexes. We have explored various polydentate ligands with the idea that high complexing ability in the ligand may compensate for the low complex-forming power of the alkali metals.

Phenacyl kojate. Simple salts of alkali metals with a halide or thiocyanate as the anion form complexes with phenacyl kojate (5-phenacyloxy-2-hydroxymethyl-4H-pyran-4-one)



a molecule with four (or possibly five including the ring oxygen O(5)) potential donor oxygen atoms. Most of these salts form complexes with the formula $\text{MX}(\text{phenacyl kojate})_2$ which give similar crystalline forms. One of them, the KI complex, has been investigated by complete crystal structure analysis and the potassium found to be eight-coordinated by oxygen atoms. Three oxygen atoms from each of two triply-chelating molecules (O(1), O(2) and O(3) attached to the same potassium) provide six donor atoms and a stoichiometry corresponding to the formula $\text{KI}(\text{phenacyl kojate})_2$; contacts from the hydroxy-oxygen atoms, O(4), of two further phenacyl kojate molecules complete the coordination of potassium, and give a polymeric structure. There is no K^+I^- interaction. For all the thiocyanates and for the larger cations and halides, i.e. those for which the lattice energy of MX was less than 150 kcal/mol, a 1 : 1 stoichiometry was found (see paper 11.4, p. 359) (Fenton). The caesium thiocyanate derivative was taken as typical of this class and its crystal structure was determined; it is a complicated polymer, the caesium ion being co-ordinated by thiocyanate ions and by oxygen atoms from phenacyl kojate molecules. Although the phenacyl kojate molecule has several single bonds about

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which free rotation is possible, the molecule exhibits the same molecular geometry, except for the CH_2OH group, in the potassium complex, in the caesium compound, and in the hydrate of the pure compound; thus no, or very little energy is required to change the shape of the molecule on complex formation. (Hughes, Phillips and Truter)

'Crown' compounds. It is a common feature of complexes of naturally-occurring antibiotics with alkali metals that oxygen atoms of the antibiotics replace most or all of the solvent molecules around the central metal, while the surface consists of carbon and hydrogen atoms. However, these natural compounds, having been found (from a chemical point of view) by chance, differ among themselves in the number and nature of the donor atoms and in many other particulars, so that it is difficult to distinguish the principles on which their structures and properties are based. Accordingly for a controlled investigation we have used synthetic compounds of a series described by Pedersen (*Journal of the American Chemical Society* (1967) **89**, 7017-7036), and given semi-systematic names which indicate the size of the macrocyclic ring and the number of oxygen and hence of donor atoms present. Examples are given in Fig. 1 which shows that they are all multi-dentate ligands.

