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ROTHAMSTED RESEARCH

Report for 1980 - Part 1

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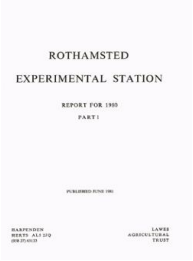
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REPORT FOR 1980
PART 1

PUBLISHED JUNE 1981

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Molecular Structures Department

Mary R. Truter

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Introduction

We report progress in our investigations of complexing (chelating) agents for alkali and alkaline earth metal cations. Aspects include the synthesis of new ligands, study of reactions and conformations in solution and isolation of crystalline solids. A promising start has been made with a new technique, field desorption mass spectrometry. Biological assay on epidermal peels of plants shows correlation with molecular structure of effectiveness in inhibition of the opening of stomata.

An inexpensive graphics termal has produced a major advance in the pictorial presentation of molecular structures. Protein crystallography started with D. L. Hughes' 8 months secondment in the United States. After the loss of our technician during the previous year, we were very short of people on the crystallographic side. Collaboration with the Unit of Nitrogen Fixation has been limited to collection of intensities for four compounds on our CAD-4 diffractometer.

Coordination chemistry

Complexing agents for alkali and alkaline earth metal cations may also prove to be complexing agents for other cations, such as RNH_3^+ or even neutral molecules. This behaviour can influence the biological activity of these agents.

Correlations and differences between molecular structures in solution and as found in crystalline derivatives are being investigated.

Open chain polyethers. The study of compounds of the type R′O *ortho*-C_6H_4O-$CH_2CH_2O)_nC_6H_4$*ortho* OR has now reached a conclusive stage. Stability constant measurements in methanol by the e.m.f. method using ion selective electrodes have shown that values for compounds with R = H, R′ = CH_2COOH are intermediate between those for the diol R = R′ = H, and the diacid R = R′ = CH_2COOH, so there is no enhancement consistent with intramolecular hydrogen bonding. We have already shown the absence of such bonding in crystalline derivatives of a typical diacid complex with potassium picrate (*Rothamsted Report for 1976*, Part 1, 194; Hughes, Mortimer & Truter, *Inorganica Chimica Acta* (1978), **28**, 83–89) and for a typical diol complex with sodium thiocyanate or with potassium thiocyanate (*Rothamsted Report 1977*, Part 1, 167; Hughes & Wingfield, *Journal of the Chemical Society, Chemical Communications* (1978), 1001–1003). Absence of intramolecular hydrogen bonding contrasts with the naturally occurring antibiotics such as monensin, and probably explains the poor transport properties of the synthetic compounds.

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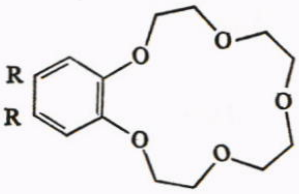
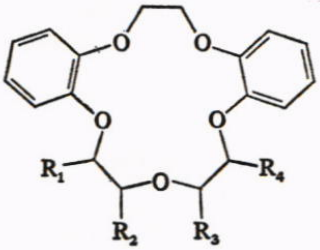
I



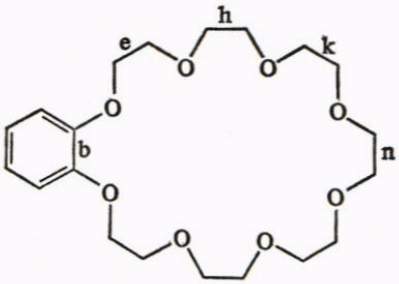
Derivatives of benzo-15-crown-5 (R = H). R = OCH_3,
4,5-dimethoxybenzo-15-crown-5 R = Br, 4,5-dibromobenzo-15-crown-5

II



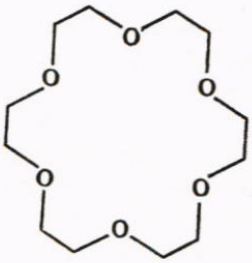
dibenzo-15-crown-5 (II)
$R_1R_2R_3R_4$ = H(II)

$R_1R_4 = CH_3$, R_2R_3 = H (meso) (IIa), racemic (IIb)
R_1R_4 = H, $R_2R_3 = CH_3$, (meso) (IIc), (racemic) (IId)



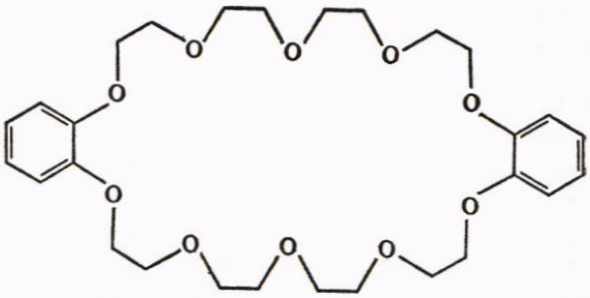
Benzo-24-crown-8. Three isomers of dibenzo-24-crown-8 are designated [b, n], [b, k] and [b, h] in the text according to the bond included in the second benzene ring.

