SYNTHETIC ASPECTS OF HOST-GUEST CHEMISTRY

A thesis submitted by

CHRISTOPHER RICHARD AYLES GODFREY

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CHEMISTRY DEPARTMENT
IMPERIAL COLLEGE
LONDON SW7 2AY.

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Finally, a very special thank you to my wife, Jayne, and to my family for their constant support.

CONTENTS

ABSTRACT

The use of macrocyclic compounds as molecular catalysts has been reviewed. Covalently modified cyclodextrins, paracyclophanes and macrocyclic polyethers have found application in this field.

The design and synthesis of functionalised aza-crown ethers have been undertaken, with the aim of developing potentially regioselective oxidising and acylating reagents.

Studies towards the synthesis of N,N',N"-trimethyl-N"'-[4-(1,4,7,10,13,16-penta-oxa-aza-cyclooctadecyl)-1-butyl]-2,11,20,29-tetra-aza-[3.3.3.3]paracyclophane (1) have been described. Host (1) may exhibit binding selectivity for phenylalanine and related peptides. Attempts to selectively monofunctionalise 2,11,20,29-tetra-aza[3.3.3.3]paracyclophane (2) were unsuccessful. However, consideration of the mechanism of cyclisation of [3.3.3.3]heterocyclophanes may lead to a more direct synthesis of the required molecule (1).

Deoxygenation of hindered esters with sodium-potassium eutectic in t-butylamine in the presence of hexamethyl-hexa-aza-18-crown-6 (3) has been found to proceed in high yield. Sodium-potassium eutectic/18-crown-6 in t-butylamine has also been shown to be effective in the deoxygenation of hindered esters.

CHAPTER 1

HOST-GUEST CATALYSIS

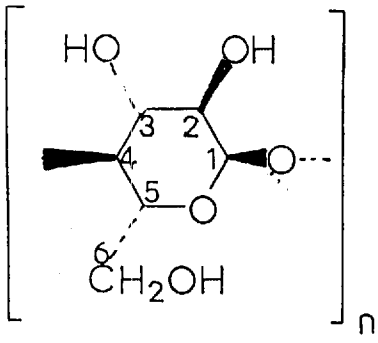
1.1 CYCLODEXTRINS AS MOLECULAR CATALYSTS

Since their initial discovery by Villiers[1] in 1891, occurring as a complex mixture in the crude digests formed by the action of the amylase of *Bacillus Macerans* (cyclodextrinase) on starch and related compounds, the cyclodextrins have continued to intrigue organic chemists with their unusual properties. This interest has led not only to their structural elucidation, and to the refinement of isolation and purification techniques, but also more recently, to their exploitation as molecular catalysts. Several hundred publications have appeared in the literature, which have been reviewed recently[2,3]. The use of cyclodextrins in catalysis has been thoroughly dealt with in a recent book[3]. The commercial availability of the best known and most closely studied lower homologues of the series ensures a continued interest in this area.

It is the purpose of this section to very briefly mention some of the earlier work dealing with the physical properties of the cyclodextrins and their application as molecular catalysts, and then to describe in greater detail the most recent research on the effects of covalent modification on catalysis.

Nomenclature and structural considerations

The cyclodextrins (1, n = 6-13), formerly known as Schardinger dextrins, cycloamyloses or cycloglucans, are a naturally occurring group



of macrocyclic homologous oligosaccharides, built up from a number of D(+)-glucopyranose units linked together by α-(1,4)-bonds in a cyclic array.

The individual members of the series are named according to the number of units (n) contained within the macrocyclic ring, and are denoted by a Greek letter prefix. Thus, the smallest known member (1, n = 6) is termed α-cyclodextrin, (1, n = 7) β-cyclodextrin, and so on. The glucopyranosyl units can be lettered A, B, C, D, etc. in sequence around the cyclodextrin ring. In this way, the substitution pattern of substituted cyclodextrin derivatives can be simply stated by quoting both the letter referring to the unit which is substituted and the corresponding position of substitution. For example, 6A, 6C refers to disubstitution of the C-6 position of the first and third units of a cyclodextrin molecule.

Although eight cyclodextrins (1, n = 6-13 inc.) have been detected, by high temperature cellulose column chromatography, amongst the degradation products of starch on treatment with cyclodextrinase, only the smallest homologues (α,β,γ and δ) occur in any appreciable quantities. These can be readily separated and purified by selective precipitation processes which depend on the selective formation of insoluble inclusion complexes according to the dimensions of the cavities of each homologue.

Some of the physical properties of the more common cyclodextrins are listed in Table 1 [3].

TABLE 1

Cyclodextrin	Number of glucose residues	M.W.	Solubility in water (g/100 ml)	$\{\alpha\}_D^{25}$	Cavity Dimensions	
					Diameter	Depth (Å)
α	6	972	14.5[a]	150.5 ± 5[a]	4.5[d]	6.7[d]
β	7	1135	1.85[a]	162.5 ± 5[a]	7.0[e]	∿7.0[e]
γ	8	1297	23.2[a]	177.4 ± 5[a]	8.5[e]	∿7.0[e]
δ	9	1459	v.sol.[b]	191 ± 3[c]	-	-

Notes: *a* - Ref. [4]; *b* - Ref [5]; *c* - Ref. [6]; *d* - Ref. [7];
e - Estimated from Courtald Molecular Models [5].

The cyclodextrins were characterised as cyclic oligosaccharides by Schardinger, as early as 1904 [8,9]. Classical degradation studies by *inter alia* Freudenberg *et al.* [10] in 1936, and by French's group prior to 1950 [11,12] further established that they were cyclic α-(1,4)-oligomers of D(+)-glucopyranose. Unambiguous confirmation of structure has since been provided by numerous X-ray crystallographic studies on α-, β- and γ-cyclodextrin inclusion complexes [2]. The D(+)-glucopyranosyl units are held in essentially undistorted $^4C_1$ (D)-chair conformations, thus forming a hollow doughnut-shaped molecule, which is slightly conical in shape, as commonly represented by Fig. 1.

The conformations of cyclodextrins in aqueous solution have been shown to be essentially the same as in the solid state, by high resolution NMR [13] and infra-red spectroscopy, [14] and by optical rotatory dispersion

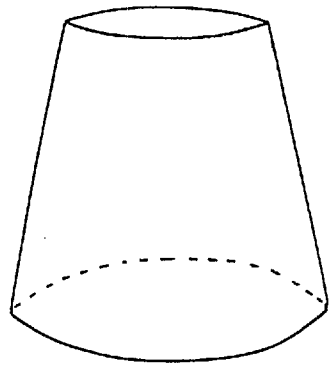


Figure 1

spectroscopy[15]. The rigidly fixed secondary hydroxyl groups at C-2 and C-3 form a boundary around the larger opening of the molecule, whereas the narrower opening is occupied by the more flexible primary hydroxyl groups at C-6. These polar groups maintain a hydrophilic outer surface of the molecule, which accounts in part for the water solubility of the cyclodextrins. The inner surface consists of several rows of relatively non-polar C-H groups and glycosidic oxygen atoms, alternately placed, and consequently is quite hydrophobic in nature. In the case of the lower homologues, the dimensions of the resultant hydrophobic cavities are ideal for the acceptance of small guest molecules. These structural factors all have important consequences related to the binding of guest compounds.

The complexation phenomenon

The ability of the cyclodextrins to form inclusion complexes with a multitude of guest molecules, both in aqueous solution and in the solid state is well documented. This area has been extensively studied, as such an effect is thought to be important in some biological systems.

Guests include such diverse molecules as aliphatic and aromatic hydrocarbons, esters, amines, carboxylic acids, small anions and even rare gases. It is apparent that the only common feature of all of the guest molecules so far studied is that they are sufficiently small to fit partly or fully within the hydrophobic cavity of the host molecule. Generally speaking, the complexes have a 1:1 stoichiometry in solution, although exceptions exist, but are non-stoichiometric in the crystalline state[16]. In the latter case, channel and cage-type structures predominate[17].

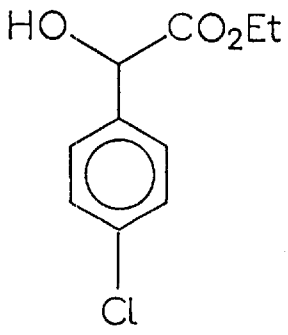
Inclusion complexation in aqueous solution can be evidenced by a variety of physical techniques[3]. NMR spectroscopy[18, 3], absorption spectroscopy[19], fluorescence spectroscopy[20], circular dichroism spectroscopy[21], titration[22], esr spectroscopy[23], and polarography[3] have all found application in this field.

The dissociation constant, K_D, has been determined by measuring *inter alia* changes in absorbance, ^{1}H- and ^{13}C-chemical shifts, fluorescence intensity, optical rotation and conductance[3], which are produced on varying the concentration of cyclodextrin.

The driving force for binding in the inclusion complexes has continued to be a matter of some debate, but is thought to involve the cooperation of a number of separate factors, which include Van der Waals and London dispersion forces, the release of "high energy water", and the relief of strain energy on complexation[2,3].

Unmodified cyclodextrins as molecular catalysts

Since Cramer's discovery in 1958[24] that the presence of α-cyclodextrin produces a 1.38 fold acceleration in the hydrolysis of ethyl p-chloromandelate (2), with slight asymmetric induction, much effort



(2)

has been directed towards developing cyclodextrin catalysis. The analogy with enzymatic systems is obvious. Both systems involve the intermediacy of inclusion complexes, exhibit saturation kinetics, competitive inhibition, D,L-specificity, etc.[2,3] Table 2[3] illustrates some of the reactions which have been catalysed by unmodified cyclodextrins. Clearly, dramatic rate enhancements are possible. Notably, m-nitrophenyl acetate is hydrolysed at pH 11 approximately 300 times faster in the presence of α-cyclodextrin than in the uncatalysed reaction[25]. The catalytic effect has been thoroughly dealt with in a recent book[3].

Dramatic improvements by covalent modification of cyclodextrins

Although large rate enhancements of the order of 10^2 have been achieved for certain reactions with cyclodextrin catalysis, such a catalytic effect is small in comparison with many enzyme catalysed reactions, such as ester cleavage by chymotrypsin[35], which often attain rate enhancements of 10^5-10^{10} [26]. This effect can be attributed to a number of factors, particularly the slow rates of turnover of covalent intermediates, unsuitable geometry of inclusion complexes, and inefficient binding between host and guest molecules in the

TABLE 2

Reactions	Substrates	Acceleration Factor[a]	Type of Catalysis[b]
1. Cleavage of esters	Phenyl esters	300	C
	Mandelic acid esters	1.38	U
2. Cleavage of amides	Penicillins, N-acylimidazoles	89,50	C
	Acetanilides	16	C
3, Cleavage of organophosphates	Pyrophosphates	200	C
	Methyl phosphonates	661	C
4. Cleavage of carbonates	Aryl carbonates	7.45	C
5. Cleavage of sulphates	Aryl sulphates	18.7	N
6. Intramolecular acyl migration	2-Hydroxymethyl-4-nitrophenyltrimethyl acetate	6	N
7. Decarboxylation	Cyanoacetate anions	44.2	N
	α-Ketoacetate anions	3.95	N
8. Oxidation	α-Hydroxyketones	3.3	N

[a] Ratio of the rate catalysed by cyclodextrin to the uncatalysed rate.

[b] C,N and U refer to Covalent catalysis (formation of covalent intermediate), Non-covalent catalysis, and Unknown catalysis respectively.

cyclodextrin systems. Evidently the cyclodextrins are somewhat limited in their application as enzyme analogues.

Several approaches have been adopted in an attempt to improve their performance in this respect[2,3]. For example, structural modification ("flexible" and "rigid" capping) of cyclodextrins, and the design of substrate geometry have led to more effective binding, and hence increased reaction rates. Greater selectivity in complexation has been achieved by the incorporation of multiple recognition sites into the host molecule. Furthermore, cyclodextrins bearing active groups have been designed and synthesised. Corey-Pauling-Koltun (CPK) models have proved to be invaluable in this field.

However, the problem of selective substitution in a cyclodextrin molecule is not a small one, owing to the plethora of functionality present. α-Cyclodextrin itself, the smallest homologue in the series, has six identical primary and twelve secondary hydroxyl groups. Clearly, standard techniques may give rise to complex, often inseparable, mixtures of products. It is worthwhile, therefore, to consider firstly the methodology available for selective transformations at specific positions in the cyclodextrin nucleus. Lehn has discussed at length the problems associated with the selective modification of all of the primary hydroxyl functions of α- and β-cyclodextrins[27].

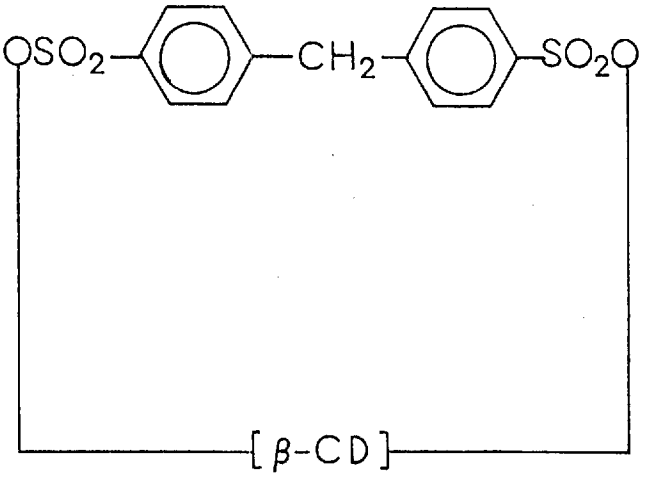
Selective monosubstitution of cyclodextrins

On prolonged treatment with 6-9 equivalents of p-toluenesulphonyl chloride in pyridine, α-cyclodextrin is fully tosylated at all of the C-6 primary alcohol groups.[28] However, if the reaction is worked up after forty minutes, monosubstituted 6-O-p-toluenesulphonyl-α-cyclodex-

trin is obtained as a major product, separable by chromatography, together with unreacted starting material and a mixture of more highly substituted products. Monosubstituted 6-O-p-toluenesulphonyl-β-cyclodextrin has been prepared similarly[29]. In direct contrast, treatment of α-cyclodextrin with ten equivalents of p-toluene sulphonyl chloride in pH 11.0 buffer solution at 25° for one hour, resulted in the exclusive tosylation of one of the less reactive secondary hydroxyl groups at C-3[30]. Presumably in this case the rapid formation of an inclusion complex occurs, the geometry of which permits - and indeed promotes - base-catalysed nucleophilic attack by one of the C-3 hydroxyl groups. In pyridine solution, however, the solvent itself may competitively inhibit inclusion complex formation between the cyclodextrin molecule and tosyl chloride, which therefore reacts preferentially with one or more of the more reactive C-6 primary hydroxyl groups. The sulphonate esters thus formed are amenable to subsequent transformation.

Selective disubstitution

The functionalisation of a cyclodextrin molecule specifically in two known positions presents an even greater problem. In 1976, Tabushi's group reported the synthesis of the "rigidly capped" cyclodextrin (3), disubstituted at primary (C-6) positions, obtainable in 20% yield from β-cyclodextrin, on treatment with diphenylmethane-4,4'-disulphonyl chloride[31]. However, the full substitution pattern was not established. Subsequent work[32] indicated that double nucleophilic displacements were possible at the activated bridgehead positions of the capping group, with such nucleophiles as thiophenol (20% yield), azide anion (50%), diethylamine (80%) and thiourea (80%). On repeating Tabushi's



(3)

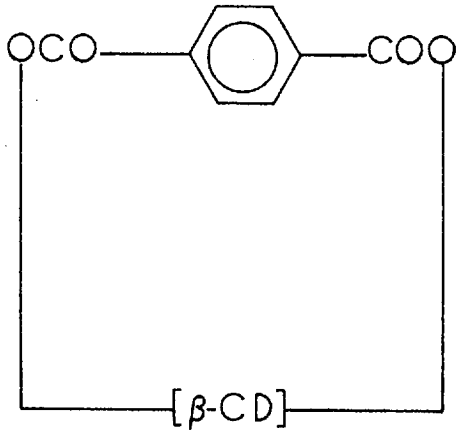
synthesis, Breslow later discovered[33] that, although pure by most criteria, the capped β-cyclodextrin (3) was inhomogeneous by HPLC. Close inspection of CPK molecular models revealed that in fact two isomeric products (6A, 6C, and 6A, 6D) could arise from the reaction. Nonetheless, Tabushi's compound has proved to be a useful starting material for several interesting modified cyclodextrins.

Selective trisubstitution

An isolated example of regiospecific trisubstitution of α-cyclodextrin has recently[34] appeared in the literature. The key synthetic step involves treatment of α-cyclodextrin with trityl chloride in pyridine (55°, 24 h) to give a complex mixture of products from which symmetrical 6,6",6""-tri-O-trityl-α-cyclodextrin can be isolated by chromatography in 23% yield. Clearly, the bulkiness of the trityl groups favours symmetrical trisubstitution at the least hindered primary (C-6) positions. The three-fold axis of symmetry of the product was unambiguously established by ^{13}C NMR spectroscopy. Further modification by standard transformations was demonstrated.

Improved binding as a result of "rigid" and "flexible" capping

The "rigidly capped" β-cyclodextrins (3) and (4) were prepared by treatment of β-cyclodextrin with diphenylmethane-4,4'-disulphonyl chloride and terephthaloyl chloride respectively[31]. Benesi-Hildebrand treatment of the fluorescence spectra of 1,8-ANS in the presence of (3) and (4) gave values for the association constants of 1.3×10^3 M^{-1} and 6.4×10^2 M^{-1} respectively, 11-24 times stronger than with β-cyclodextrin itself. Clearly, the effect of capping is to increase



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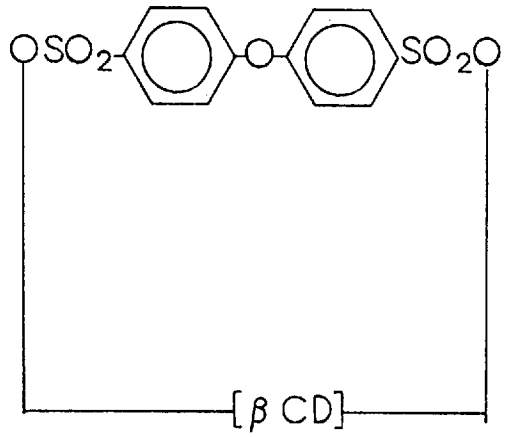
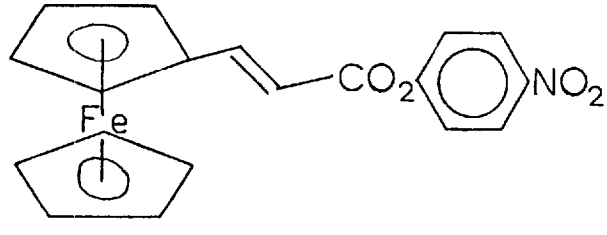


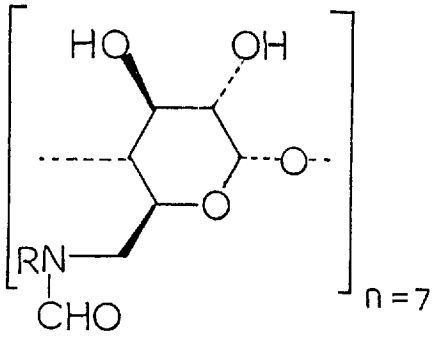
(5)

the hydrophobicity of the cavity. Breslow[26] later studied the effect of rigid capping on the catalytic activity. A striking rate enhancement of 10^6 relative to the uncatalysed reaction was observed for the reaction of ferrocenyl-2-acrylic ester (6) with capped β-cyclodextrin (5), although the association constant was found to be only 133 M^{-1}. This effect can be explained in terms of the favourable geometry for reaction



(6)

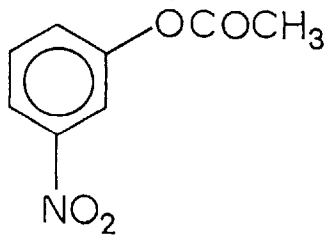
of the intermediate inclusion complex as a result of the hydrophobic cap. Breslow also observed that whereas a substrate may be able to bind fully within the cyclodextrin cavity, it could be pulled up on formation of a tetrahedral intermediate[26]. This debinding effect was diminished[26,35] by modification by "flexible capping". Thus, preparation of the flexibly capped derivatives (7) and (8) bearing relatively non-polar "intrusive floors", produced reductions in the depths



(7) R = Me

(8) R = Et

of the hydrophobic cavity from 7Å (β-cyclodextrin) to 3.7 Å and 2.5 Å respectively. These new systems showed dramatic rate enhancements when compared to β-cyclodextrin in the hydrolysis of the phenol esters (9) and (10).