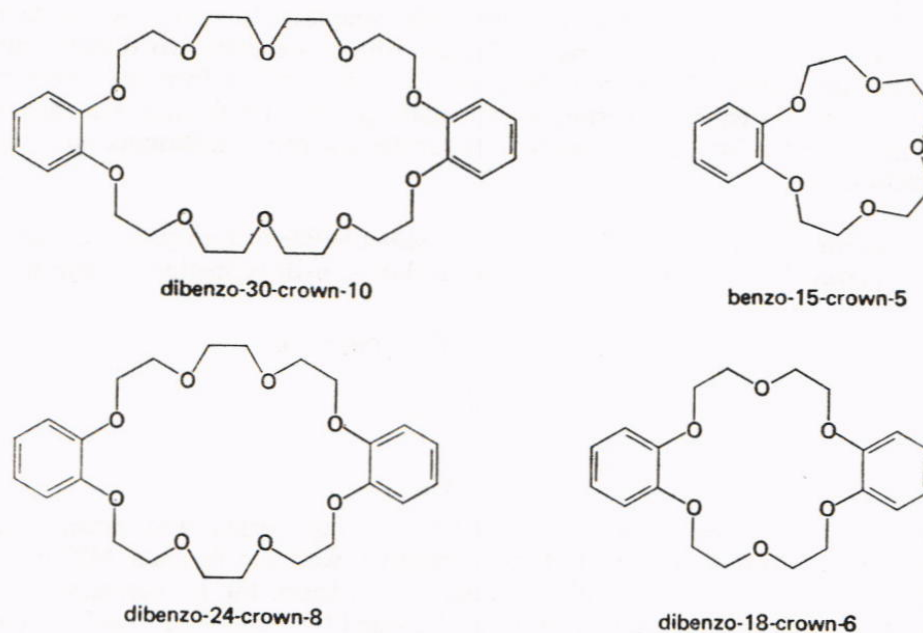


FIG. 1

These crown compounds had been shown to extract some alkali metal salts into non-polar solvents. We compared the behaviour of potassium and sodium salts of chelating anions, e.g. *o*-nitrophenolate, and of simple anions, bromide, iodide or thiocyanate, with the four crown compounds of Fig. 1. For potassium the ratio of metal to crown depends primarily upon the number of oxygen atoms, being 1 : 2 for (crown-5), 1 : 1 for (crown-6), 2 : 1 for (crown-8) and 1 : 1 for (crown-10). Previous work reviewed recently (Truter, see paper 11.1, p. 359) had shown that one potassium ion is sandwiched between two

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molecules of the crown-5 compound, so that it is 10-coordinated; one occupies the centre of the crown-6 ring; two potassium ions occupy the crown-8 ring which, like the smaller one, is approximately planar; in contrast the crown-10 ring is folded up to wrap around one potassium ion. In the last compound the end-product has all the ten oxygen atoms and no solvent or iodide ions coordinating the metal. Recently we have isolated intermediate solvated products which should help our understanding of the step-wise formation process.

For sodium the situation is more complicated, the product depending upon the nature of the anion and the presence of water. One of the products was (sodium-*o*-nitrophenolate)₂ dibenzo-24-crown-8, in which unexpectedly two of the atoms of the crown compound are not coordinated to the cation; the crystal structure is still being refined but it is clear that the two sodium ions are bridged by *o*-nitrophenolate ions above and below the plane of the crown compound of which three oxygen atoms are coordinated to one sodium ion and another three to the other sodium ion. (Hughes)

Investigation with the large (and usually non-complexing) anion, tetraphenylborate, BPh₄⁻, shows that this favours formation of 1 : 1 complexes with the 8 and 10 oxygen macrocycles for sodium, potassium and caesium. Anhydrous compounds are formed which are probably of the wrap-around type. For sodium tetraphenylborate and dibenzo-30-crown-10 however, in the presence of water, complexes with two sodium ions to one crown with various degrees of hydration are obtained. (Wingfield)

Membrane studies. The influence of various crown compounds on the efflux of potassium from red blood cells, from 'ghosts' of these and from liposomes prepared from lecithin was measured with a potassium-sensitive electrode. With erythrocytes or ghosts suspended in an aqueous medium the potassium potential was measured after the addition of an 'uncoupling' agent (to maintain electrical neutrality by allowing H⁺ to pass into the cell or ghost as K⁺ left) and then of the test substance dissolved in a small volume of non-aqueous solvent. For liposomes the test substance had to be added during their preparation; they were then suspended in an aqueous medium, the 'uncoupler' was added and the potassium potential measured. In all cases higher concentrations of the crown compounds were required to produce effects comparable with those of dilute solutions of the naturally-occurring antibiotic, valinomycin. The small differences between the 15 crown compounds examined were not significant. From the experiments it was clear that a critical factor is the solubility; complex-forming compounds with a greater solubility in water and/or hydrocarbon solvents are required. (Gossett with Dr. B. Gomperts, Department of Chemical Pathology, University College Hospital)

Stability constants. Crown compounds more soluble in water have been made but not yet subjected to the tests with membranes; these are amino derivatives synthesised for stability constant measurements.