III



18-crown-6

(IV)



V

FIG. 1. Monocyclic, 'Crown' polyethers.

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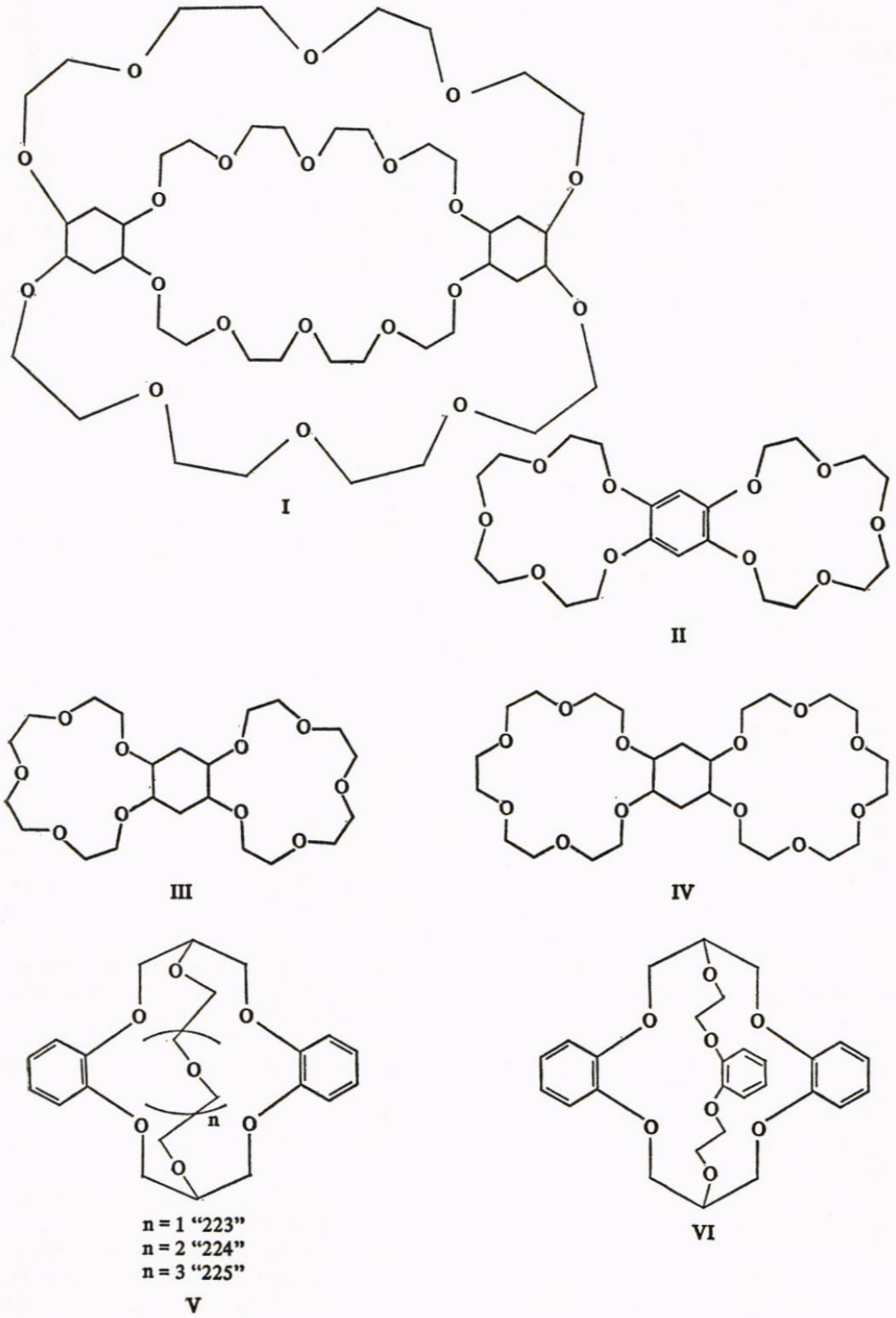

FIG. 2. Polycyclic compounds.