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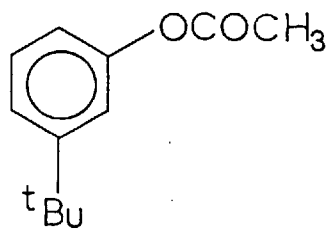

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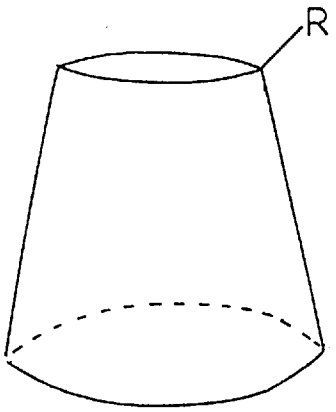
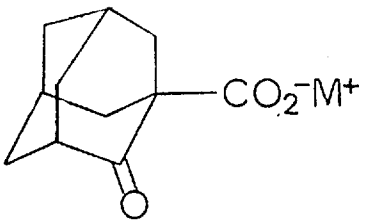
Increased specificity as a result of multiple recognition

The introduction of more than one recognition element onto a host molecule would be expected to increase the substrate binding selectivity for specific substrates. However, only a few examples of multiple

recognition exist in the literature.

The flexible capping of β-cyclodextrin with certain divalent metal cations[36] has resulted in remarkably enhanced binding of guest molecules simultaneously bearing both hydrophobic and anionic residues. The β-cyclodextrin derivatives (11) and (12), (termed "apohosts"), prepared by treatment of 6-O-p-toluenesulphonyl-β-cyclodextrin with diethylenetriamine and triethylenetetramine respectively, interacted strongly





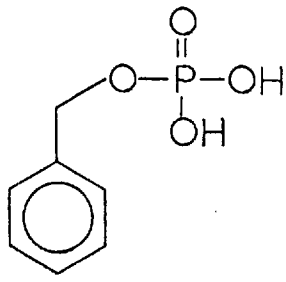
(11) R = $-NH(CH_2)_2NH(CH_2)_2NH_2$

(12) R = $-NH(CH_2)_2NH(CH_2)_2NH(CH_2)_2NH_2$

(13)

with Cu^{2+}, Mg^{2+} and Zn^{2+} cations. The resultant metal complexes, (termed 'holohosts'), therefore possessed mutually independent double recognition sites, and as consequence, showed marked specificity in the binding of hydrophobic carboxylates, sulphonates and alkoxides in aqueous solution. Most dramatically, the zinc complex of (11) binds adamantan-2-one-1-carboxylate (13) 330 times more strongly than does β-cyclodextrin itself. In the absence of a metal cation, binding was only slightly more effective than with β-cyclodextrin, thus illustrating the importance of the co-operation of both hydrophobic and electrostatic interactions in the metal-bound systems.

Knowles *et al.* recently described[34] the synthesis and characterisation of the hydrochloride salt of the highly symmetrical 6,6",6""-triamino-per-O-methyl-α-cyclodextrin and its use as a specific host for benzyl phosphate (14).



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Specific inclusion complex formation was predicted, in this specially designed system, by virtue of a combination of both hydrophobic and electrostatic binding interactions. The host embodies both a hydrophobic cavity and a set of three symmetrically placed cationic groups. CPK models indicate that when the aromatic ring of the potential guest molecule (14) is placed within the cavity, it is possible for the three charged phosphate oxygen atoms to lie in the same plane as, and in close proximity to, the charged ammonium groups of the host. This added stabilisation of the complex should be expected to give rise to strong complexation in aqueous solution.

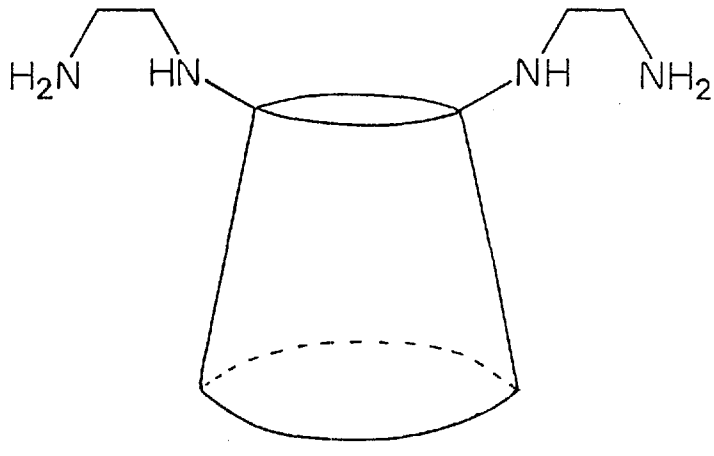
The dissociation constants for the inclusion complex at various pH values, determined by competitive inhibition of the binding of 2,4-dinitrophenol, are shown in the table (Table 3).

TABLE 3[34]

pH	K_D ($\times 10^{-3}$ M)	
	Benzyl Alcohol	Benzyl Phosphate
5.50	33 ± 5	2.1 ± 0.2
7.00	24 ± 4	0.031 ± 0.0005
9.50	25	> 100

Evidently, the binding is very susceptible to changes in pH, whereas the binding of benzyl alcohol remains virtually unaffected. These results support the proposed binding pattern and, more importantly, demonstrate that the charged host is selective in its binding preference for benzyl phosphate at pH 7.

Duplex cyclodextrin (16)[37] specifically binds methyl orange, which has two hydrophobic recognition elements. The association constant was 3160 M^{-1} whereas the corresponding value for the β-cyclodextrin tetramine (15) was only 520 M^{-1}. This result strongly supports the operation of a multiple recognition mechanism for binding.



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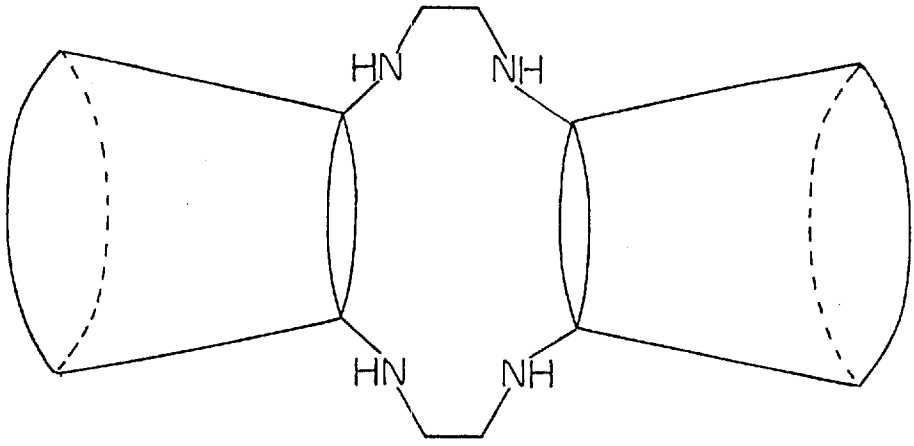

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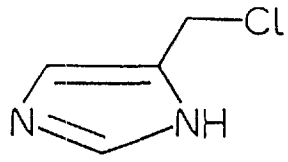
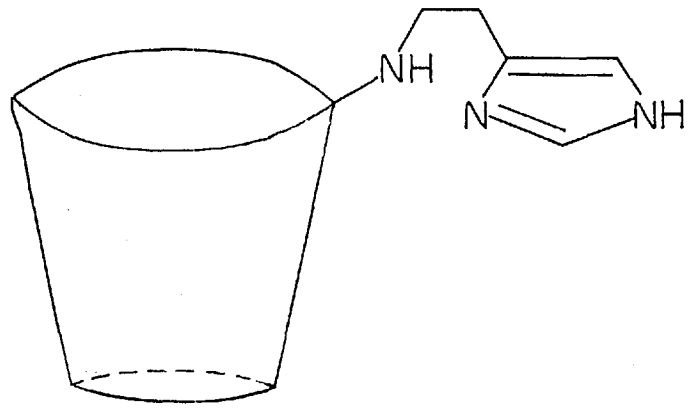
Cyclodextrins modified by the introduction of active groups

The catalysis of ester hydrolysis by enzymes such as chymotrypsin involves the co-operative participation on imidazolyl and hydroxyl groups present in the active site of serine and histidine residues respectively. The first attempt to synthesise a modified cyclodextrin with both imidazolyl and hydroxyl groups in close proximity to the binding site, was carried out by Cramer and Mackensen.[38,39] They treated β-cyclodextrin with 4(5)-chloromethylimidazole (17) in the presence of base, and obtained derivatives bearing an average of two imidazolyl moieties per molecule. Although incompletely characterised, it seems reasonable that substitution occurred at the more reactive C-6 positions, and not at the catalytically active C-2 or C-3 positions. This was indeed reflected in a rate enhancement of only 1.3 fold in the hydrolysis of p-nitrophenyl acetate as compared to the same reaction in the presence of β-cyclodextrin itself and two equivalents of imidazole.



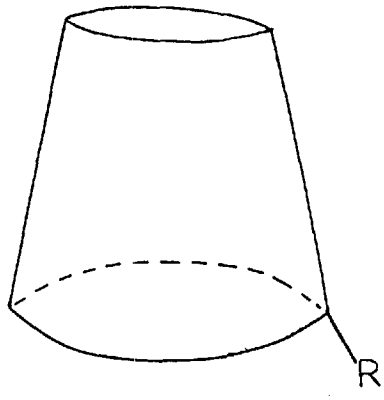
(17)

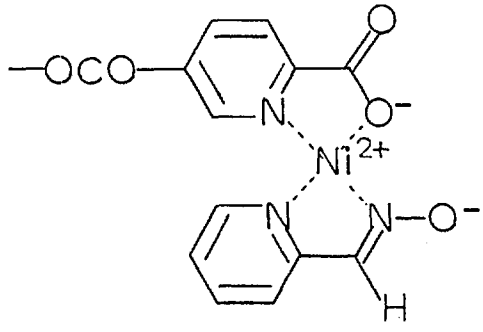
The α-cyclodextrin-histamine (18)[30] selectively substituted at the C-3 position as evidenced by ^{13}C NMR spectroscopy, was subsequently prepared. p-Nitrophenyl acetate was hydrolysed eighty times faster in the presence of (18) at pH 8.37 than in the presence of α-cyclodextrin, and 6.3 times faster than with a mixture of α-cyclodextrin and histamine (19). Furthermore, the presence of cyclohexanol was found



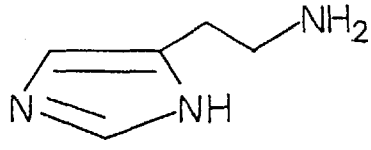
(18)

to competitively inhibit the reaction of cyclodextrin (18), whereas the latter system was apparently unaffected.

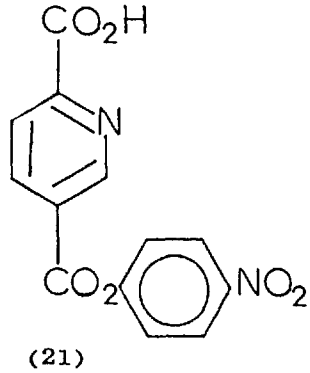


(20) R = 

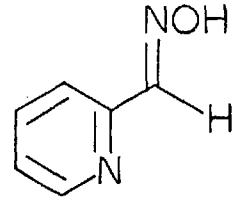
(23) R = $-NH(CH_2)_2NH_2$



(19)



(21)



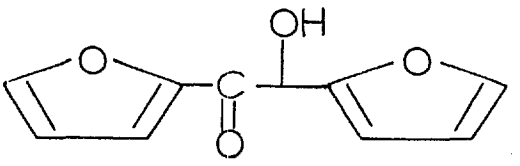
(22)

Breslow[40] had earlier demonstrated that increased rates of deacylation of 4-nitrophenyl acetate could be achieved by the metalloenzyme analogue (20), derived from the α-cyclodextrin ester of pyridine-2,5-dicarboxylic acid (21) and pyridine carboxaldoxime (22). Selective substitution at a secondary hydroxyl function was elegantly

executed by treatment of α-cyclodextrin with the 5-m-nitrophenyl ester of pyridine-2,5-dicarboxylic acid (21). Rate accelerations of greater than 10^3 over the uncatalysed rate, and nearly four times greater than in the presence of the nickel-pyridine carboxaldoxime (22) complex, were observed. These results are consistent with a mechanism involving rate-determining acetylation of the pyridine-carboxaldoxime moiety subsequent to inclusion complex formation, followed by rapid metal-ion catalysed hydrolysis of the resultant intermediate.

That complexation within the cyclodextrin moiety of (20) was an integral part of the catalytic effect was further demonstrated by the observations that cyclohexanol competitively inhibited the reaction and that 8-acetoxy-5-quinoline sulphonate, which is too bulky to fit inside the hydrophobic cavity, was hydrolysed more rapidly in the presence of the nickel-complex of (22) than cyclodextrin (20).

Mono - (6-β-aminoethylamino-6-deoxy)-β-cyclodextrin forms a 2:1 complex with Cu^{2+}, which accelerates the oxidation of furoin (24) by a factor of about 20 over the uncatalysed reaction [3,41].

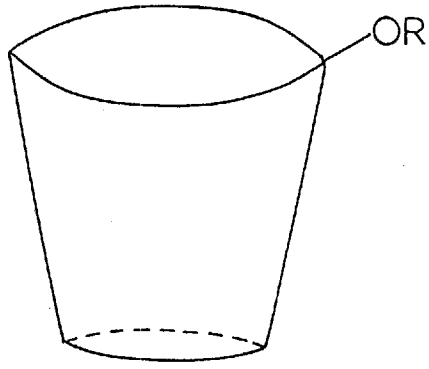


(24)

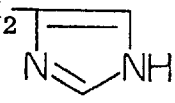
The catalytic effect can be explained in terms of co-ordination of the enolate anion directly to the Cu^{2+} ion. However, an intermediate complex in which the furan moieties of furoin (24) are simultaneously

complexed by the cyclodextrin rings in the 2:1 complex, and in which the enolate anion of furoin is stabilised by the complexed Cu^{2+} ion, cannot be discounted [3]. This would represent an early example of multiple recognition in a cyclodextrin system.

Bender has described the effect of incorporation of acetohydroxamic acid residues into the C-2 or C-3 positions of α-cyclodextrin[3]. 4-Nitrophenyl thiolacetate, 4-nitrophenylacetate and 3-nitrophenyl acetate were hydrolysed in the presence of (25), 2775, 2500 and 240 times respectively, faster than with α-cyclodextrin. Modified cyclodextrin (26) also showed similar regioselectivity in the cleavage of 3- and 4-nitrophenylacetates, the 4-isomer reacting approximately ten times faster than the 3-isomer. Such an effect can be attributed



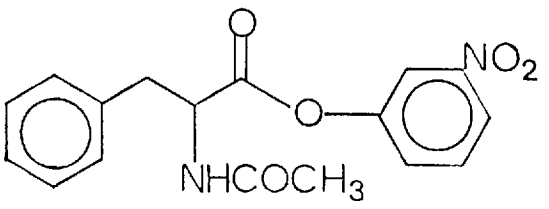
(25) R = $-CH_2CON(OH)CH_2CH_2N(CH_3)_2$

(26) R = $-CH_2CON(OH)CH_2$ 

(27) R = $-CH_2CON(OH)CH_3$

to the more favourable geometries of the inclusion complexes formed between the 4-isomer and the cyclodextrin derivatives. Furthermore,

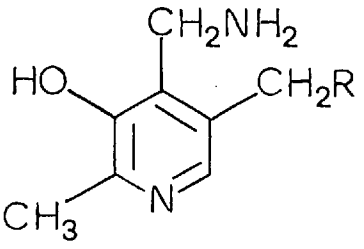
the hydrolysis of acetylphenylalanine 3-nitrophenyl ester (28) in the presence of modified cyclodextrin (25) was accompanied by moderate



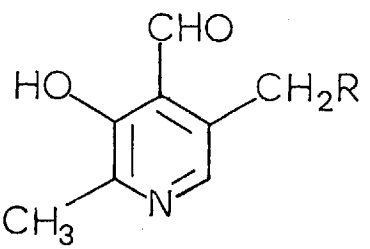
(28)

D,L-selectivity (L/D = 0.65). The derivative (27) also showed a notable catalytic effect.

More recently, Breslow[29] has designed and synthesised a modified β-cyclodextrin which elegantly mimics the action of the coenzymes pyridoxamine phosphate (29, R = OPO_3H_2) and pyridoxal phosphate (30, R = OPO_3H_2). These compounds, in conjunction with a large number of enzymes, are especially important in transamination during amino acid metabolism. Thus pyridoxamine phosphate (29, R = OPO_3H_2) reacts in

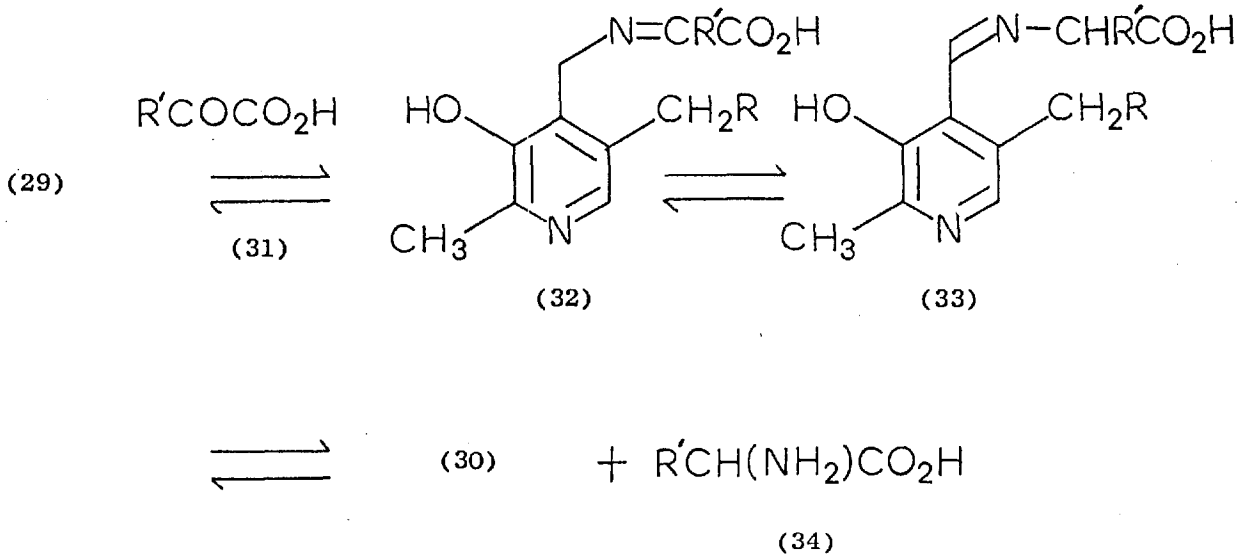


(29)



(30)

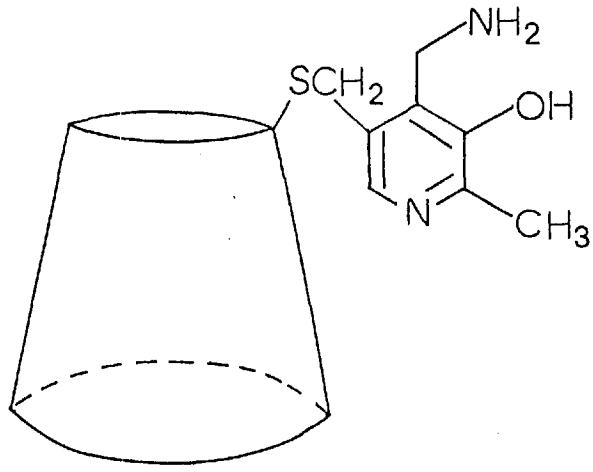
an enzyme mediated fashion with an α-keto acid (31) to form a Schiff's base (32), which, after tautomerisation to imine (33), subsequently cleaves stereospecifically to give the corresponding amino acid (34)



Scheme 1

and pyridoxal phosphate (30, R =OPO_3H_2) (Scheme 1). As the reverse reaction is also possible, this represents a catalytic cycle.

In the absence of enzymes, the catalytic cycle still operates, as demonstrated by model studies[42], but it is inefficient and lacks selectivity. However, Breslow reasoned that the introduction of a substrate binding site in close proximity to a pyridoxamine moiety should lead to enhanced rates of transamination and greater selectivity. Accordingly, treatment of the dihydrobromide salt of the thiol (29, R = SH), derived in a short synthetic sequence from pyridoxamine (29, R = OH), with 6-O-p-toluene sulphonyl-β-cyclodextrin at 60° for 16 h in ammonium bicarbonate solution, yielded the suitably functionalised product (35) as its hexahydrate. The reactions of three α-keto acids, pyruvic acid (31, R′ = CH_3), phenylpyruvic acid (31, R′ = $PhCH_2$) and indolepyruvic acid (31, R′= 3-indolyl-CH_2-), were studied in the presence of (a) pyridoxamine (29, R = OH), (b) pyridoxamine (29, R = OH) plus one equivalent of β-cyclodextrin, and (c) modified cyclodextrin (35).