Stability constants in water and in methanol have been measured for potassium complexes with benzo-15-crown-5 and dibenzo-18-crown-6 derivatives substituted in the benzene rings by amino- or nitro-groups to decrease or increase the electron donating power of the ring. Both types of substitution result in lower stability constants, suggesting that an unfavourable steric effect operates in solution. These systems and analogous ones of silver complexes (1 : 1, even with the 15-crown-5 ligands) are to be studied further by i.r. and Raman spectroscopy. (Parsons and Wingfield)

Synthesis. New ligands have been designed and synthesised to produce a stereochemical grouping of oxygen atoms in the free molecules as close as possible to those to be expected in complexes. For example, potassium forms 1 : 2 complexes in which it is

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sandwiched by two molecules of benzo-15-crown-5; the new ligands, shown in Fig. 2, link the rings together and, through variation in the length and shape of the chain, allow for change in specificity. (Parsons)

Asymmetric carbon atoms have been introduced into the macrocyclic ring; all five

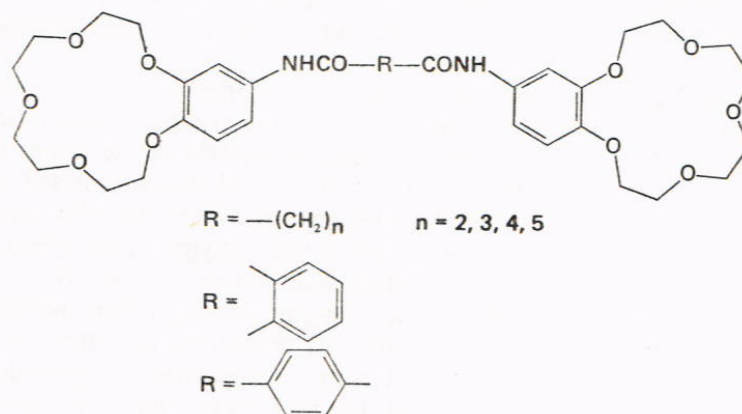


FIG. 2

isomers of the tetramethyl compound, of which two are shown in Fig. 3, have been synthesised and isolated. These isomers F and G were found to react with caesium thiocyanate to give complexes of different stoichiometries and quite different molecular arrangements (see paper 11.8, p. 360). One molecule of each 'hand' of the optically active isomer G coordinates a caesium ion so that the cation : crown ratio is 1 : 2 and the coordination number of the caesium is 12, while the meso isomer F, gives a 1 : 1 compound in which some coordination is from the thiocyanate ions as well as from the six oxygen atoms.

Identification and authentication

Powder photography. New compounds can be authenticated by X-ray methods. A single crystal specimen will give a 'finger print' and, with the measured density, yields the molecular (strictly the formula) weight of the new compound; this can be used with chemical analysis to determine the stoichiometry and presence of solvent. Not infrequently the new compound is not the sole product of reaction and the use of powder diffraction on a larger sample will reveal this and allow all the components to be identified. We have used this technique extensively; for example, we found that the reaction of caesium thiocyanate with a macrocyclic ether, isomer F of Fig. 3, gives a 1 : 1 complex

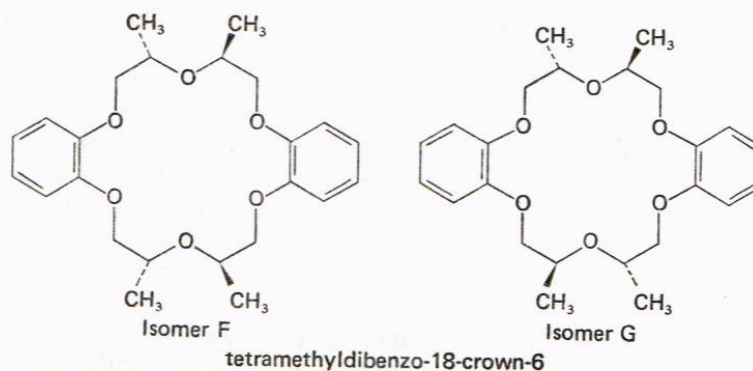


FIG. 3

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and a new crystalline form of the ether. It was the essential method for identification of the anionic complexes in the systems with $\text{CF}_3\text{COCHCOCF}_3$ mentioned above (see paper 11.5, p. 360).