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E.m.f. titrations of open chain polyethers with $R = R' = CH_2C_6H_5$ showed little or no interaction with sodium in solution, but it proved quite easy to isolate crystalline complexes of these ligands with sodium tetraphenyl borate. It is thus advisable to use more than one physical method for determining interactions in solution. (Wingfield)

Monocyclic polyethers, 'crown ethers'. ^{13}C nuclear magnetic resonance titrations in deuteroacetone were carried out with substituted 15-crown-5 ring systems (Figs 1, I and II). Studies of the chemical shifts of individual carbon atoms confirmed that potassium complexes have 1 : 2-stoicheiometry (metal/ligand) in solution, whereas for sodium a 1 : 1 ratio is found. These results agree with stoicheiometries determined in methanol by e.m.f. measurements. The conformations of the crown ether rings in sodium complexes differed from those in potassium complexes in solution as in the crystalline state. (Wingfield)

Symmetrical dibenzo-24-crown-8 [b, n] in III of Fig. 1 readily gives complexes which crystallise with two molecules of ammonium or metal salt per ligand. The less symmetrical molecules [b, k] and [b. h] in III of Fig. 1 yield 1 : 1 complexes with sodium or calcium salts. Determination of the formation constants in methanol of the sodium, potassium and rubidium salts gave values corresponding only to 1 : 1 stoicheiometry for all three isomers (Wingfield, *Inorganica Chimica Acta* (1980), L157–159). (Wingfield)

Crystal structure analysis of the (1 : 1) complex formed between sodium perchlorate and the [b, k] isomer of dibenzo-24-crown-8 shows the ligand to 'wrap up' the cation, Na^+, to the exclusion of solvent and anion; all eight oxygen atoms coordinate the sodium forming an approximate bicapped trigonal prism. (Owen)

Following the study of an N–H bonded complex of 18-crown-6 (IV of Fig. 1), (guanidinium nitrate)$_2$ 18-crown-6, reported last year (*Rothamsted Report for 1979*, Part 1, 135) we have now established bonding by three hydrogen atoms of one methyl group in a neutral molecule, dimethyl sulphone, in the crystalline form of $[(CH_3)_2SO_2]_2C_{12}H_{24}O_6$. The crown ether has approximately D_{3d} symmetry, as found in a number of its complexes with alkali metal ions. (Bandy and Truter, with Professor Vögtle, University of Bonn).

Field desorption mass spectrometry has been used to investigate representative complexes. The technique has the advantage that a low temperature is used and a high percentage of the parent ion is obtained. Compounds, M = Na or K, X = Br, I or NCS and L = crown ether, investigated were those found by crystal structure analysis to be (a) $(ML)^+X^-$, (b) $(ML, H_2O)^+X^-$, (c) $(MXL)^\circ$, (d) $(ML_2)^+X^-$, and (e) $((MX)_2L)^\circ$. At low emitter currents the parent ions consisted of (a) $(ML)^+$, (b) $(ML)^+$, (c) $(ML)^+$, (d) $(ML_2)^+$ and (e) $(ML)^+$. Neither solvent, as in (b), nor anion, as in (c) and (e), was retained under the conditions in the mass spectrometer. However, there was a diagnostic feature for compounds containing complex ion pairs; compounds (c) and (e) gave species corresponding to $(M_2X)^+$ and $(MX)^+$, whereas those consisting of complex cations and separate anions gave no species containing M and X. Compound (d) shows that the sandwich of two molecules of crown is stable in the field desorption conditions, but compound (e) actually $(KNCS)_2$ [b, n]dibenzo-24-crown-8 proved as elusive as it is in solution, see above. (Parsons and Truter, with Dr D. E. Games and Dr L. A. P. Kane-Maguire, University College Cardiff, and Dr P. W. Brookes and Dr K. Hall, V. G. Organics Ltd)

Further attempts to study ion-pairing in solution were made by conductivity methods. The electrical conductivity of sodium bromide in methanol as a function of concentration was measured in the presence of excess benzo-15-crown-5, 4,5-dimethoxybenzo-15-crown-5 or 4,5-dibromobenzo-15-crown-5 (I of Fig. 1). Qualitative differences between the three compounds were observed and the results are currently being examined to yield quantitative estimates of the ion-pairing association constant. (Payne)