(35)

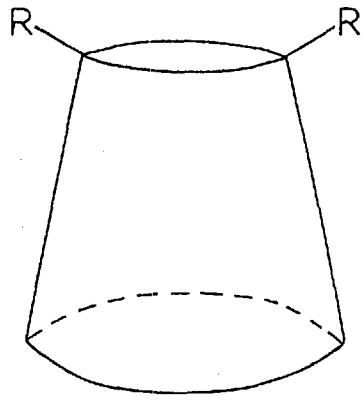
The substrates were found to react with pyridoxamine (29, R = OH) at similar rates to give the corresponding amino acids (34), which were converted to their dinitrophenyl derivatives and estimated by LC. The additional presence of β-cyclodextrin, however, led to reduced reactivity of the aromatic substrates as compared to pyruvic acid (31, $R' = CH_3$), presumably as a result of steric hindrance due to inclusion complex formation.

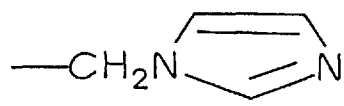
Most significantly, cyclodextrin (35) catalysed the rate of conversion of (31, R = 3-indolyl-CH_2-) to tryptophan (34, R = 3-indolyl-CH_2) approximately 200 fold as compared to the reaction with pyridoxamine (29, R = OH), but pyruvic acid (31, R = CH_3) reacted at the same rate as before. Clearly the aromatic substrate would be expected to bind preferentially within the cyclodextrin ring, close to the catalytic site, thus increasing its reactivity. Further proof that this was indeed the case was provided by a competition reaction between pyruvic acid (31, R = CH_3) and indolepyruvic acid (31, R = 3-indolyl-CH_2) in the presence of cyclodextrin (35) which led to rapid exclusive formation of trypto-

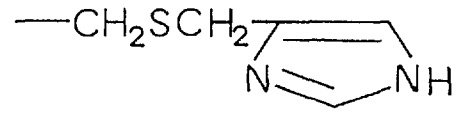
phan. A similar result was obtained with phenylpyruvic acid (31, R = $PhCH_2$-). However, in both cases, as would be expected, prolonged reaction times resulted in equilibration.

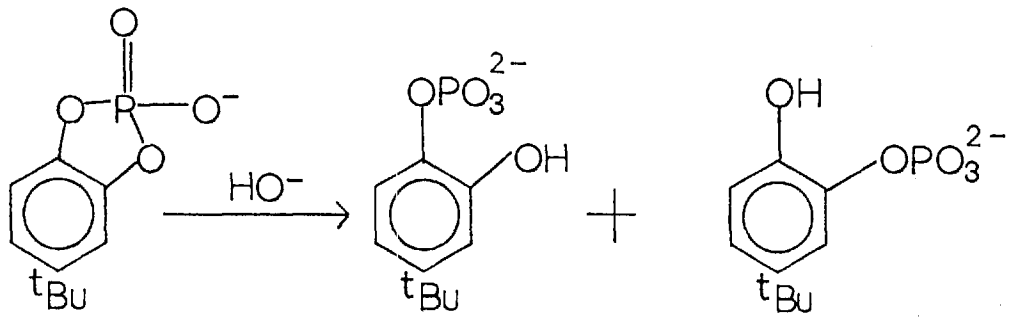
A modest chiral induction was observed, in the reactions with the aromatic substrates. Thus, the dinitrophenyl tryptophan was found to have 12% enantiomeric excess (e.e.) of the L-isomer, whereas the dinitrophenylphenylaniline had a 52 ± 5% excess of the L-enantiomer.

A striking example of the control of regioselectivity in an artificial system has recently been provided by the work of Breslow's group on ribonuclease analogues.[33,43]



(36) R = R = 

(40) R = R = 



(37) (38) (39)

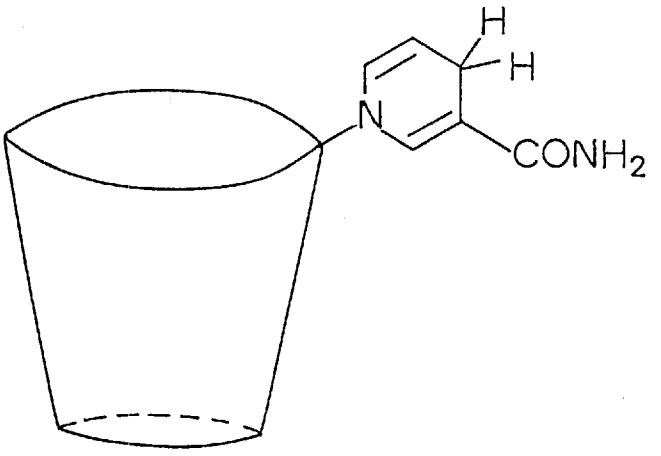
Scheme 2

The 6,6'-bisimidazole derivative (36), probably a mixture of 6A, 6C and 6A, 6D isomers, was found[33] to catalyse the cleavage of the N-methylpyridinium salt of the cyclic phosphate (37) of 4-tert-butylcatechol in a highly selective manner to give exclusively the 2-phosphate (39). Simple alkaline hydrolysis of (37), however, gave both the 1- and 2-phosphates (38) and (39) in a 50:50 ratio (Scheme 2). The kinetics of the reaction showed a bell-shaped pH versus rate profile with a maximum at pH 7.25, indicating the operation of bifunctional catalysis by a neutral imidazole moiety and an imidazolium cation. The enzyme ribonuclease gives a similar profile with a maximum at pH 7, and is thought to hydrolyse cyclic phosphate substrates in an analogous fashion. The regioselectivity of the system was explained in terms of the geometry of the intermediate host-guest complex.

Later work[43] by the same group illustrated that the regioselectivity could be completely reversed by suitable modification of the structural geometry of the catalyst. Thus, in the presence of the bisimidazole derivative (40) in which the active groups are further displaced from the binding site, the cyclic phosphate (37) was hydrolysed exclusively to the 1-phosphate (38). The same bifunctional catalysis as before was evidenced by a similar pH-rate profile, although

the pH maximum was shifted to pH 7.

Very recently, a β-cyclodextrin bearing a dihydronicotinamide moiety at a C-3 position (41) has been synthesised[44]. Modified



(41)

cyclodextrin (41) showed a large rate enhancement of approximately 40-fold in the reduction of ninhydrin as compared to the corresponding reaction with NADH. Such a result, together with the observation of saturation behaviour, strongly supports a mechanism which involves initial inclusion complex formation followed by rapid reduction of the bound substrate, which is thus held in close proximity to the dihydropyridine moiety.

1.2 ALTERNATIVE HYDROPHOBIC SYSTEMS

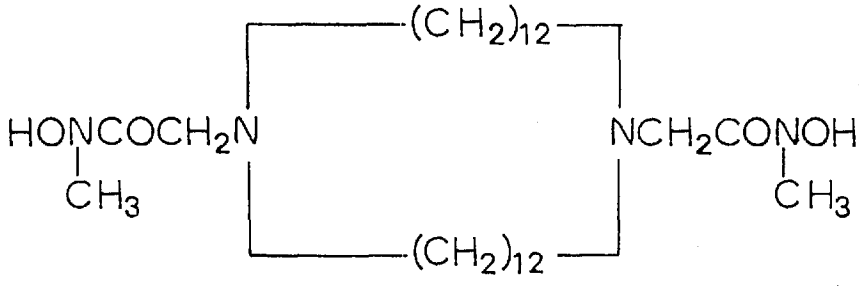
As the active sites of certain hydrolytic enzymes, such as chymotrypsin and trypsin are believed[45] to involve the imidazole function of one or more hystidyl residues, functioning either as a general-base or nucleophilic catalyst, several early attempts were directed at producing artificial analogues of these systems based on relatively

small polypeptides. However, the macrocyclic polypeptides cyclo-glycyl-L-hystidyl-L-serylglycyl-L-hystidyl-L-seryl (42)[46] and cyclo-glycyl-L-hystidylglycyl-L-tyrosylglycylglycyl (43)[47] for example, failed to show significant activity above that expected for a hystidine containing peptide, in the catalysis of the hydrolysis of 4-nitrophenyl acetate. Similarly, Bacitracin, a much larger macrocyclic polypeptide of uncertain structure[48], was examined as a potential catalyst[49], but found to be less effective than imidazole itself in the hydrolysis of aryl esters. Clearly, the lack of provision of a hydrophobic binding site suitably designed to incorporate substrates in close proximity to the active group(s) was a major flaw of these systems. Furthermore, the use of polypeptides is rather restrictive in this respect.

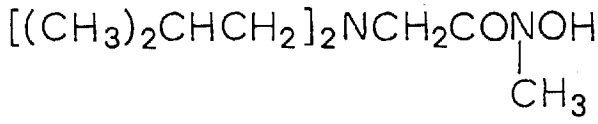
Subsequently, more emphasis has been placed on the design and synthesis of artificial, macrocyclic host molecules which embody more rigid and well-defined hydrophobic binding sites of known dimensions, and with simple proven host:guest stoichiometry. Additionally, ease of preparation and modification are important factors, as is solubility in aqueous media. Although the cyclodextrins meet most of these requirements, their use is limited.

Paracyclophane systems

In an isolated report in 1972[50], Hershfield and Bender described the synthesis of the novel macrocyclic N-methyl dihydroxamic acid (44) which behaves as a simple hydrolytic enzyme analogue, bearing an active functional group in close proximity to the binding site. A comparison of the effects of macrocycle (44) and the acyclic analogue



(44)



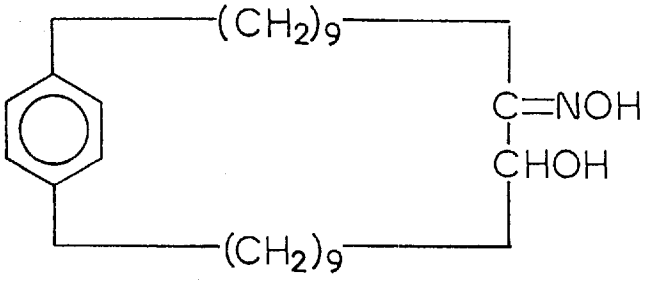
(45)

(45) on the rates of hydrolysis of a series of p-nitrophenyl carboxylates at pH 6.80 under conditions which disfavoured micelle formation of the substrates, revealed that whereas the acyclic analogue (45) failed to discriminate between the substrates, the macrocycle (44) showed rate enhancements for substrates bearing increasingly hydrophobic acyl moieties. (Table 4). This was attributed to the ability of macrocycle (44) to hydrophobically bind substrates within a cavity approximately 5.6 Å in diameter formed by the aliphatic chains. Further evidence for complex formation was provided by the observation of Michaelis-Menten (saturation) kinetics with p-nitrophenyl butyrate, and competitive inhibition by potassium iodide. However, the possibility of binding outside the cavity cannot be ignored. Interestingly, the additional presence of an equivalent amount of copper (II) chloride gave rise to a ten-fold rate acceleration of the esters in the presence of (44) but was ineffective in the presence of (45).

TABLE 4

p-Nitrophenyl ester	K(44)	K(45)	$K_r = \frac{K(44)}{K(45)}$
Acetate	1.18	0.693	1.7
Propionate	1.32	0.527	2.5
Butyrate	4.00	0.420	9.0
Isobutyrate	2.29	0.230	10
Valerate	3.31	0.340	9.8
Hexanoate	6.35	0.350	15
Octanoate	34.2	0.190	150
Dodecanoate	152	0.02	76500
Chloroacetate	240		

Murakami's group subsequently prepared[51] the macrocyclic oxime (46) which showed notable catalytic effects on the acyl transfer reactions of long-chain p-nitrophenyl carboxylates[53] and L-leucine-p-nitroanilide (47)[53], the sulphate transfer of aryl sulphates[53] and the phosphate transfer of bis-p-nitrophenyl phosphate[53]. Under the same conditions, 2-hydroxycyclodecanone oxime (48) was unreactive. The additional presence of N,N_-dimethyl-N-hexadecyl-N-(4-imidazolium) methylammonium dichloride (49) at concentrations lower than its critical micelle concentration, produced a rate enhancement for the hydrolysis of p-nitrophenyl palmitate of 22-fold over oxime (46)



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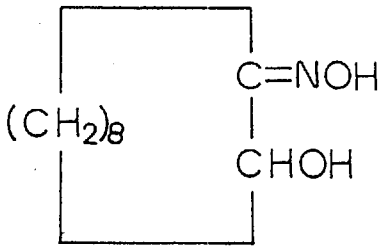

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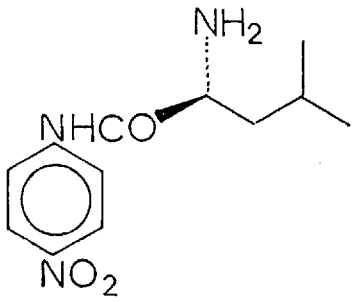

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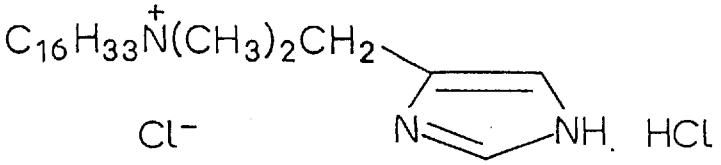
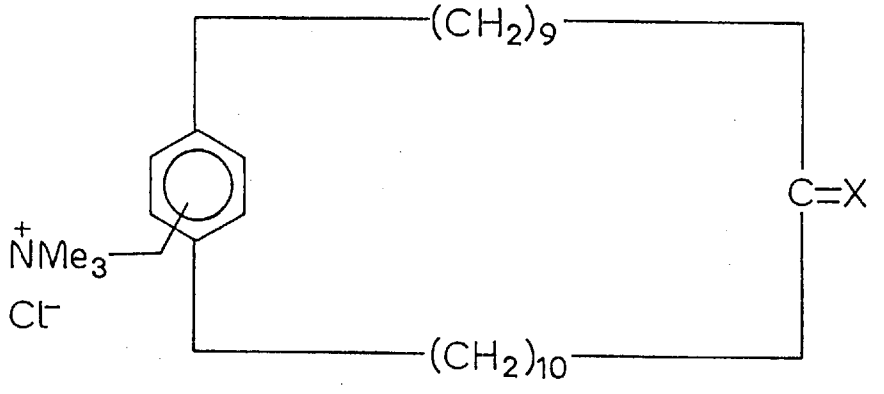


(49)

catalysis, and 39-fold over (49) catalysis. The intermediacy of a ternary complex, and the operation of bifunctional catalysis involving de-acylation of the substrate by co-factor (49), followed by trans-acylation to the oxime function of the host molecule (46), were postulated. However, although inclusion complex formation was suggested for these reactions, in which the alkyl chain of the substrate is encapsulated within the host molecule, this seems unlikely. The hydrophobic cavity formed by the paracyclophane skeleton of macrocycle (46) has a diameter of only 6.5 Å, and a depth of 4.5 Å. Evidently, such complexation would necessitate severe folding of the guest molecule. More plausibly, complexation involves both inclusion of

the p-nitrophenyl moiety within the host molecule, and additional hydrophobic interactions between the alkyl chains of the host and guest molecules.

The [20]paracyclophane (50), bearing a quaternary ammonium group attached to the aromatic ring, showed[54] enhanced rates of hydrolysis in aqueous media at pH 9-10 of p-nitrophenyl hexadecanoate in the presence

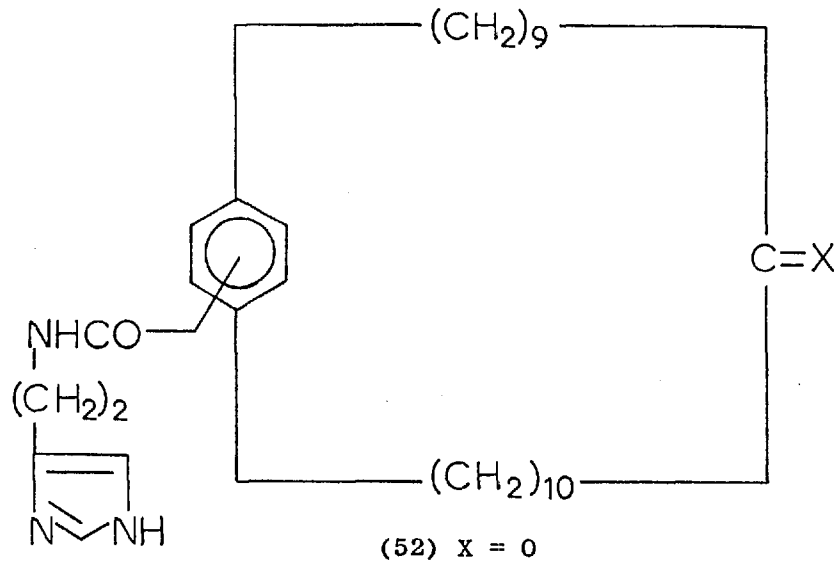


(50) X = O

(51) X = NOH

of ethanolamine or glycine. Such an effect, termed "electrostatic-hydrophobic double-field catalysis", was attributed to an electrostatic interaction which held the amino function of the nucleophile in close proximity to the ester carbonyl group of the bound substrate. The corresponding oxime (51) showed similar behaviour[55,56] in the deacylation of p-nitrophenyl laurate and palmitate, even at pH 4-7 when the oxime group is completely unionised.

Later, Murakami's group prepared a [20] paracyclophane (52) bearing an imidazole group, and studied[57] its catalytic behaviour in the deacylation of hydrophobic p-nitrophenyl carboxylates under neutral conditions. Although the rates of hydrolysis of these substrates in the presence of macrocycle (52) were considerably faster

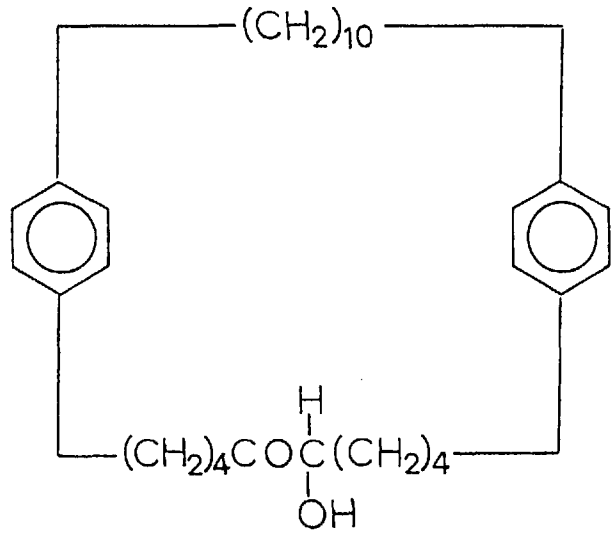


(52) X = O

(53) X = NOH

than the corresponding imidazole catalysed reactions, the rate of regeneration of macrocycle (52) (turnover) was small compared to the corresponding acylation rate, under the reaction conditions employed. Consequently stoichiometric amounts of "catalyst" were required. The corresponding oxime (53) was found[58] to co-ordinate Cu^{2+} ion through its imidazole group, thus forming a multifunctional system which successfully mimicked the catalytic activity of carboxy peptides A, in that the carbonyl group of the bound substrate was activated to attack by the un-ionised oxime function, by co-ordination to the metal cation. Carboxypeptidase A catalysis operates in a similar fashion via co-ordination of the carbonyl group to a Zn^{2+} ion and subsequent nucleophilic attack by the γ-carboxylate function of the glutamate - 270 residue[59].

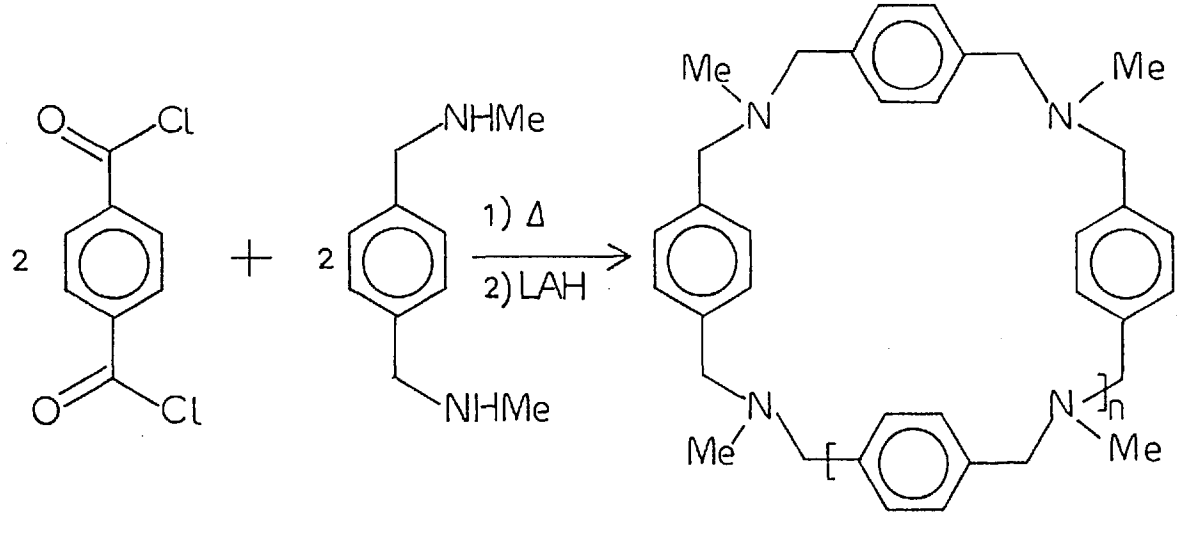
A series of water-soluble [10.10] paracyclophanes bearing the same active groups as the aforementioned examples, has been prepared by the same group[60]. The availability of these alternative structures, all derived from (54) should allow an investigation into the variation of catalytic activity upon structural modification.