To enable other scientists to identify compounds by X-ray powder diffraction, the Joint Committee for Powder Diffraction Standards produces a card file listing standard patterns for chemically-authenticated substances of known unit cell dimensions. Every line in the pattern submitted must be indexed and the relative intensities estimated. [During the year, 18 of our patterns have been incorporated and published in the File.] (Nave)

Collaboration with other Institutes and Units

We have determined crystal structures to solve problems arising from work elsewhere in the agricultural research service.

Nitrogen fixation. Dinitrogen complexes of transition metals are investigated in the ARC Unit of Nitrogen Fixation, the central problem being how the enzymes of nitrogen-fixing bacteria manage not merely to form such complexes, but to carry out reduction to ammonia in an aqueous medium at room temperature. A compound with the N_2 molecule attached to rhenium at one end and molybdenum at the other was found to have a much lower N–N stretching frequency than other dinitrogen complexes. Determination of the crystal structure showed that the nitrogen–nitrogen bond was appreciably longer (implying some weakening) than in other complexes and in free N_2 . The crystal structure analysis incidentally showed that the compound was not $\text{Cl}[\text{Ph}(\text{CH}_3)_2\text{P}]_4\text{Re}(\text{N}_2)\text{MoOCl}_4$, i.e. a derivative of Mo(VI) but $\text{Cl}[\text{Ph}(\text{CH}_3)_2\text{P}]_4\text{Re}(\text{N}_2)\text{MoCl}_4\text{OCH}_3$ a methoxy derivative of Mo(V). This particular analysis exemplifies an ideal situation; five weeks elapsed from the collection of the observations to the solution of the structure. (Mercer, with Drs. R. H. Crabtree and R. L. Richards, ARC Unit of Nitrogen Fixation, see paper 11.11, p. 361)

Thallous ascorbate. This compound was made as part of their investigations on ascorbalamic acid by Professor R. L. M. Syngé and Mr. W. M. Laird (Food Research Institute). (Couchman, Eagles, Hegarty, Laird, Self & Syngé, *Phytochemistry* (1973) **12**, 707–718). In the crystal there are two thallium ions and two ascorbate anions in the asymmetric unit. Comparison of the geometry of coordination about the cation with that in sodium ascorbate (Hvoslef, *Acta Crystallographica* (1969) **B25**, 2214–2223) showed that the thallium was quite different, being very unsymmetrical with all its oxygen neighbours on one side. This was in agreement with our findings for thallium compounds synthesised to be analogous to potassium compounds (Hughes & Truter (1972) *Journal of the Chemical Society (Dalton Transactions)*, pp. 2214–2219) and casts further doubt on the validity of using Tl^+ as a 'probe' for alkali metals in biological systems. (Hughes)

Computing

Large and small calculations are required to 'solve' crystal structures, i.e. find the arrangement of the atoms in space, and to determine the molecular geometry. For this we have a departmental computer, an IBM 1130, and the backing of a large installation. Copies of our 1130 programmes have been sent and used in other laboratories throughout the world. As part of a continuous process of improvement, we have implemented the Cooley–Tukey Fast Fourier Transform and developed a multi-solution programme, MULSA, which has been used to solve several centrosymmetrical crystal structures by

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direct methods. Standard deviations in torsion angles are now calculated by rigorous (Stanford & Waser, *Acta Crystallographica* (1972) **A28**, 213–215) instead of semi-empirical methods. (Hughes, Mallinson, Owen and Teskey)

Staff and visiting workers

We started the year with a vacant post which was filled by J. N. Wingfield in September; he is working on coordination chemistry. Our computer expert, P. R. Mallinson, left at the end of September to take up an appointment in the University of Glasgow, and was replaced by J. D. Owen who has started to determine the structure of insecticides (in collaboration with M. Elliot, Insecticides and Fungicides Department). Mary Mercer relinquished her temporary appointment and C. Nave left to take up a post-doctoral fellowship in the University of Keele.

Dr. N. S. Poonia of the University of Vikram returned home in February. D. L. Hughes, P. R. Mallinson and Mary R. Truter attended the first European Crystallographic meeting in Bordeaux.

One sandwich student, R. Gossett, and one vacation student, N. Teskey, worked in the department.