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Polycyclic polyethers. Some puzzling features of the isomeric 'clam' compounds described last year (*Rothamsted Report for 1979*, Part 1, 131) were resolved by determination of the crystal structure of a compound with an elemental analysis corresponding to potassium picrate : 'clam' (1 : 1). It proved to be a 2 : 1 complex of the pentacyclic molecule (I of Fig. 2). The cations are each coordinated to ten oxygen atoms in the ligand, in a conformation similar to that in the dibenzo-30-crown-10 complex (V of Fig. 1) (Bush & Truter, *Journal of the Chemical Society, Perkin II* (1972), 345–350), those in the same molecule being 7·4 Å apart. The picrate anions are stacked 3·4 Å apart with some considerable overlap indicating a strong interaction. An electron impact mass spectrum of the isomer used to make this complex showed a parent ion corresponding to the pentacyclic molecule. Nuclear magnetic resonance measurements in solution proved that only one compound was present and X-ray powder photography of a bulk sample confirmed that the crystal was not atypical of the whole. (Bandy, Owen, Parsons and Wingfield)

Investigation of the reaction path indicated an early stage at which an *o*-quinone rearranged to a *p*-quinone to yield the pentacyclic compound. A new route to the 'clam' was sought. The syntheses were finally achieved by direct reaction from 1,2,4,5-tetrahydroxybenzene, the resulting aromatic bis crown ether (II, Fig. 2), being catalytically hydrogenated to the cyclohexane derivative (III, Fig. 2). In a similar way, the larger cyclohexyl bis-18-crown-6, (IV, Fig. 2), has been prepared. The mass spectra (Pickett, Insecticides and Fungicides) established the molecular weights. The potency of these compounds as complexing agents is being investigated. (Parsons)

The formation constants of complexes formed in methanol between ammonium bromide and the series of macrobicyclic ligands, 223, 224, benzo-224 and 225 (V and VI of Fig. 2), have been measured by the e.m.f. method. 223 does not form a stable complex, supporting the postulate that NH_4^+ requires at least six oxygen atoms in the open face to achieve coordination. The addition of a benzene ring to 224 reduces the formation constant. (Bandy)

Effect of ionophores on stomata

Stomatal apertures in epidermal peels of *Commelina communis* when treated with crown ethers have been investigated. The concentration of crown required just to inhibit stomatal opening decreases markedly as lipid soluble groups are added to the benzene ring, and also, there is a close correlation with structures found in crystals. Thus benzo-15-crown-5 which sandwiches a potassium ion between two ligands, is more effective than benzo-18-crown-6 which coordinates the potassium ion only in a plane. Dibenzo-30-crown-10, which completely wraps around potassium, is still more effective, and the di-tertiarybutyl derivative inhibits opening at 0·005M concentrations (Georgiou, Truter and Wingfield)

Protein crystallography

The compound trifluoro-N-acetyl-Lys-Ala(*p*-trifluoromethylphenyl)-anilide (Fig. 3) is the most potent member of a series of trifluoroacetylated di-, tri- and tetra-peptides designed to inhibit the hydrolysis/cleavage reactions of the pancreatic serine protease, elastase.

In the laboratories of Dr L. H. Jensen (University of Washington, Seattle), suitable crystals of native elastase and co-crystals of elastase/inhibitor were grown. X-ray photographic and diffractometer measurements (to a resolution of 2·0 Å for the native crystals and 2·5 Å for the co-crystals) were made, and the intensity data were processed and scaled on a dedicated VAX computer.

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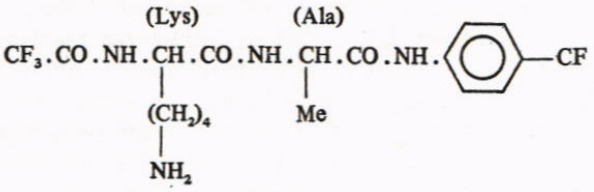

FIG. 3. Inhibitor molecule.

The location of the inhibitor molecule (close to the active site of elastase) was determined from a difference Fourier synthesis in which the amplitudes were derived from the difference in intensities of the native and co-crystal samples, and the phases from the published coordinates of native elastase (Sawyer, Shotton, Campbell, Wendell, Muirhead, Watson, Diamond & Ladner, *Journal of Molecular Biology* (1978), **118**, 137–208; Brookhaven Protein Data Bank, Department of Chemistry, Brookhaven National Laboratory, Upton, NY 11973, USA).