(54)

Heterocyclophane systems

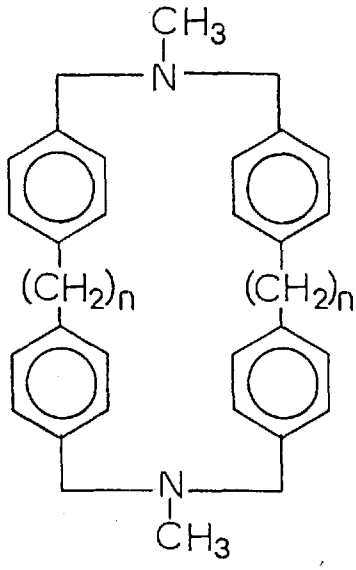
The first indication that heterocyclophanes also had potential as inclusion host molecules came in 1971[61], when a Japanese group synthesised three such compounds including the highly symmetrical N,N',N",N"'-tetramethyl-2,11,20,29-tetraaza[3.3.3.3]paracyclophane (57, n = 1), prepared in 25% overall yield by treatment of terephthaloyl chloride (55) with N,N'-dimethylxylylene diamine (56) under high dilution conditions[67], followed by lithium aluminium hydride reduction of



(55) (56) (57)

Scheme 3

the resultant macrocyclic tetramide (Scheme 3). Interestingly, crystallisation of (57, n = 1) from either benzene or dioxan gave rise to two stable crystalline complexes, shown to have a 1:1 stoichiometry by spectral and analytical methods. Conversely, attempts

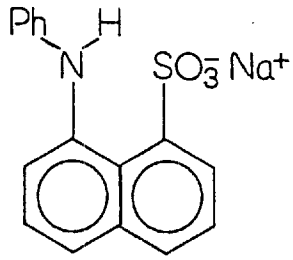


(58)

to isolate complexes of the other heterocyclophanes prepared (58, n = 1) and (58, n = 2) failed. It was tentatively suggested, without supporting evidence, that the solvent molecules were occluded within the rigid hydrophobic cavity formed by the paracyclophane skeleton of (57, n = 1).

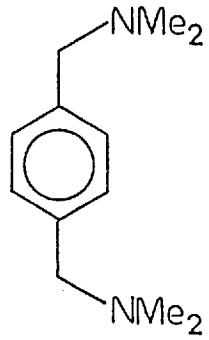
Later, Tabushi and coworkers[62] conducted a closer survey of the physical properties of (57, n = 1) and demonstrated its stronger binding capacity for aromatic substrates when compared to unmodified cyclodextrins. CPK models, and NMR evidence[63] indicated that the aromatic rings of the heterocyclophane favour the "face" conformation, thus forming a square-shaped hydrophobic cavity with an internal diameter of approximately 5.5 Å, and therefore comparable in size to α- and β-cyclodextrin. Additionally, the water solubility of (57, n = 1) below pH 6 is significant, as hydrophobic interactions should be optimal in polar media. Indeed, the fluorescence spectrum of sodium-

-1-anilino-8-naphthalene sulphonate (1,8-ANS) (59) was found to be dramatically enhanced in the presence of (57, n = 1) at pH 4.2,



(59)

which corresponds to mainly the triprotonated form, as shown by separate titration experiments. Such an effect is believed to indicate increased hydrophobicity of the immediate environment of the 1,8-ANS molecule, and/or a conformational change, and is well known to occur with some enzymes[64] and cyclodextrins[3]. This may indicate the existence of an inclusion complex. Hildebrand-Benesi[65] analysis of the fluorescence data gives a value of the association constant (K_{Assoc}) at pH 4.2 of

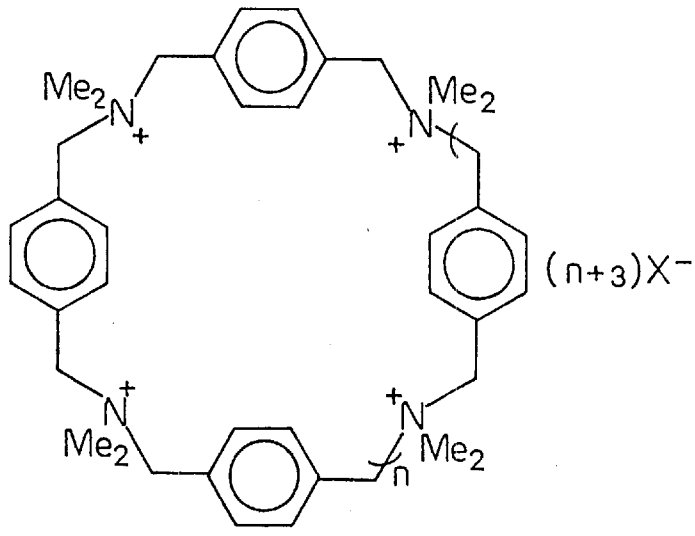


(60)

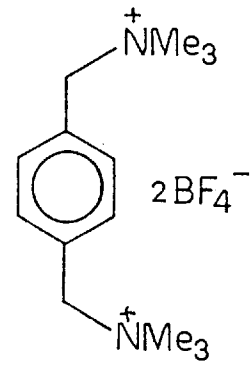
380 M^{-1}, approximately sixteen fold greater than for β-cyclodextrin. Interestingly, at pH 2 (fully protonated (57, n = 1)), K_{Assoc} was found to be 550 M^{-1}. However, further evidence that inclusion complex formation was actually taking place, was provided by the fact that N,N',N",N"'-tetramethylxylylene diamine (60), clearly incapable of any inclusion whatsoever, but bearing similar functionality to (57,

n = 1), shows negligible enhancement of the fluorescence of 1,8-ANS in the same concentration range.

In 1978, the same group reported[66] in a short communication the synthesis and characterisation of the water-soluble heterocyclophane (61, n = 1) and detailed its use as an effective catalyst. Compound (61, n = 1) was simply prepared by treatment of heterocyclophane (57, n = 1) with Meerwein's salt.



(61) X = BF_4
(64) X = I



(63)

Again, fluorescence studies with 1,8-ANS supported the formation of an inclusion complex. The kinetics of the hydrolyses of a series of chloroacetates (62, a-c) in aqueous media were studied in the presence of heterocyclophane (61, n = 1). Some of the results are summarised in Table 5. Evidently, heterocyclophane (61, n = 1) catalysed the hydrolysis of each substrate in the order (62a) > (62c) > (62b).

TABLE 5

Entry	Substrate	pH	Rate enhancement
1	(62 a)	8.10 p	25
2	"	" b	19
3	"	6.96 p	18
4	"	" b	17
5	(62 b)	8.10 p	2.6
6	"	" b	1.7
7	"	6.96 p	2.4
8	"	" b	1.8
9	(62 c)	8.10 p	4.3
10	"	6.96 b	10.6

p- phosphate buffer, b - borate buffer

$ClCH_2CO_2R$

(62)

a R = β-naphthyl

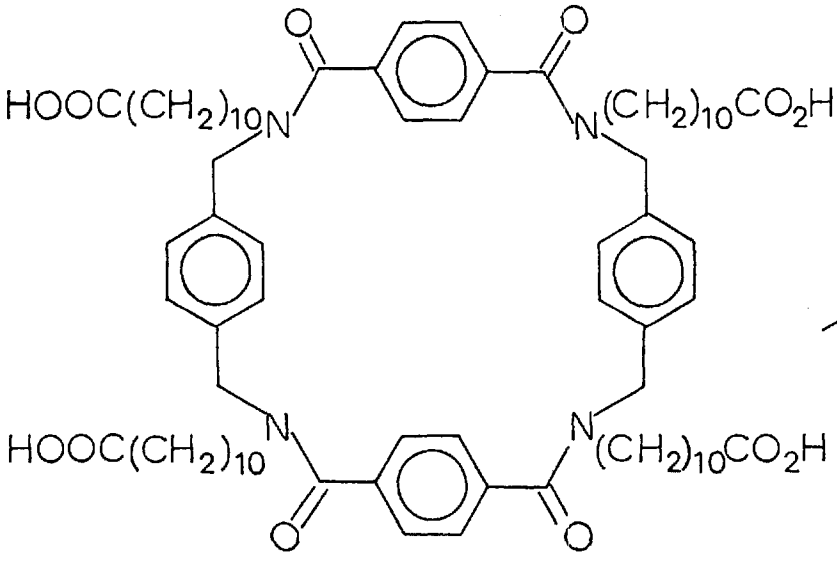
b R = p-nitrophenyl

c R = α-naphthyl

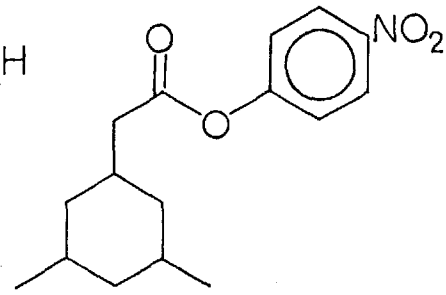
The mechanism for the catalysis was assumed to be electrostatic in nature. The acyclic analogue (63) showed a much smaller catalytic effect, indicating that the inclusion of the substrates was an important factor. However, despite the much greater reactivity of substate (62a) when compared to substrates (62b) and (62c), the binding strength was found to be approximately the same in each case. It was concluded that the observed substrate specificity was due to differences in the

ease of stabilisation of each transition state, as a result of inherent geometrical differences.

The water-soluble iodide salts of heterocyclophanes (64, n = 1) and (64, n = 3) were independently prepared by Murakami *et al.*, who investigated their binding potentials in aqueous media using hydrophobic spin-labelled probes[67]. Surprisingly, although the hydrophobic cavity of the larger homologue has a maximum diameter of 8-10 Å, approximately twice that of the smaller homologue, binding was essentially of the same order of magnitude for both compounds . This phenomenon was attributed to the "induced-fit" effect postulated by Koshland for some enzymatic reactions[68].



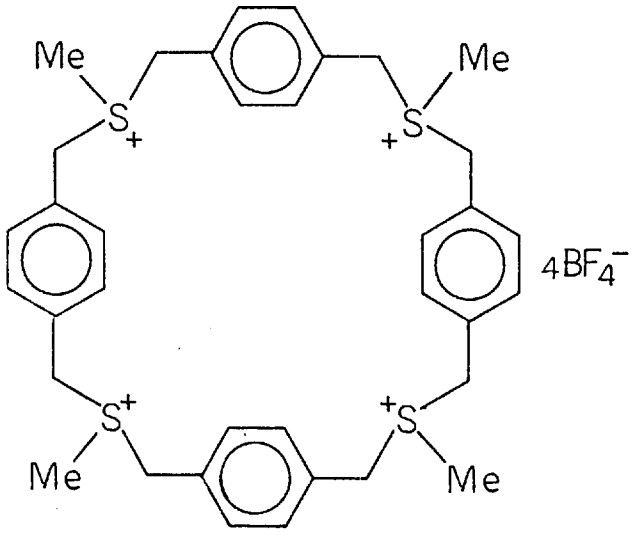
(65)



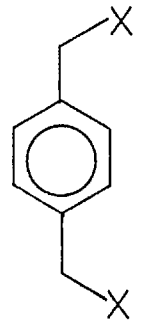
(66)

The "octopus-like" azacyclophane (65) was also synthesised, and shown to bind bulky dye molecules such as Rhodamine 6G and Quinaldine Red (both cationic) and 1-(2-pyridylazo)-2-naphthol (neutral) with the formation of 1:1 complexes. Contrastingly, an anionic dye Methyl Orange and sodium p-nitrophenolate were not complexed. Heterocyclophane (65) caused a 147-fold retardation in the hydrolysis of p-nitrophenyl 3,5-dimethylcyclohexylacetate (66) as a result of hydrophobic encapsulation.

The sulphur analogue of macrocycle (61, n = 1), S,S',S",S"'-tetramethyl-2,11,20,29-tetrasulphonium [3.3.3.3]-paracyclophane tetrafluoroborate (67) has also been prepared in unspecified yield[69] by treatment of xylylene dibromide (68) with xylylene dithiol (69) followed by methylation of the resultant macrocyclic tetrasulphide.



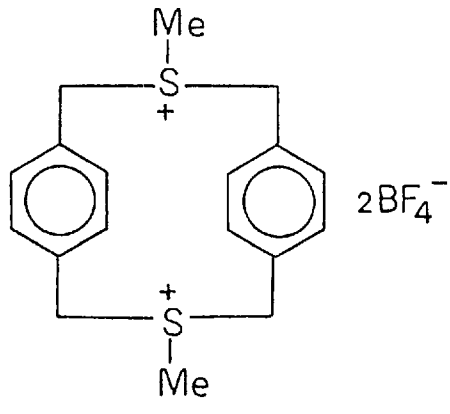
(67)



(68) X = Br

(69) X = SH

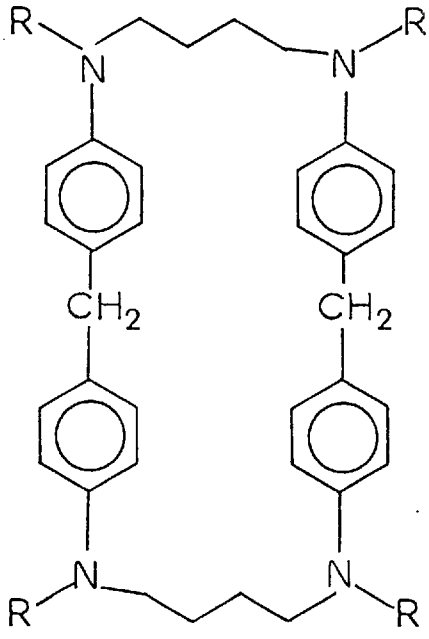
Heterocyclophane (67) is soluble in water at neutrality and consequently may find use as a molecular catalyst. The dimensions of the sides of the square hydrophobic cavity were ascertained by CPK models to be 7 Å, significantly larger than for the analogous nitrogen heterocyclophane (61, n = 1), and judged to be sufficiently large to occlude



(70)

both phenyl and napthyl guest molecules with ease. In accord with these findings, 1,8-ANS exhibited a strong enhancement of fluorescence intensity in the presence of macrocycle (67) and Hildebrand-Benesi analysis produced a higher value of 1.6×10^3 M^{-1} for the association constant. As expected, the much smaller S,S'-dimethyl-2,11-disulphonium [3.3] paracyclophane tetrafluoroborate (70) caused only a small enhancement of fluorescence intensity of 1,8-ANS, corresponding to an association constant of less than 50 M^{-1}. No further developments of this unusual system have since been reported.

The first clear-cut evidence to substantiate the theory that the guest molecules are actually bound within the hydrophobic cavity of the aforementioned water-soluble heterocyclophane hosts, at least in the solid state, has been provided very recently, in the form of an X-ray crystallographic structural determination of an inclusion complex[70].



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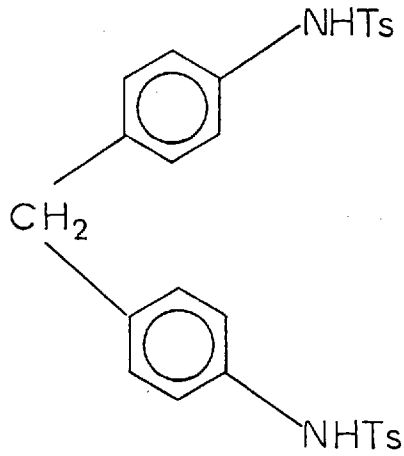
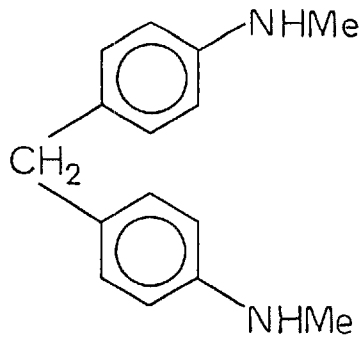


(72)

The specially designed host 1,6,20,25-tetraaza[6.1.6.1]paracyclophane (71, R = H) was prepared in 67% yield from the corresponding tetratosyl compound (71, R = Ts) which was in turn obtained in 25% yield by the cyclisation under high dilution conditions of equimolar amounts of N,N'-ditosyl-4,4'-diaminodiphenylmethane (72) and 1,4-dibromobutane in DMF in the presence of potassium carbonate.

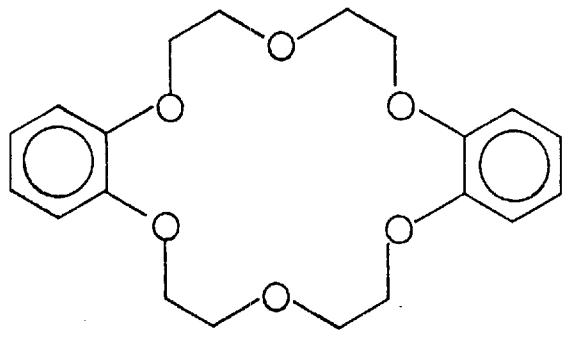
This novel macrocycle, soluble in water at pH 2, formed crystalline 1:1 complexes with 1,3-dihydroxynaphthalene, 2,7-dihydroxynaphthalene, naphthalene, p-xylene and durene. Additionally, the fluorescence intensity of 1,8-ANS was enhanced in the presence of (71, R = H) in aqueous solution at pH 2, corresponding to an association constant (K_{Assoc}) of approximately 6 x 10^3 M^{-1}. Furthermore, the ^1H NMR spectrum (D_2O/DCl at pD 1.2) of a solution containing macrocycle (71, R = H) and 2,7-dihydroxynaphthalene exhibited dramatic upfield shifts of the protons at C-1 and C-4 of the guest of 1.90 and 1.75 ppm respectively. In direct contrast, the acyclic analogue (73) showed neither of these effects to any appreciable extent. The crystalline 1:1 complex with durene was characterised as (77, R = H).4 HCl.durene.$4H_2O$ and its structure elucidated by X-ray crystallography.



(73)

1.3 MACROCYCLIC POLYETHERS AS MOLECULAR CATALYSTS

Pedersen's accidental discovery[71] of dibenzo-18-crown-6 (74) in 1967 sparked off an intense interest in the chemistry of macrocyclic polyethers and their aza-analogues. Of particular interest has been the complexation of a wide variety of guest molecules, including alkali and alkaline earth metal cations, ammonium cations, and alkylammonium cations. Increasingly elaborate host-guest systems are being synthesised



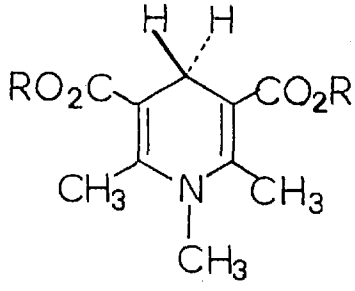
(74)

which may find application as effective enzyme analogues and molecular catalysts. For example, Cram[72] has elegantly demonstrated chiral recognition of optically active alkylammonium guest molecules by chiral hosts containing binaphthyl units. The use of carbohydrates as cheap, readily accessible precursors to chiral host molecules, has been examined by Stoddart[73]. Lehn's group in Strasbourg has also made significant contributions to this area. Notably, macrobicyclic receptor molecules have been developed and their application to carrier mediated ion transport studied[74]. This section will briefly outline the progress that has been made in the use of macrocyclic

polyethers as molecular catalysts.

Intramolecular hydride transfer to bound substrates

Although the "Hantzsh esters" (75) have been used extensively as models for NAD(P)H[75], they show little reactivity towards unactivated carbonyl compounds, which in keeping with the effects believed to be operating in the hydrogenase enzymes[76] usually require the assistance of a bound metal cation or of hydrogen bonding[77].