After refinement of the atomic parameters, the geometry of the inhibitor molecule and the nature of its binding site are being examined with the aid of programs brought from Seattle and presently being adapted for use on the System 4 here with the help of A. J. Boston (Computer Department). (Hughes, with Dr L. H. Jensen)

Powder diffraction

Indexed patterns of pesticides from the Rothamsted Reference Collection, plant growth hormones and some of the polyethers and their complexes have been measured as standards for the Powder Data File. The technique has been used to establish that crystals used for structure analysis are typical of the bulk sample. (Bandy)

Computing

Graphics. A Tektronix 4051 graphics terminal has been installed in the Daniel Hall building and the major programming effort this year has been to allow pictures of molecules to be drawn. The program, for which K. E. Bicknell (Computer Department) provided some crucial routines, runs on System 4 and drawings appear on the screen of the Tektronix. This allows a two-dimensional representation of a three-dimensional molecule to be drawn. The direction of view can be chosen before each drawing, and diagrams showing how the molecules pack together in the crystal can easily be set up. The drawing may be either a single orthographic projection or a stereo pair of images, which can be viewed using a conventional direct stereo viewer. This brings out the impression of depth and enables relations between the atoms to be seen directly. When a satisfactory view has been found, it may be drawn on paper with the Benson graph plotter.

The Tektronix terminal has its own processor and magnetic tape cassette. A flexible communications program, in BASIC, allows the terminal to operate on three different computers, and to send files of data from the tape to the mainframes and vice versa. Pictures can also be copied from the mainframes on to the tape for later viewing using a small stand-alone program.

One of the computers is System 4; the other two, reached via public telephone lines, are the IBM 370 computer at Cambridge University and the DEC 10 computer at the Edinburgh Regional Computer Centre node of the Science Research Council (SRC) Interactive Computing Facility. We can interrogate the Cambridge Crystal Data Base

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at both localities, but only at Edinburgh can this be done interactively. From this Data Base, bibliographic and numerical information on all crystal structures of organic molecules can be retrieved. With a graphics terminal, diagrams of the structures can be drawn directly, though to minimise telephone charges we prefer to retrieve the relevant file, store it on the magnetic tape cassette, then send it to the System 4 and use our own drawing program. However, the full potential of this device will not be realised until the Post Office installs a fast line to the System 4. (Owen)

IBM 1130. Our suite of programs is mainly used for molecular geometry. The journal of the International Union of Crystallography, *Acta Crystallographica*, has recently raised its standards, although they were already among the highest; programs have been modified to bring our presentation of results up to these new standards. (Owen)

Prime. In the expectation that our work will be transferred from System 4 and the IBM 1130 to an enhanced Prime 550 in the Computer Department, some programs have been transferred and tested on the present Prime installation. (Owen)

Staff and visitors

During the year Bergljot Nyhus, University of Oslo, worked in the Department.

Mary R. Truter was re-appointed Visiting Professor in University College, London. She was elected a Manager of the Royal Institution and Chairman of the Davy Faraday Research Laboratory Committee.

D. L. Hughes spent 8 months on secondment at the University of Washington learning. the techniques of protein crystallography in the laboratory of Professor L. H. Jensen. While he was there he attended the American Crystallographic Association meeting in Calgary. D. G. Parsons attended a Symposium on Macrocyclic Ligands at the University of Basle, Switzerland. Mary R. Truter visited Hong Kong and the People's Republic of China under the Royal Society exchange scheme.

Publications

General Paper

1 Truter, M. R. (1980) Molecular structure by diffraction methods. *Annual Reports on the Progress of Chemistry* **76** Section C. *Physical Chemistry*, 161–184.

Research Papers

2 Durley, R. C. E., Hughes, D. L. & Truter, M. R. (1980) The crystal structure of the 2 : 1 complex of bis(1,1,1,5,5,5,-hexafluor-2,4-pentanedionato)copper(II) with 1,4-diazabicyclo[2.2.2]octane. *Acta Crystallographica* **B36**, 2991–2997.

3 Herbert, J. A. & Truter, M. R. (1980) A hydrogen-bonded complex. The crystal structure of 1,5,12,16,23,26,29-heptaoxa[$7^{3,14}$][5.5] orthocyclophane-naphthalene-2,3-diol monohydrate. *Journal of the Chemical Society—Perkin Transactions II* 1253–1258.

4 Owen, J. D. (1980) Crystal structures of complexes between alkali-metal salts and cyclic polyethers. Part 11. Complexes formed between 2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecin (benzo-15-crown-5) and sodium perchlorate (1 : 1), sodium perchlorate (2 : 1), and sodium tetraphenylborate (2 : 1). *Journal of the Chemical Society—Dalton Transactions* 1066–1075.

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5 PARSONS, D. G., TRUTER, M. R. & WINGFIELD, J. N. (1981) Methyl substituted macrocyclic 'crown' polyethers and their complexation. *Inorganica Chimica Acta* **47**, 81–86.

6 WINGFIELD, J. N. (1980) The synthesis and complexation of two 24-crown-8 cyclic polythers. *Inorganica Chimica Acta* **45**, L157-L159.

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