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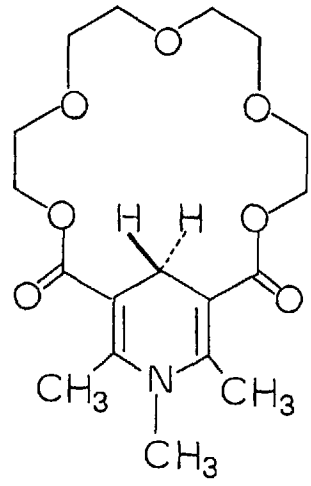
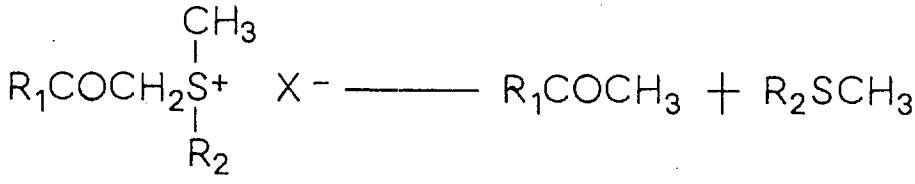


(76)

The incorporation of a 1,4-dihydropyridine moiety into a macrocyclic polyether was first achieved by Kellogg and van Bergen[78] who synthesised crown (76) by an elegant route which involved a novel template-directed ring closure. Initial attempts to effect the reduction of various carbonyl compounds with this system were unproductive, even after activation at the potential catalytic site by prior complexation of (76) with sodium perchlorate[79]. An X-ray crystallographic study of such a complex in association with one molecule of

acetone, later showed[30] that at least in the solid state the potential hydride donating site of the 1,4-dihydropyridine moiety is too remote (ca.4.04 Å) and incorrectly orientated to interact with the carbonyl group of acetone. The loss of reactivity may also have been due to the enforced boat conformation adopted by the 1,4-dihydropyridine ring, which is in contrast to the planar conformation of such species in nicotinamide derivatives. Additionally, phenacylammonium perchlorate failed to react with macrocycle (76), although, as expected, strong complexation was observed.

On the other hand, the sulphonium salts (77 a-d) reacted smoothly with (76) via the unprecedented intermediacy of a binary complex between a sulphonium salt and a macrocyclic polyether, to give the corresponding methyl ketones (78, a-d) and sulphides (79 a-d) (Scheme 4). Competitive reversible inhibition was observed when the reaction was carried out in the presence of sodium perchlorate, thus



(77) (78) (79)

a R_1 = Ph, R_2 = Ph, X = BF_4

b R_1 = Ph, R_2 = CH_3, X = ClO_4

c R_1 = Me, R_2 = Ph, X = ClO_4

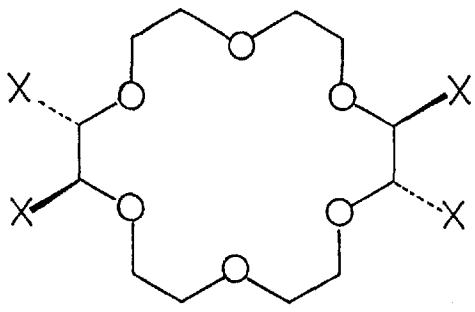
d R_1 = OMe, R_2 = Ph, X = BF_4

Scheme 4

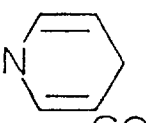
indicating preferential complexation of the sodium cation in the crown ether portion of the molecule. The kinetic data revealed

a rate enhancement of approximately 2700 fold at 70°C, relative to the reaction of Hantzsh ester (75, R = Et) with the same substrates. CPK models indicate that in the case of the sulphonium salt complexes, the positively charged sulphur atom is ideally positioned for displacement by intramolecular hydride attack at the adjacent methylene group.

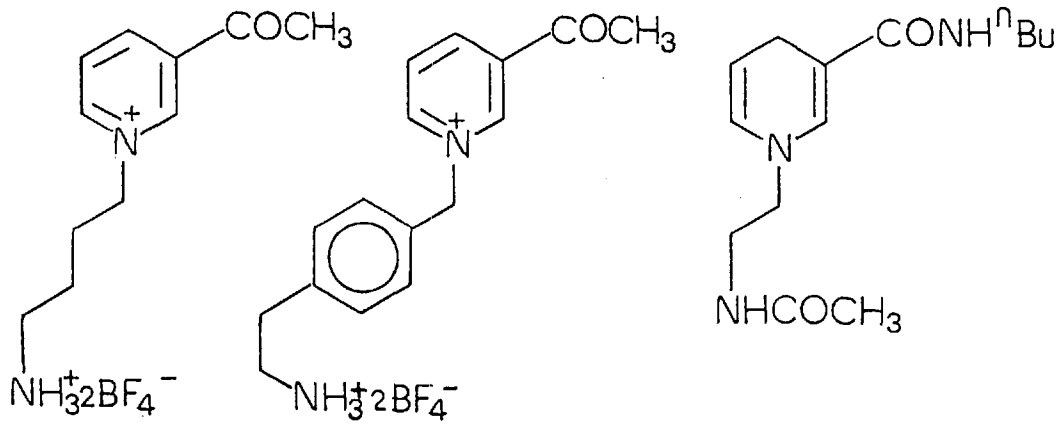
Subsequent work by Lehn's group[81,82] demonstrated the first example of accelerated 1,4-dihydropyridine (DHP) to pyridinium (P^+) transhydrogenation in a synthetic receptor-substrate complex. Such a model system, although not catalytic, elegantly represents the hydride transfer process which occurs in mitochondrial redox processes[83]. The requisite macrocyclic tetra-dihydropyridyl crown ether (81) was prepared in several steps from the corresponding chiral tetra-acid (80), itself readily available.from N,N,N',N'-tetramethyltartramide[84, 85, 86, 87]. Macrocycle (81) was apparently characterised merely by uv spectroscopy (λ_{max} = 345 nm, ε = 2.9 x 10^4 in acetonitrile).



(80) $X = CO_2H$

(81) $X = CONH(CH_2)_2N$  $CONH^nBu$

As 3-acetyl pyridinium salts were known[88] to be reduced by 1,4-dihydronicotinamides at convenient rates, the salts (82) and (83) were chosen for study.



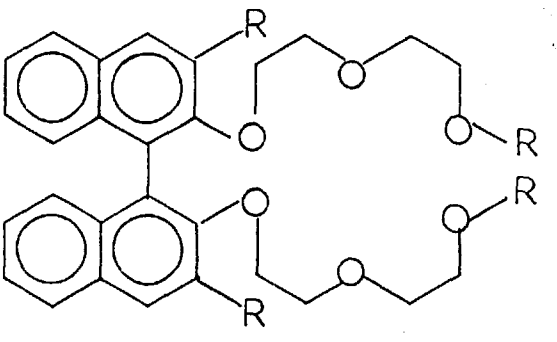
(82) (83) (84)

Strong complexation of these substrates by (81), in which the protonated amino groups are bound within the macrocyclic ring, was predicted on the basis of preliminary experiments. On addition to a solution of macrocycle (81) in acetonitrile, rapid reaction was observed, giving rise to the corresponding reduced products, as evidenced by changes in the uv spectrum. The first order kinetics for this process indicated an intramolecular mechanism, via prior (probably diffusion controlled) complexation. In contrast, second order kinetics with the expected overall decrease in reaction rate, were observed in the presence of excess potassium cation and, to a much greater extent tetramethylene diammonium cation. The rate constants were of a similar magnitude to the intermolecular reaction between substrate (83) and the reference compound (84). These results imply the operation

of competitive inhibition by these cations, which were shown earlier to be more strongly complexed by similar receptor molecules . In the case of the diammonium salt, additional electrostatic and repulsion effects may be important. It was suggested that modification of this system could lead to a greater understanding of the mechanism and the geometrical requirements of biological hydride transfer reactions. Clearly, in order to be truly catalytic, a subsequent reduction step would be required to regenerate the DHP units after reaction.

Intramolecular transacylation to bound substrates

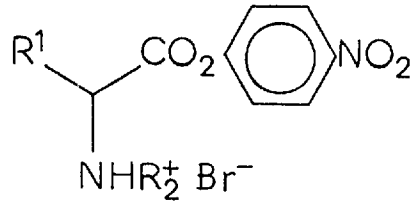
In 1976, Cram's group elaborated the first abiotic system based on a macrocyclic polyether, to effectively mimic the transacylation reactions thought to occur in certain enzymes, such as trypsin and papain[89]. In a comprehensive series of experiments, they studied the thiolysis of enantiomeric p-nitrophenyl esters of α-amino salts by the chiral hosts ((S)-(85)) and (R)-(85)), and demonstrated that



(85) R = CH_2SH, R^1 = $-(CH_2)-$
(86) R = CH_2OH, R^1 = $-(CH_2)-$
(87) R = CH_2SH, R^1 = $-CH_3$

moderate chiral recognition could be achieved in these reactions. Thiolysis involved transacylation onto sulphur followed by rapid hydrolysis of the resultant intermediate thioester.

The (R) and (S) antipodes of (85) were simply prepared in optically pure form, from the corresponding alcohols (86) by a short synthetic sequence. Similarly, the acyclic analogues ((S)-87)) was prepared from optically pure (S)-3,3'-bis(hydroxymethyl)-2,2-dihydroxy-1,1'-binaphthyl[88]. Dramatic rate enhancements for the liberation of p-nitrophenol, measured spectrophotometrically, were observed in the presence of these host molecules, and the intermediacy of a thioester was clearly shown. In a medium of 20% ethanol in dichloromethane (S)-aminoester salts bearing primary ammonium groups ($\overset{+}{N}H_3$) (88) were found to react with the cyclic dithiol ((S)-(85)) at rates about two to three powers of ten faster than with the open chain analogue ((S)-(87)). However, (S)-proline ester salts (89)which bear a secondary ammonium group ($\overset{+}{N}H_2$) reacted with these dithiols at approximately the same rate.



(88) R = H

Furthermore, increasing the polarity of the medium led to an overall rate decrease. Clearly the free energy of the rate-limiting transition state for reaction is lowered by complexation.

CPK space-filling models of the hypothetical diastereomeric tetrahedral intermediates, formed by intramolecular attack by one of the thiol groups of the host, at the ester carbonyl group of complexed guest, led to the prediction that the (S)-to (S)-configurational relationship of guest to host was the most stable. This was indeed borne out in practice. Thus, the (S)-antipode of (85) reacted with the (S)-amino ester salts faster than the (R)-antipode, by rate factors which depended on the size of the α-substituent (see Table 6).

TABLE 6

Entry	Crown (85)	$R.C^*H(\overset{+}{N}H_3)CO_2PNP\ \bar{B}r$ R	Configuration	Rate 10^3k, s^{-1}	Rate Factors
1	S	CH_3	S	70	1
2	R	"	S	70	
3	S	$(CH_3)_2CHCH_2$	S	70	6
4	R	"	S	11	
5	S	$C_6H_5CH_2$	S	340	8.3
6	R	"	S	41	
7	S	$(CH_3)_2CH$	S	22	9.2
8	R	"	S	2.4	

Koga and Matsui[90] later made a study of the effect of structural modification on the regioselectivity of a similar system. Marked catalytic effects were observed for the hydrolyses of the complexed hydrobromide salts of 4-nitrophenyl esters (90, 91, 92, 93 and 94) in the presence of the chiral crown ethers (95), (96) and (97). The extent of catalysis could be rationalised in terms of intramolecular

participation of the thiol groups according to the lengths of the connecting chains.

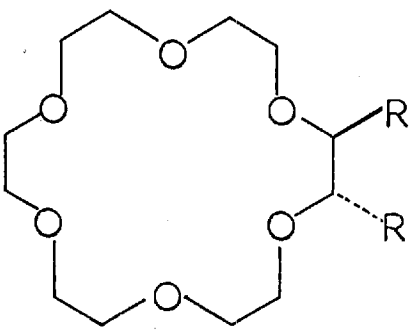
(90) Br^- $\overset{+}{N}H_3$-CH_2-CO_2PNP PNP ≡ 4-nitrophenyl

(91) Br^- $MeNH_2^+$-CH_2-CO_2PNP

(92) Br^- $\overset{+}{N}H_3$-$(CH_2)_2$-CO_2PNP

(93) Br^- $\overset{+}{N}H_3$-$(CH_2)_3$-CO_2PNP

(94) Br^- $\overset{+}{N}H_3$-$(CH_2)_5$-CO_2PNP



(95) R = CH_2SH

(96) R = $-(CH_2)_3SH$

(97) R = $-CH_2O(CH_2)_2SH$

The reaction rates, determined spectrophotometrically, are presented in Table 7. Clearly the rate of hydrolysis of substrate (90) (Entry A) in the presence of crown (95) is extraordinarily large, thus supporting the author's prediction by CPK models that in this case, host and guest are ideally positioned for reaction. Furthermore, extension of the thiol-bearing side chain, as in receptor (96) led to

a decrease in the rate of hydrolysis of ester (90), whilst esters (92) and (93) were hydrolysed at an increased rate (17.5 and 7 fold enhancements respectively).

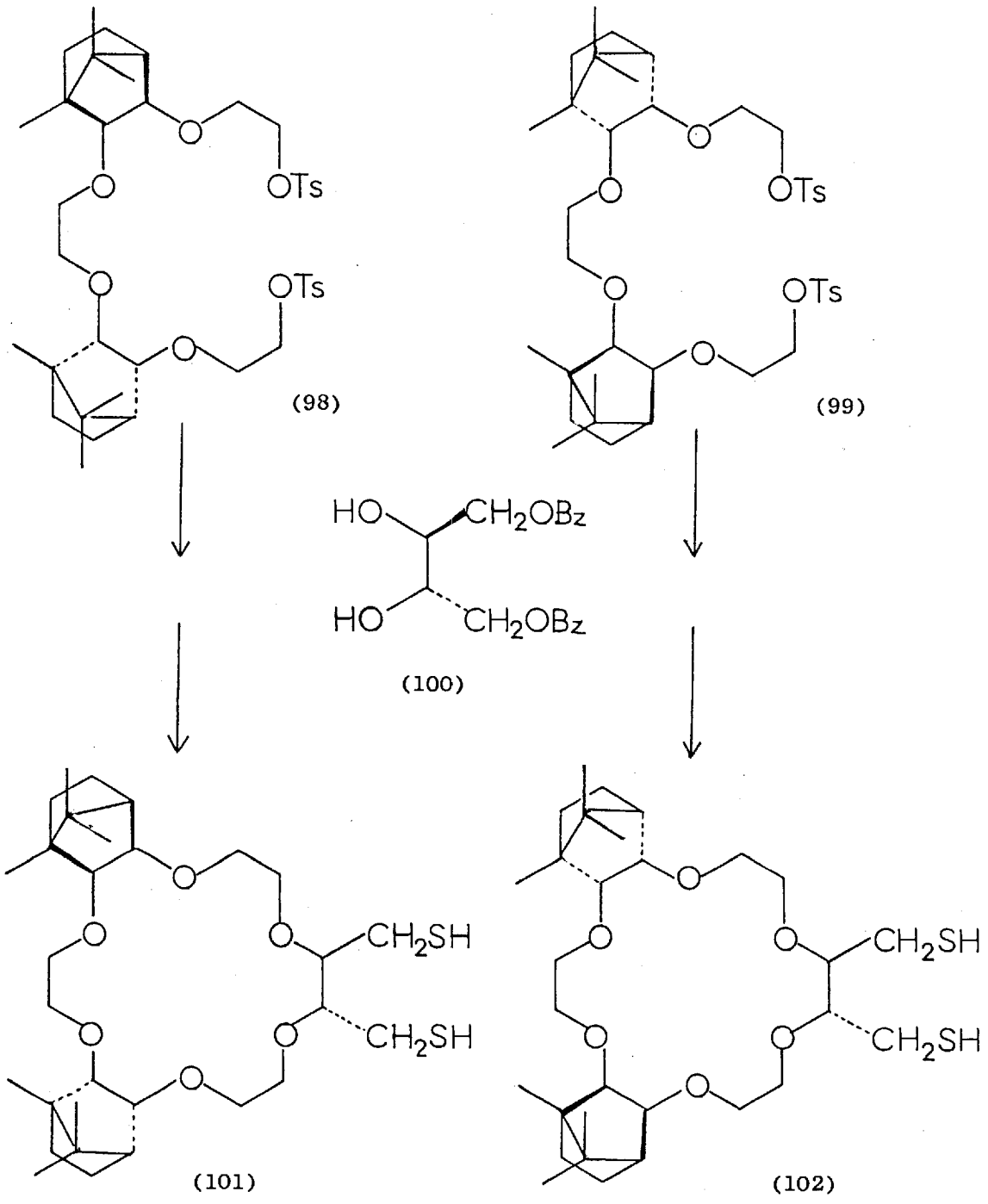
TABLE 7

Entry	Substrate	Rate (x $10^5 s^{-1}$) None	18-crown-6	$^nBuSH+$ 18-crown-6	(95)	(96)	(97)
A	(90)	3	0.9	1	1170	50	2500
B	(91)	5	5	4	6	4	37
C	(92)	<0.1	<0.05	<0.05	0.4	7	2
D	(93)	310	1	0.9	6	42	41
E	(94)	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

Surprisingly, and contrary to prediction, crown (97) was very effective in the catalysis of the hydrolysis of substrate (90). Presumably the thiol-bearing side-chain of this particular crown ether, which contains another ether linkage in the side chain is held closer to the complexed substrate by some pole-dipole interaction between the oxygen atom and the ammonium cation, or alternatively by hydrogen bonding.

In 1979, Koga[91] extended these experiments further with an improved approach which featured the incorporation of both chiral recognition and regioselectivity elements into the thiol-bearing crown ether, which led to moderate enantioselectivity in similar thiolysis reactions.

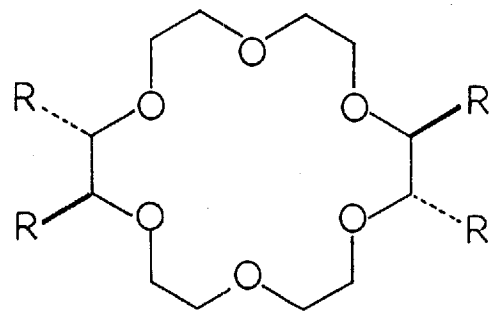
The chiral recognition sites of crown ethers (101) and (102) were originally derived from (+)- (1R, 2R, 3S, 4S)-camphane-2,3-diol and (-)-(1R, 2S, 3R, 4S)-camphane-2,3-diol respectively.



SCHEME 5

Thus, ditosylates (98) and (99) were separately synthesised in several steps. Cyclisation with the (+)-tartaric acid derivative (100) and subsequent modification, led to crowns (101) and (102) in unspecified yield (Scheme 5). The kinetic data for the release of 4-nitrophenol from the 4-nitrophenyl ester salts of glycine (88, R = R_1 = H), alanine (88, R = H, R_1 = Me), phenylalanine (88, R = H, R_1 = $PhCH_2$) and valine (88, R = H, R_1 = $CHMe_2$) revealed an overall rate enhancement in the presence of crowns (101) and (102) as expected from the earlier results. However, increasing size of α-substituent in the substrate resulted in progressively decreasing rates, presumably as a result of complex destabilisation. Such an effect has been demonstrated previously [92,93]. Most significantly, enantioselectivity by a factor of 1.7-1.9 was observed in the rates of thiolysis of enantiomeric alanine ester salts in the presence of (101) and (102). Again, this result can be rationalised in terms of the relative stabilities of the hypothetical tetrahedral intermediate complexes, as predicted by CPK models.

The chiral crown ether (103), obtained in 66% yield by condensation of (S)-cysteine methyl ester with the acid chloride (105) showed similar behaviour. Even greater enantioselectivity in the hydrolysis of a series of 4-nitrophenyl esters of α-amino acids and dipeptides was demonstrated[94]. The S-benzyl derivative (104) showed none of these effects, thus proving that the thiol groups are essential for catalysis. Structural selectivity was pronounced in this system; the dipeptide esters being more reactive as a result of more favourable structural geometry of the bound intermediates. Furthermore, although the enantiomers of Gly-Phe-OPNP reacted with buffer at the same rates, the (S)-isomer reacted approximately 50-90 times faster with chiral crown (103) than the (R)-isomer. The marked preference of complexation for one isomer in the presence of



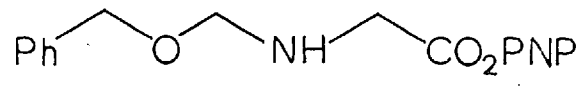
(103) R = CONH-(S)-CH(CO_2Me)CH_2SH

(104) R = CONH-(S)-CH(CO_2Me)CH_2SCH_2Ph

(105) R = COCl

the other (e.g. a racemic mixture) therefore represents a kinetic resolution process.

Interestingly, the ester (106) clearly incapable of complexation with crown (103), was hydrolysed in the presence of crown (103) fifteen times faster when potassium cation was present. Plausibly, the complexed



(106)

potassium cation can either lower the pK of the thiol group, thus increasing its reactivity, or can induce a favourable conformational change in the system. That such an effect is operating on complexation of the primary ammonium group of the other substrates is an interesting possibility.

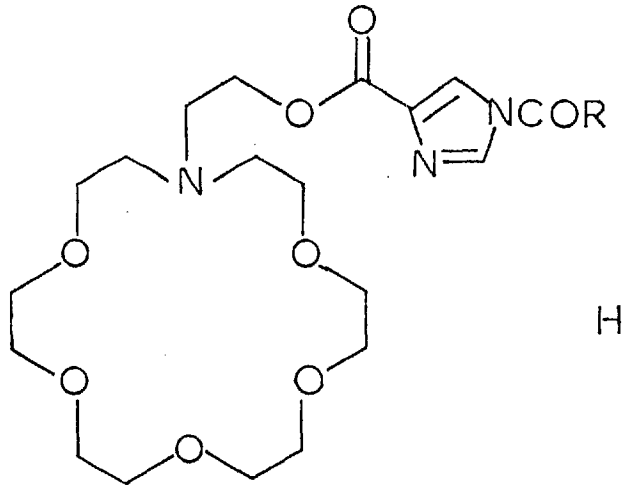
CHAPTER 2

SYNTHETIC ASPECTS OF HOST-GUEST CHEMISTRY

2.1 ATTEMPTED PREPARATION OF POTENTIALLY REGIOSELECTIVE MACROCYCLIC REAGENTS

The ability of macrocyclic polyethers and their nitrogen analogues to form stable 1:1 complexes with a variety of guest molecules, including alkylammonium salts, is well documented [95]. As outlined above, several groups have demonstrated the operation of effective intramolecular transacylation reactions between thiol-bearing host molecules and 4-nitrophenyl esters of amino acid and dipeptide salts[89,90,94]. Furthermore, it has been shown that by systematic structural modification of both the host and guest molecules in these systems, increased regioselectivity can be achieved[90,91].

Prior to publication of much of this work, we undertook the design and synthesis of a functionalised host molecule which would react regioselectively with a complex guest molecule possessing two (or more) similar functional groups which differed only in their position relative to the active group of the host.



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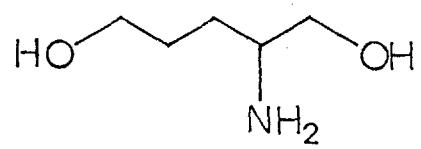
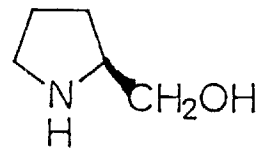


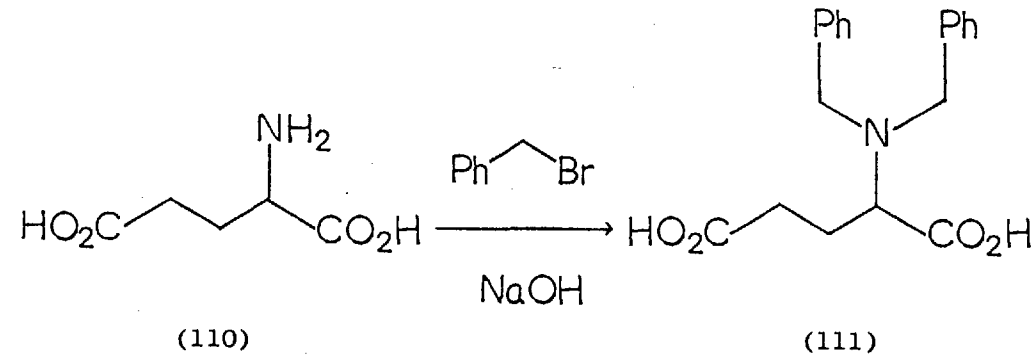
(108)

In the first instance, we intended to examine the reaction between the novel host molecule (107) and a salt of 2-aminopentan-1,5-diol (108). CPK Models of a hypothetical 1:1 complex indicated that a high degree of regioselectivity might be possible for transacylation from the acylimidazole moiety of crown (107) to the C-5 hydroxyl function of the guest (108). Such a prediction allowed for the ambiguous positioning of the acyl group on the imidazole ring. It was our intention to test our predictions by analysis of the product mixture subsequent to derivatisation and isolation.

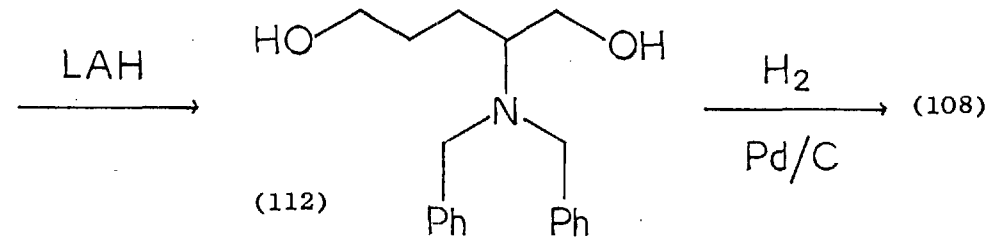
Herbrandson and Wood[96] have prepared 2-aminopentan-1,5-diol (108) in 56% yield by the reduction of the hydrochloride salt of diethyl S-glutamate with lithium aluminium hydride. However, intramolecular attack by the amino group at the C-5 ester carbonyl group, under the reaction conditions, and subsequent reduction of the resulting γ-lactam led to the additional formation of 2-hydroxymethylpyrrolidine (109) in 23% yield.

(109) 

More recently, Saund *et al.*[97,98] claimed to have obtained diol (108) directly from glutamic acid (110) by reduction with sodium bis(2-methoxyethoxy)aluminium hydride. Repeated attempts by us to carry out this reaction met with no success. Similarly, attempted reduction of glutamic acid (110) with the much more reactive lithium aluminium hydride in refluxing tetrahydrofuran failed to give the desired product, presumably as a result of the insolubility of the substrate.



(110) (111)

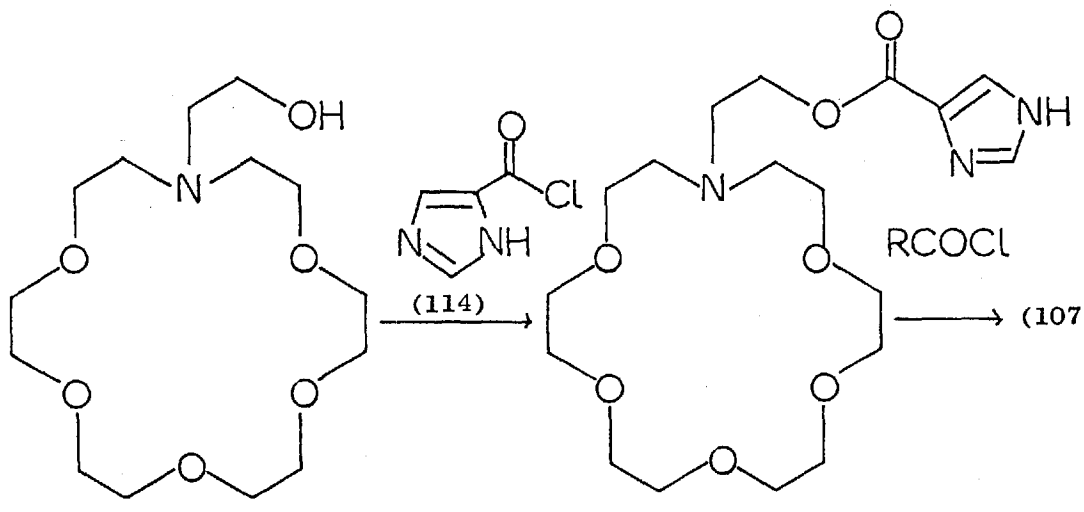


(112)

Scheme 6

Clearly, it was necessary to prepare a more soluble derivative of glutamic acid, which after reduction to the corresponding diol and subsequent deprotection, would cleanly furnish the required product. Thus, glutamic acid was treated with excess benzyl bromide in the presence of sodium hydroxide, according to the method of Kanao[99], to give the known D,L-N,N-dibenzyl derivative (111). Subsequent reduction with lithium aluminium hydride in tetrahydrofuran proceeded smoothly to afford D,L-2-(N,N-dibenzylamino)pentan-1,5-diol (112) in excellent yield. However, deprotection proved to be more difficult than expected. Thus, the removal of the N-benzyl groups of the diol (108) was effected in only 50% yield, by catalytic hydrogenolysis over 10% palladium or carbon catalyst over a period of three days (Scheme 6).

The route chosen to synthesise the functionalised host molecule (107) is outlined in Scheme 7. Acylation of N-hydroxyethyl-mono-aza-18-crown-6

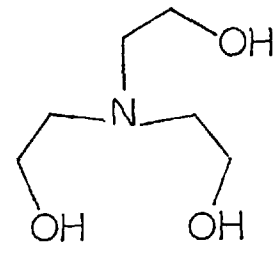


(113) (115)

Scheme 7

(113) with 4(5)-imidazolecarboxylic acid chloride (114) was expected to give the corresponding ester derivative (115). Subsequent N-acylation of the imidazole function may then afford the required product (107).

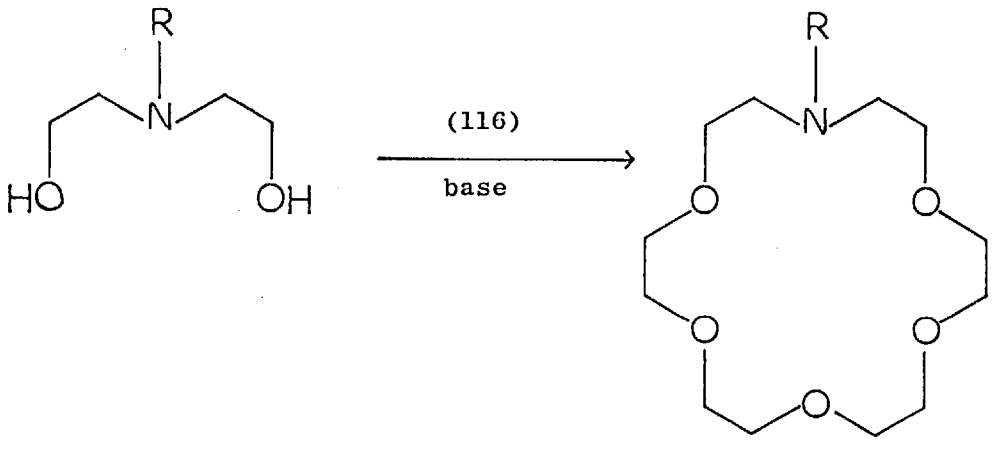
Our initial attempts to synthesise alcohol (113) by a direct route were unsuccessful. Thus, treatment of tetraethylene glycol with toluene-4-sulphonyl chloride in pyridine gave the di-(toluene-4-sulphonate) (116)[100] in 71% yield after chromatography. Subsequent reaction with commercially



(116) (117)

available triethanolamine (117) in tetrahydrofuran, in the presence of potassium t-butoxide, led only to a complex mixture of polar products, from which alcohol (113) could not be isolated. Clearly, an unambiguous stepwise approach was necessary, which would permit isolation of alcohol (113) in a pure state.

The preparation of mono-aza-18-crown-6 (122) was therefore examined, as it was reasoned that subsequent reaction of this compound with ethylene oxide would cleanly afford the corresponding N-hydroxyethyl derivative (113). Mono-aza-18-crown-6 (122), a known but poorly characterised compound had already been prepared by several routes. The first synthesis was briefly alluded to by Greene in 1972[101]. Treatment of N-trityldiethanolamine (119) with ditosylate (116) in the presence of potassium t-butoxide gave N-trityl-mono-aza-18-crown-6 (123) in 43% yield (Scheme 8). The high yield for the



(118) R = H

(119) R = CPh_3

(120) R = CH_2Ph

(121) R = $SO_2.C_6H_4.CH_3$

(122) R = H

(123) R = CPh_3

(124) R = CH_2Ph

(125) R = $SO_2.C_6H_4.CH_3$

Scheme 8

formation of an eighteen membered macrocycle was attributed to the now well established template effect[95], whereby the reactants are organised around a central potassium cation template in such a way as to promote cyclisation and to minimise polymerisation. Subsequent deprotection under mildly acidic conditions afforded mono-aza-18-crown-6 (122) in 65% yield. However, experimental details and physical properties of the products were not reported.

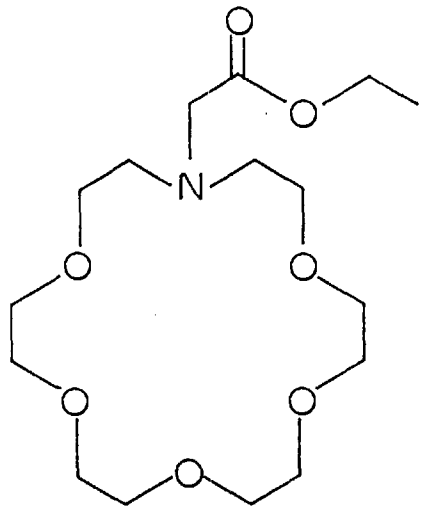
Later, Gokel and Garcia reported the synthesis of the N-benzyl derivative (124) by an analogous route[102]. Deprotection was effected by catalytic hydrogenolysis, in unspecified yield. This latter approach was chosen as the most convenient. The necessary starting material, N-benzyldiethanolamine (120)[103], was readily prepared in 84% yield, by the treatment of diethanolamine (118) with excess benzyl bromide in the presence of base. Subsequent reaction with tetraethylene glycol ditosylate (116) and sodium hydride in dry N,N-dimethylformamide or tetrahydrofuran, under conditions of high dilution, gave N-benzyl-mono-aza-18-crown-6 (124) in good yield (47%). Debenzylation by hydrogenolysis proceeded smoothly to give mono-aza-18-crown-6 (122), readily available in analytical purity by recrystallisation from acetonitrile at -30^{o}. Both compounds gave spectral data consistent with the proposed structures, and were further characterised by microanalysis of their monohydrated, crystalline picrate derivatives. Similar "hydronium" complexes of crowns have been previously reported[102,104], and an X-ray crystallographic structural determination of the monohydrated hydrochloride salt of crown (122) has been carried out[102].

An alternative approach to mono-aza-18-crown-6 (122) was also examined. Thus, N-(toluene-4-sulphonyl)-diethanolamine (121) was obtained readily by treatment of diethanolamine (118) with toluene-4-sulphonyl chloride, according to the method of Eisleb[105]. Subsequent reaction with tetraethylene glycol ditosylate (116) and sodium hydride in tetrahydrofuran, under the

same high dilution conditions as before, furnished the known[102] N-(toluene-4-sulphonyl) derivative of mono-aza-18-crown-6 (125) in good yield. However, although the product was apparently homogeneous by most criteria, and identical to an authentic sample prepared by the action of toluene-4-sulphonyl chloride on mono-aza-18-crown-6 (122) in pyridine, it resisted all attempts at crystallisation.

Attempted de-sulphonylation of this material with lithium aluminium hydride in refluxing tetrahydrofuran, contrary to the results of Sutherland *et al.*[106], led to the formation of a complex mixture of products, including crown (122) as ascertained by tlc analysis. Isolation of this material by fractional distillation at reduced pressure or by fractional crystallisation from acetonitrile at low temperature met with little success. An alternative mode of deprotection was therefore sought. N-sulphonyl cleavage normally requires drastic conditions[107], such as prolonged heating with concentrated sulphuric or hydrobromic acids. Dissolving metal reduction has also found application in this field. Reduction of the N-(toluene-4-sulphonyl)derivative (125) with sodium in a mixture of liquid ammonia and tetrahydrofuran proceeded rapidly to afford a mixture of products, of which the desired compound (122) was the major component. Again, no satisfactory method of isolation could be found. This approach was therefore abandoned.

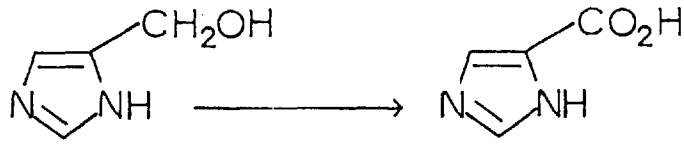
The reaction of mono-aza-18-crown-6 (122) with ethylene oxide in a sealed tube at 80°, gave rise to intractable mixtures of products. Similarly the sodio- and lithio-derivatives of crown (122) failed to give clean reactions with ethylene oxide at room temperature. An alternative approach to alcohol (113) was therefore examined. Treatment of mono-aza-18-crown-6 (122) with ethyl bromoacetate in the presence of base gave the ethyl ester (126) in high yield (93%). Reduction of ethyl ester (126) with lithium aluminium hydride in tetrahydrofuran at room temperature proceeded smoothly and cleanly to give the required alcohol (113) as a colourless oil.



(126)

However, attempted purification by bulb-to-bulb distillation at reduced pressure led to slight decomposition.

At this stage, problems were being encountered in the preparation of 4(5)-imidazole carboxylic acid (128). The first synthesis of 4(5)-imidazolecarboxylic acid (128) from histidine was described by Knoop in 1907[108]. Later Windaus and Ulrich obtained it by treatment of glucose with a cuprammonium solution over a period of three years[109]. More recently, however, Pyman reported the oxidation of 4(5)-hydroxymethylimidazole (127) with dilute nitric acid to give acid (128)[110] (Scheme 9).

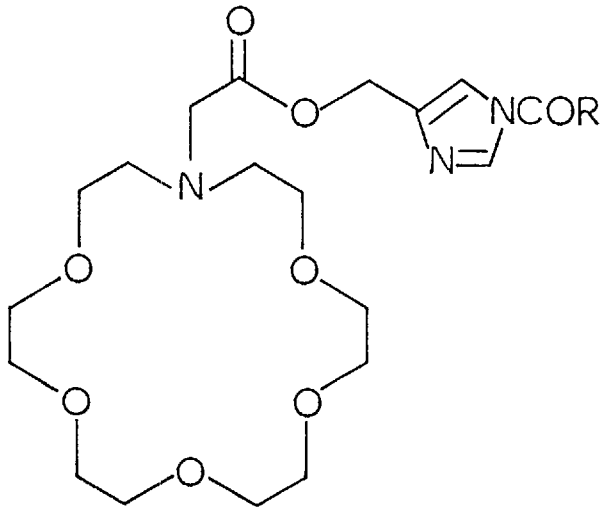


(127) (128)

Scheme 9

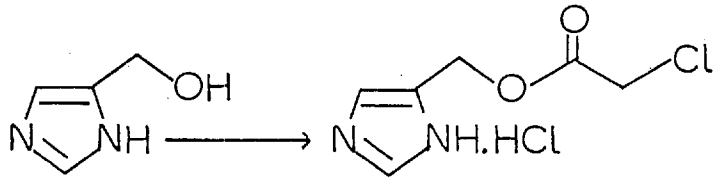
4(5)-Hydroxymethylimidazole (127) was obtained by the oxidative degradation of fructose, according to the procedure of Totter and Darby[111]. The product was isolated from the reaction mixture by formation and fractional recrystallisation of the crystalline picrate derivative (50% yield). The corresponding hydrochloride salt was subsequently prepared in 94% yield by treatment with hydrochloric acid. However, on oxidation with dilute nitric acid, a mixture of carboxylic acid (127) and the corresponding aldehyde was formed in low yield.

It was, therefore, resolved to attempt instead the synthesis of the structurally similar compound (129). CPK Models indicated that this molecule would be equally suitable for our purposes as a potentially regioselective acylating agent. Attempted ester exchange between ethyl ester (126) and 4(5)-hydroxymethylimidazole (127) under acid catalysis gave only unreacted starting material, even under forcing conditions.



(129)

On treatment with chloroacetyl chloride at -30° in N,N-dimethylformamide, 4(5)-hydroxymethylimidazole (127) yielded the corresponding chloroacetate derivative as its hydrochloride salt (130) (Scheme 10) in



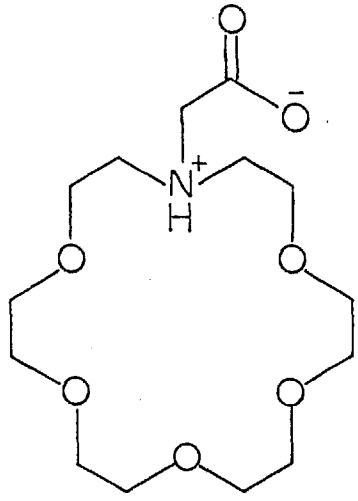
(127) (130)

Scheme 10

76% yield. Subsequent reaction with mono-aza-18-crown-6 (122) in N,N-dimethylformamide, in the presence of di-iso-propylethylamine gave rise to a mixture of four more polar products, as evidenced by tlc analysis.

In a separate experiment, the reaction was carried out in the presence of sodium iodide with the expectation that the resulting iodoacetate derivative would give a cleaner reaction. However, tlc analysis again indicated that a mixture of products had been produced. Furthermore, the absence of the required product was demonstrated by mass spectral analysis.

Reaction of the acid chloride derivative of the novel amino acid (131) with alcohol (128) was expected to result in the formation of the required product (129). As expected, reaction of the commercially available bicine (132) with tetraethylene glycol ditosylate (116) in the presence of potassium t-butoxide failed to give acid (131). Hydrolysis of the ethyl ester (126) with potassium hydroxide in aqueous tetrahydrofuran, however, proceeded cleanly and rapidly to give a single more



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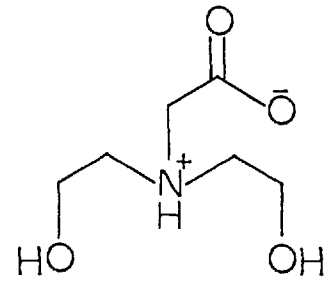
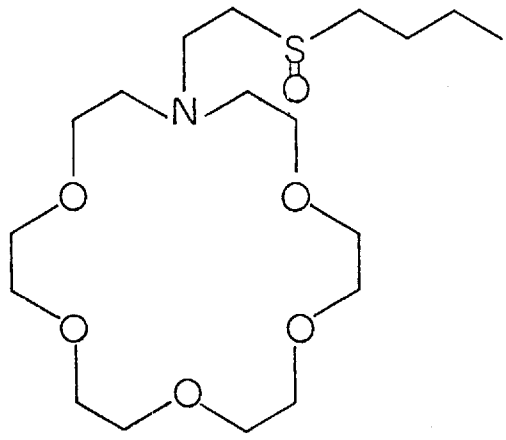


(132)

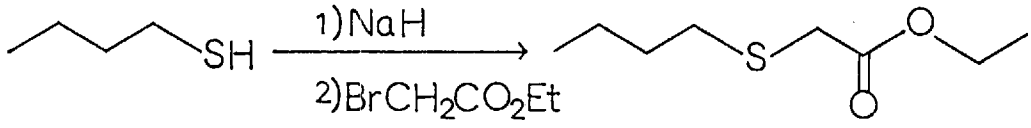
polar product. Attempts to isolate this material, after acidification, were consistently unsuccessful. It was resolved, therefore, to isolate the corresponding potassium salt of acid (131), if possible. Careful hydrolysis of ester (126) with exactly one equivalent of base, and evaporation to dryness, furnished the monohydrated crystalline potassium salt in quantitative yield. Subsequent reaction with oxalyl chloride in dichloromethane at 0^{o} afforded the corresponding acid chloride derivative, as evidenced by infrared spectroscopy. Reaction with 4(5)-hydroxymethylimidazole (127) was expected to give the hydrochloride salt of the required ester (129), possibly *via* rearrangement of a less stable *N*-acyl intermediate. In the event, treatment of the acid chloride derivative of crown (131) with 4(5)-hydroxymethylimidazole (127) in *N*,*N*-dimethylformamide gave a single more polar product. Attempts at isolation, however, consistently resulted in decomposition. Furthermore, mass spectral analysis of the resulting crude product mixture failed to show a peak corresponding to the desired product. The instability of the ester (129) could be explained in terms of intramolecular participation by the imidazole moiety. Bruice[112, 113] has studied the facile hydrolysis of esters of 4(5)-hydroxymethylimidazole and has postulated an alkyl-oxygen scission mechanism involving a diazofulvene intermediate. In view of the problems encountered in the synthesis of a suitably functionalised host molecule, this approach was abandoned.

Having met with little success in the synthesis of the potentially regioselective acylating host molecule (129), we turned our attention to an alternative system. CPK Models indicated that, in the hypothetical 1:1 complex between sulphoxide (133) and a salt of 2-aminopentan-1,5-diol (108), the sulphoxide group was held in close proximity to the C-5 hydroxyl function of the guest molecule. We predicted that it would be possible to effect the regioselective oxidation of this hydroxyl function to the corresponding aldehyde, in the presence of the C-1 hydroxyl group, using an "activated sulphoxide procedure".

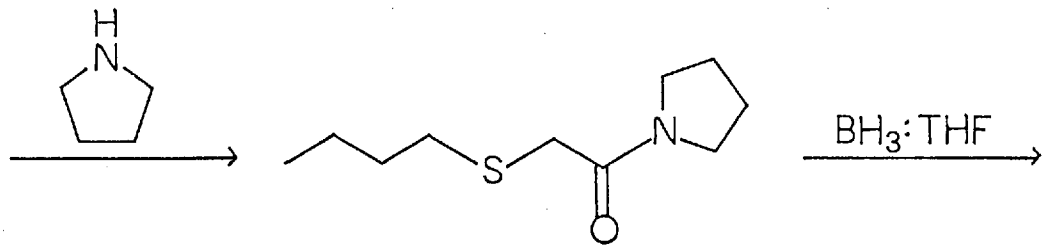


(133)

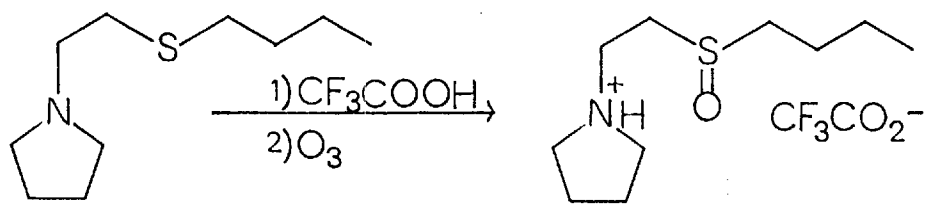
The synthesis of the model system (134) was undertaken first (Scheme 11). Reaction of n-butanethiol (135) with ethyl bromoacetate in tetrahydrofuran, in the presence of sodium hydride, gave the corresponding sulphide (136) (65%) and unreacted ester (22%). Subsequent treatment with excess pyrrolidine at reflux for four hours afforded N-(3-thiaheptanoyl) pyrrolidine (137) in 94% yield after distillation. Attempted reduction of amide (137) with lithium aluminium hydride in refluxing tetrahydrofuran



(135) (136)



(137)



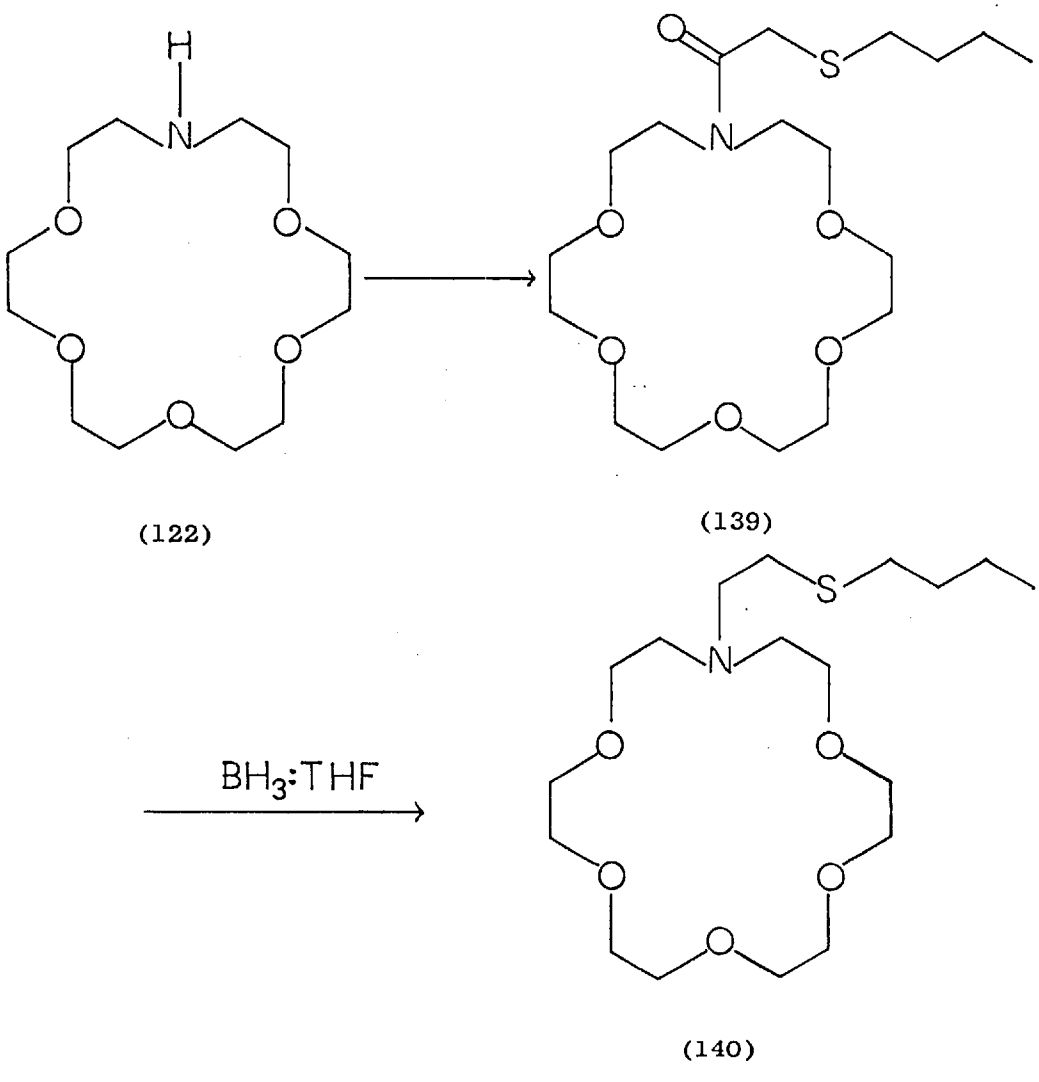
(138) (134)

Scheme 11

led to low yields of the required tertiary amine (138). However, on treatment with borane-tetrahydrofuran complex, in tetrahydrofuran at reflux the tertiary amide (137) was smoothly and cleanly reduced to N-(3-thia-heptanoyl)pyrrolidine (138), in 85% yield after distillation. Formation of the corresponding sulphoxide derivative (134) was most conveniently accomplished by reaction with ozone. Thus, treatment of aminosulphide (138) sequentially with trifluoroacetic acid, and then ozone at -78° furnished the required sulphoxide trifluoroacetate (134) in quantitative

yield. The structure was fully supported by spectral and microanalytical evidence, which also indicated the absence of by-products produced as a result of over-oxidation.

Having successfully carried out this series of reactions on the model compound pyrrolidine, we applied the reaction sequence to the synthesis of the crown series (Scheme 12). Attempted reaction between mono-aza-18-crown-6 (122) and the ethyl ester (136) failed to produce significant amounts of the corresponding tertiary amide (139). Clearly, the secondary amino function of crown (122) is too sterically hindered to react, unless forcing conditions are employed.

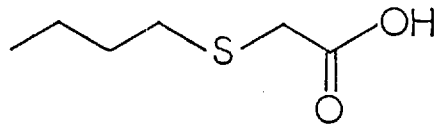


(122) (139)

(140)

Scheme 12

Consequently, a less direct approach was examined. Basic hydrolysis of ethyl ester (136) in aqueous tetrahydrofuran, readily furnished the corresponding carboxylic acid (141), in 95% yield after distillation.

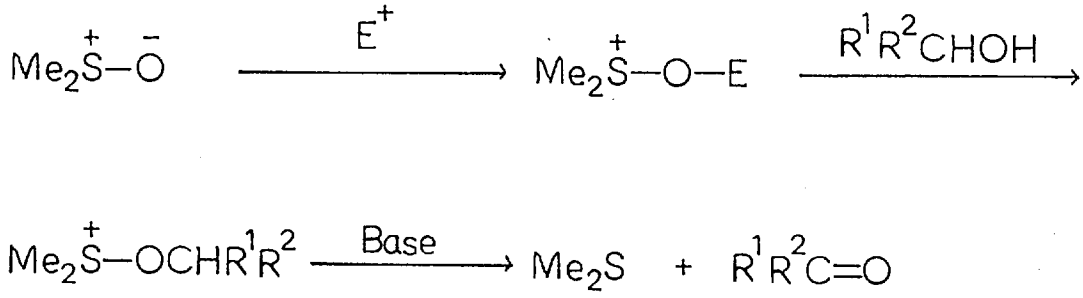


(141)

Subsequent reaction with sodium hydride and oxalyl chloride gave 3-thia-heptanoyl chloride. Reaction *in situ* with mono-aza-18-crown-6 (122), in the presence of triethylamine then afforded the required amide (139) in 85% yield, after chromatography on alumina. Amide (139) gave spectral and analytical data consistent with the given structure.

Reduction with borane-tetrahydrofuran under the same conditions employed in the model system, afforded the novel aminosulphide (140) cleanly and in high yield (94%). This compound was obtained in analytical purity by chromatography on alumina. Attempted distillation at reduced pressure consistently resulted only in decomposition.

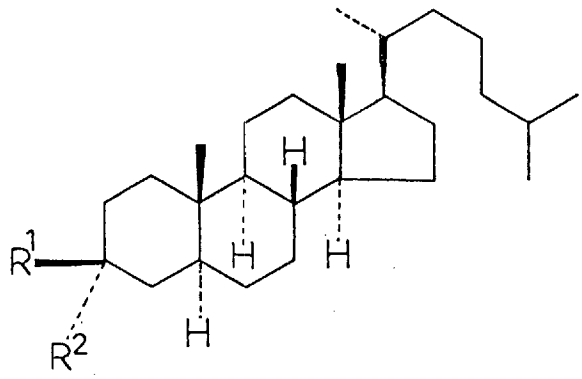
Treatment of dimethyl sulphoxide with electrophilic "activators" (E^+) has found wide application in the oxidation of alcohols to carbonyl compounds (Scheme 13).[114]



Scheme 13

Recently, Swern and Omura have carried out a systematic comparison of a series of activators[115]. However, all of the systems studied required the use of excess oxidising agent to obtain good yields of carbonyl products. Clearly, the present study required an oxidising system which would operate effectively when only one equivalent was employed. We therefore resolved to examine the available systems, in an attempt to find one which would meet our requirements. The results of the oxidation studies are summarised in Table 8 (Experimental Section).

Oxidation of 5α-cholestan-3β-ol (142), according to the procedure of Pfitzner and Moffatt[116] (dimethyl sulphoxide/dicyclohexylcarbodi-imide/ trifluoroacetic acid) gave 5α-cholestan-3-one (143) in only 36% yield



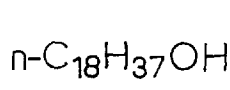
(142) R_1 = OH, R_2 = H

(143) R_1 = R_2 = O

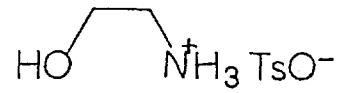
when stoichiometric amounts of reagent were used. Clearly, this method was of little use in the present study. Oxidation of the same steroidal alcohol (142) with dimethyl sulphoxide, activated with trifluoroacetic anhydride[117], afforded the corresponding ketone (143) in reasonable yield (74%). Under essentially the same conditions, however, use of the sulphoxide (134) led to the formation of ketone (143) in only 29% yield. Corey and

Kim[118] have reported the use of dimethyl sulphide/N-chlorosuccinimide as an effective oxidising system. However, on treatment with an equivalent amount of dimethyl sulphide and N-chlorosuccinimide at -20°, 5α-cholestan-3β-ol (142) gave ketone (143) in moderate yield (50%). Furthermore, replacement of dimethyl sulphide with the aminosulphide (138), in the presence of one equivalent of trifluoroacetic acid to prevent oxidation of the tertiary amino function, resulted in negligible reaction.

Oxalyl chloride was shown by Swern[115] to be the most efficient activator of dimethyl sulphoxide. However, the sulphoxide (134), activated by treatment with oxalyl chloride, reacted with alcohol (142) at -78° to give after work-up the ketone (143) in only 25% yield. At -10°, a complex mixture of products was produced. Oxidation of the primary alcohol (144) at -60° was unproductive possibly as a result of the low solubility of the substrate.



(144)



(145)

The oxidation of the toluene-4-sulphonate salt (145) in the presence of 18-crown-6 was also examined as this combination closely resembled the intended host-guest system. However, no identifiable oxidation products could be detected on treatment with dimethyl sulphoxide activated with oxalyl chloride, under a variety of experimental conditions.

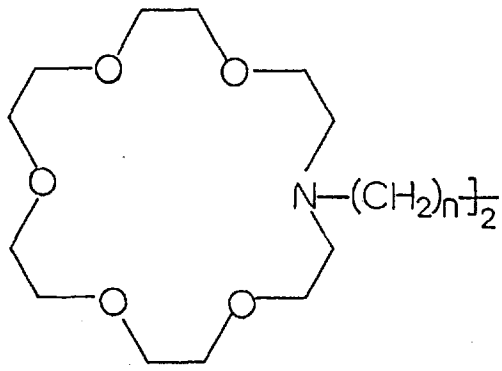
It was concluded that regioselective intramolecular oxidation would be impracticable with the reagents herein described.

2.2 APPROACHES TOWARDS MULTIPLE RECOGNITION IN A HOST-GUEST SYSTEM

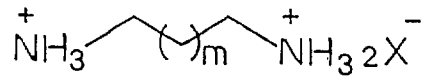
Much effort has been directed in recent years towards the design of synthetic and semi-synthetic host-guest systems which may mimic, in a relatively simple way, some of the enzymic processes which occur in living systems. This research may lead not only to the discovery of synthetically useful molecular catalysts, but also to a greater understanding of the binding forces involved in molecular complexation. One of the more interesting aspects of this work has been the design and synthesis of more elaborate host molecules which demonstrate increased binding selectivity for guest molecules possessing two or more recognition elements. However, very few examples have been reported in the literature.

Notably, Sutherland has recently demonstrated[119] that host molecules of the type (146), consisting of two aza-crown ether moieties linked together by a simple alkyl chain, show binding specificity for dialkylammonium salts of the type (147). Such complexation probably involves simultaneous binding of the two alkylammonium groups of the guest molecules (146) by the two complementary polar binding sites of the host molecules. As mentioned above several examples of multiple recognition have also been reported in the area of cyclodextrin chemistry. Most recently Tabushi's 'Duplex Cyclodextrin' (16), which possesses two hydrophobic binding sites, shows binding selectivity for methyl orange, a guest molecule with two complementary hydrophobic residues[37].

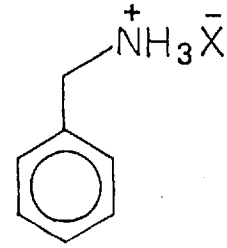
It was the aim of this work to design and synthesise a novel host molecule which would show for the first time, selectivity in binding for a guest molecule possessing both polar ($-\overset{+}{N}H_3$) and non-polar ($-CH_2Ph$) groups, such as a benzylammonium salt (148) or phenylalanine (149). In the latter case, the formation of a soluble complex in non-aqueous media, and the subsequent preparation of a phenylalanine derivative, such as a dipeptide, without recourse to conventional protecting group methodology, was an intriguing



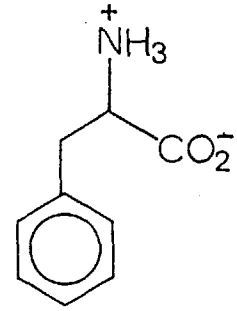
(146)



(147)



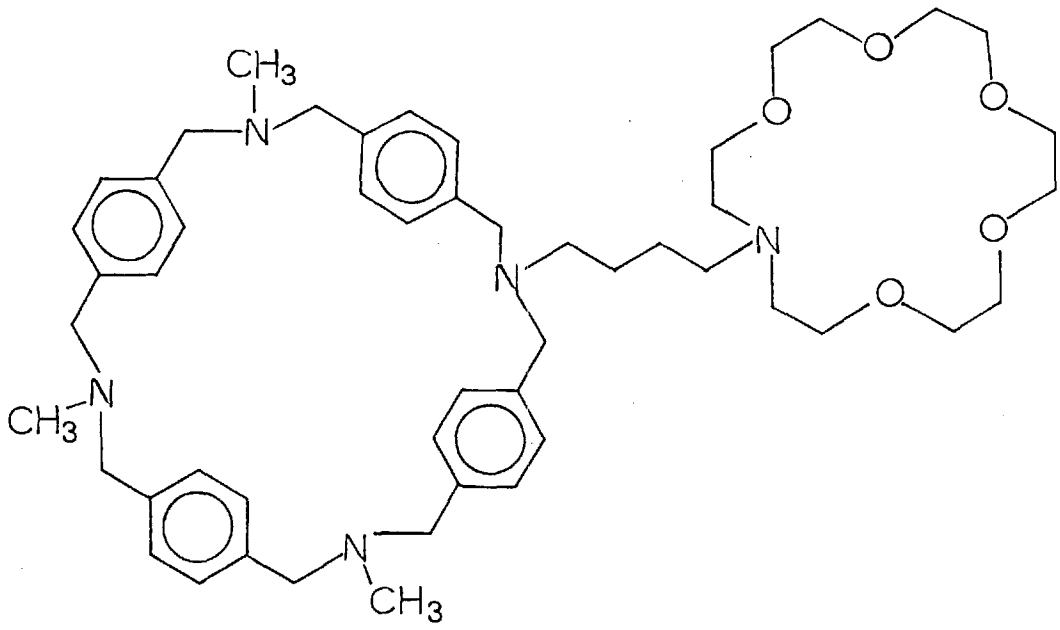
(148)



(149)

prospect.

CPK Models indicated that the novel bicyclic molecule (150) which consists of an N-substituted mono-aza-18-crown-6 unit linked by a four

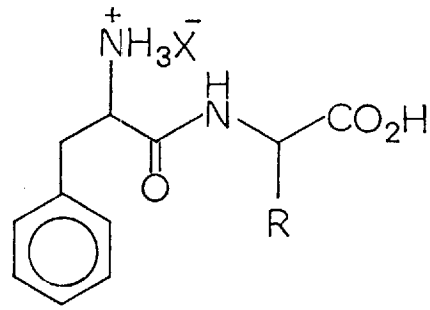


(150)

or five carbon alkyl chain to a [3.3.3.3]heterocyclophane would be suitable for our purposes. The alkylammonium group of the guest molecules, in a hypothetical 1:1 complex between host (150) and either guest (148) or (149) can bind in the well established face-to-face mode to the polar binding site. At the same time, the benzyl group can be readily accommodated within the hydrophobic cavity of the [3.3.3.3]heterocyclophane unit.

Symmetrical [3.3.3.3]heterocyclophanes have been shown to possess rigid, well-defined hydrophobic cavities due to the preferred 'face' conformation adopted by the aromatic rings of the heterocyclophane skeleton[62]. Furthermore, these compounds form inclusion complexes in solution with small aromatic molecules, with a 1:1 stoichiometry[62], with binding strengths comparable to, and in some cases greater than, the cyclodextrins. An added advantage over the cyclodextrins is that there is far less functionality present in the heterocyclophane systems which should thus facilitate both selective monosubstitution and purification procedures.

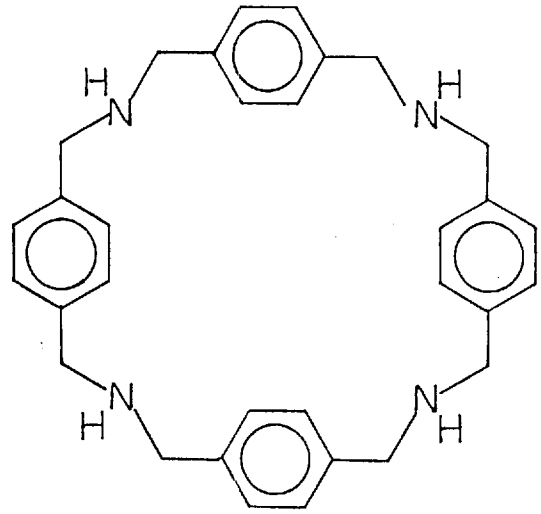
The hypothetical complex presents an overall hydrophobic surface, and may therefore be reasonably soluble in non-polar solvents, thus strengthening polar interactions between host and guest. On the other hand, the presence of five tertiary amino functions should promote solubility in aqueous solution at low pH, thus favouring the comparatively weak hydrophobic interactions. In the case of the phenylalanine complex, however, the carboxylate function appears from the model to be too sterically hindered to permit chemical transformation. However, it was predicted that this may be possible with the complex between host (150) and a suitably chosen dipeptide salt, such as (151) in which the carboxyl function is more exposed.



(151)

It was therefore undertaken to synthesise the host molecule (150) by a convergent route and to study the complexation behaviour with guests (148) and (149).

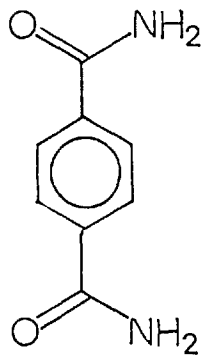
Prior to this work, no methodology was available for the preparation of unsymmetrically substituted [3.3.3.3]heterocyclophanes. It was resolved to synthesise the symmetrical secondary tetramine (152) by a procedure based on Urushigawa's synthesis of the permethylated derivative [61], and then to devise a means of selective monofunctionalisation, which made use



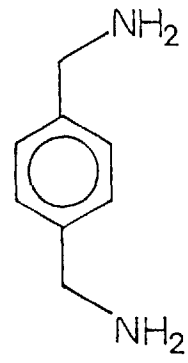
(152)

of the complexing ability of these compounds.

Initial attempts to prepare heterocyclophane (152) were unsuccessful. Thus, treatment of terephthaloyl chloride (55) with ammonia gave terephthalamide (153), which on reduction with lithium aluminium hydride in refluxing tetrahydrofuran afforded 1,4-xylylenediamine (154). Reaction with terephthaloyl chloride (55), under high dilution conditions, then gave rise to an insoluble mixture of polymeric amides as evidenced by infrared spectroscopy. Subsequent reduction of the crude product mixture with lithium aluminium hydride gave a complex mixture of polyamines, from which the desired product (152) could not be isolated. Clearly, in view of the



(153)

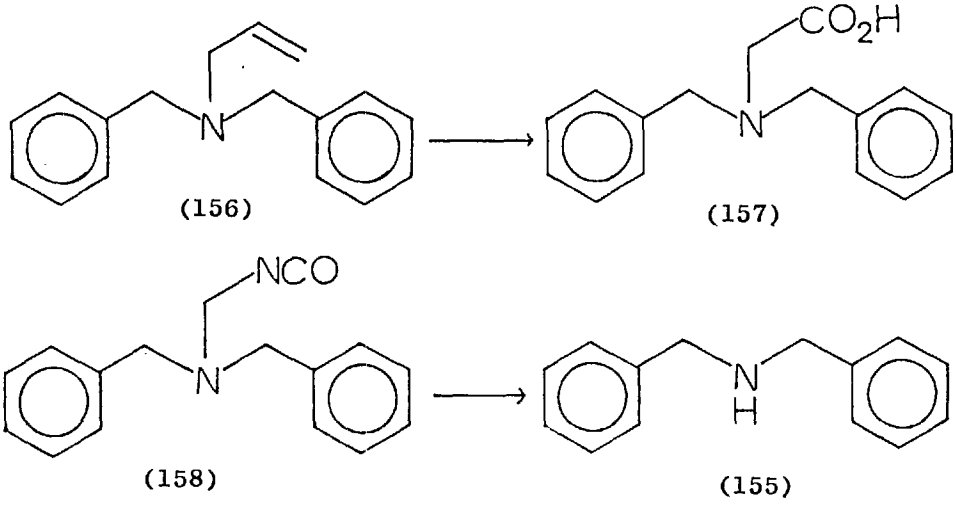


(154)

difficult isolation of the product (152) by this method, an alternative less direct approach was necessary.

It was reasoned that the problem could be overcome by the preparation of a [3.3.3.3]heterocyclophane, symmetrically substituted with an alkyl blocking group which could (a) increase the solubility, (b) decrease the polarity - thus facilitating purification by conventional chromatography, and (c) be removed selectively and cleanly in the presence of the benzylic functions present in the heterocyclophane skeleton. In order to select a suitable group which could meet all of these criteria, some preliminary model studies were undertaken.

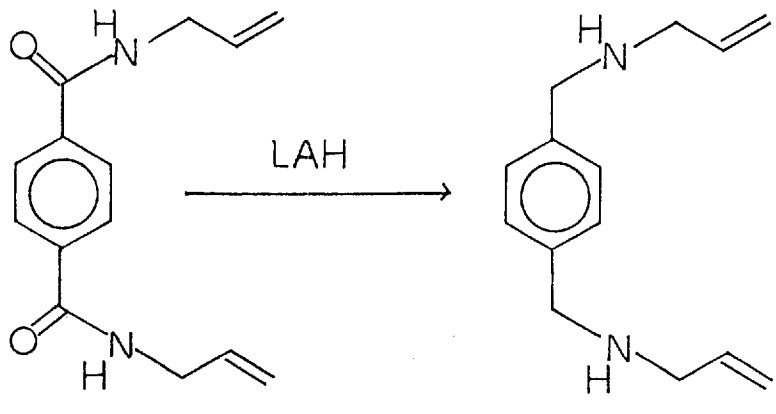
Derivatives of dibenzylamine (155) were chosen for study, as this compound is readily available, and possess essentially similar structural features to the heterocyclophane system. The N-allyl derivative (156) was subsequently prepared in 85% yield, by the treatment of dibenzylamine (155)



Scheme 14

with allyl bromide in the presence of sodium hydride. It was proposed to regenerate the secondary amine (155) by the degradative sequence outlined in Scheme 14. Thus, ozonolysis of an acidic solution of the tertiary amine (156), followed by an oxidative work-up, was expected to result in the formation of the α-amino acid (157). Subsequent conversion to the corresponding acid azide derivative, followed by Curtius rearrangement would then afford the isocyanate (158) which on acid hydrolysis should then cleanly afford the required product (155), via formation of an acid-labile geminal diamine. In the event, dibenzylamine (155) was produced directly in the first step. Ozonolysis of a solution of N-allyldibenzylamine (156) in hydrochloric acid, followed by treatment with hydrogen peroxide yielded an unidentified solid substance which, on basification, afforded dibenzylamine (46%) characterised as the known N-toluene-4-sulphonyl derivative. However, at this stage it was apparent that problems were arising in the macrocyclic system, and consequently this reaction was not investigated further.

Treatment of terephthaloyl chloride (55) with allylamine furnished the corresponding diamide (159) in excellent yield. However, subsequent reduction with lithium aluminium hydride in refluxing tetrahydrofuran (Scheme 15) gave, in addition to the expected product (160), significant

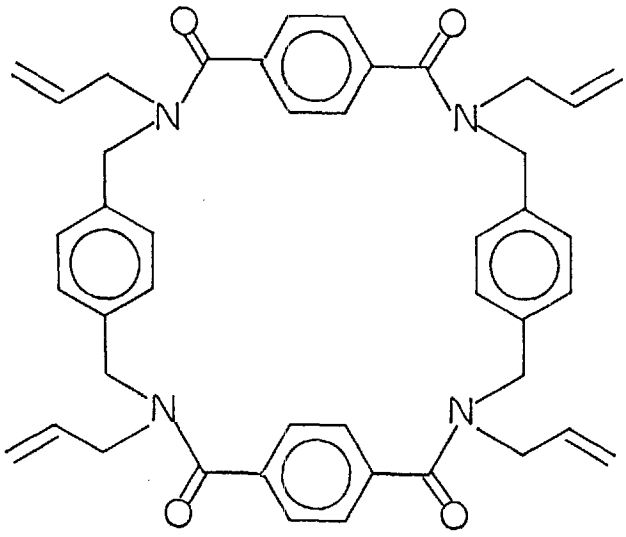


(159) (160)

Scheme 15

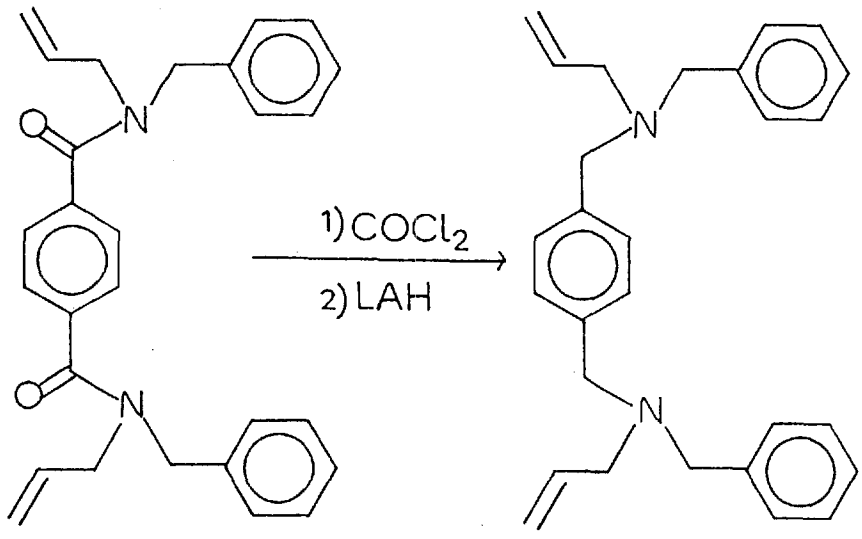
amounts of diamines bearing saturated n-propyl substituents as a result of alkene reduction. Analogous behaviour has been observed[120] in the lithium aluminium hydride reduction of cinnamic acid to dihydrocinnamyl alcohol via cinnamyl alcohol. In this case, the situation was remedied by the application of an inverse addition technique. This was not possible in the case of diamide (159) owing to its low solubility in ether solvents and its resistance to reduction.

The diamide (162) was prepared as a model for the intermediate macrocyclic tetra-amide (161) which would be produced in the preparation of the



(161)

corresponding [3.3.3.3]heterocyclophane (152). Alkylation of diamide

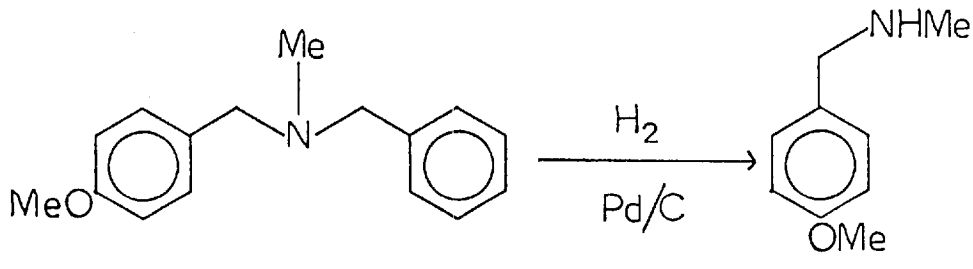


(162) (163)

Scheme 16

(159) was readily effected in 85% yield by treatment with benzyl bromide in the presence of sodium hydride. It was proposed to obviate over-reduction of diamide (162) by prior conversion to the corresponding Vilsmeier salt which should be more susceptible to reduction by lithium aluminium hydride. This was achieved by reaction with phosgene at 0^{o} as evidenced by infrared spectroscopy. Subsequent reduction with lithium aluminium hydride (Scheme 16) gave a mixture of products, including the required diamine (163) in low yield (16.6%). Clearly the use of the allyl protecting group was unsatisfactory.

In view of the greater stability of the 4-methoxybenzyl cation relative to the benzyl cation, as a result of the stabilising influence of the 4-methoxy group, it seemed plausible that some degree of selectivity could be achieved in the dealkylation of a tertiary amine bearing both types of substituent. Debenzylation of amines is a synthetically useful transformation. Most commonly, the reaction is effected by catalytic hydrogenolysis[121]. However, early studies on competitive debenzylation by Baltzly and Buck[122] revealed that, in general, unsubstituted benzyl groups are preferentially cleaved. Indeed, tertiary amine (164) is quantitatively converted to secondary amines (165) by exclusive hydrogenolysis of the N-benzyl bond (Scheme 17).

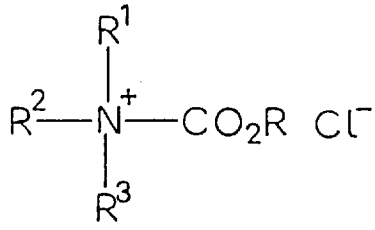


(164) (165)

Scheme 17

The classical von Braun dealkylation procedure[123], in which tertiary amines, usually methylamine derivatives are cleaved by cyanogen bromide to give disubstituted cyanamides and alkyl bromides as products, has been shown to selectively remove 4-methoxybenzyl groups[124]. The synthetic utlity of this reaction in the present study was marred by the expected resistance to hydrolysis of the disubstituted cyanamide product.

More recently alkyl chloroformates have been reported as efficient dealkylating agents[125,126,127]. The reaction involves nucleophilic attack by the amine at the carbonyl group of the chloroformate to form an intermediate of type (166). Subsequent dealkylation by chloride ion affords a



(166)

ROCOCl

(167) R = CCl_3-CH_2-

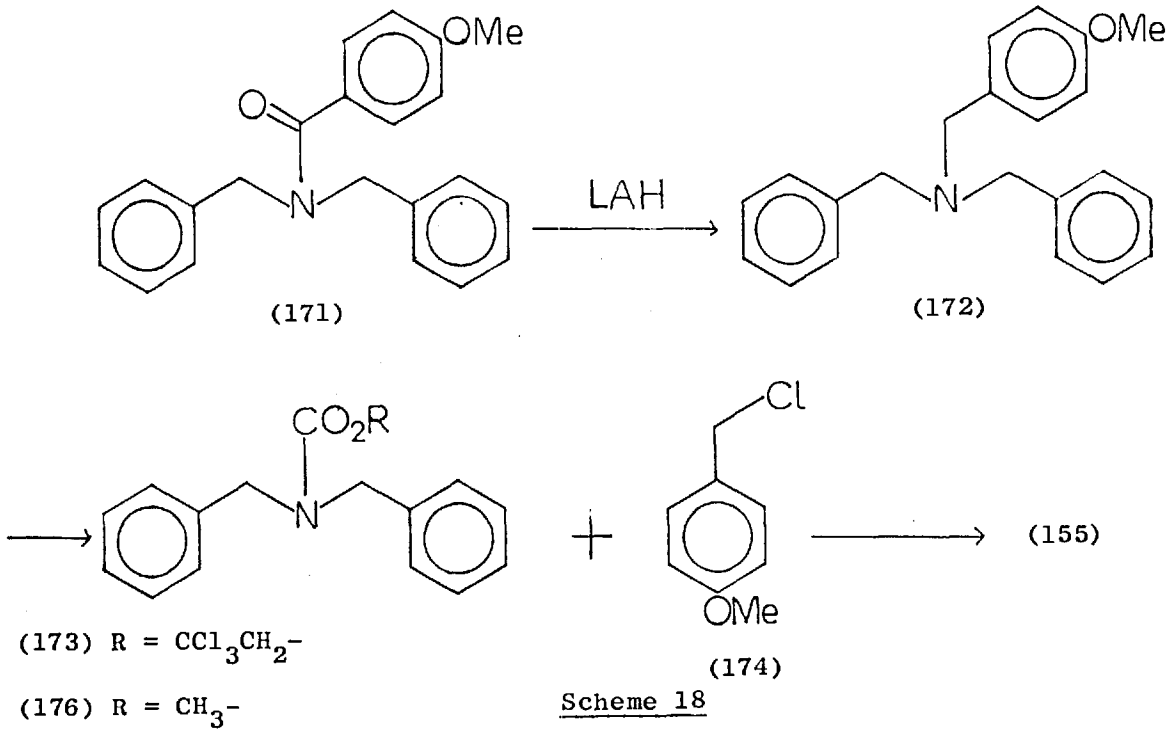
(168) R = CH_2=CH-

(169) R = TMS-CH_2-CH_2-

(170) R = CH_3-

carbamate and an alkyl chloride. One of the main advantages of this method is that carbamates derived from chloroformates (167)[125], (168)[126], (169)[127] are readily deprotected to the corresponding secondary amine under mild conditions. However, no work has been reported on competitive debenzylation in these systems.

The model compound N-(4-methoxybenzyl)-dibenzylamine (172) was therefore prepared. Acylation of dibenzylamine (155) with 4-methoxybenzoyl chloride gave the corresponding amide (171) in 85% yield. Subsequent reduction with lithium aluminium hydride furnished the required product in excellent yield (98%). Reaction of tertiary amine (172) with 2,2,2-trichloroethyl chloroformate (167) rapidly and cleanly gave the corresponding carbamate derivative (173) and 4-methoxybenzyl chloride (174) in high yield (Scheme 18). Significantly, no other products were detectable,

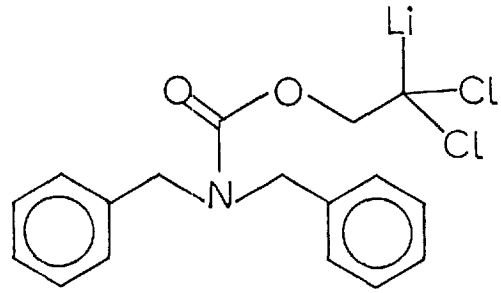


Scheme 18

thus demonstrating the expected greater lability of the N-(4-methoxybenzyl) bond relative to the N-benzyl bond. The 2,2,2-trichloroethyl carbamate (173) was also readily available in quantitative yield by the action of chloroformate (167) on dibenzylamine (155).

However, deprotection to the secondary amine (155) by zinc metal reduction proved to be unsatisfactory, leading to unwanted side-reactions. Thus, on treatment with zinc dust in aqueous acetic acid, 2,2,2-trichloro-carbamate (173) afforded a mixture of products, including dibenzyl-amine (155) which was isolated as its benzamide derivative in 78% yield after chromatography. Similarly, zinc reduction of carbamate (173) in refluxing methanol, yielded dibenzylamine (155) as the major product (75%). In both cases, the neutral by-products were not characterised. Clearly, an alternative mode of deprotection was required which would minimise the occurrence of unwanted side-reactions. The reaction of carbamate (173) with t-butyllithium at low temperature was therefore examined. It seemed plausible that initial lithiation of the substrate via cleavage of one of the C-Cl bonds, and subsequent decomposition of the metallated species (175)

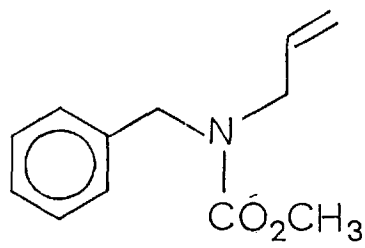
in a fashion analogous to the zinc metal reduction, would lead to clean deprotonation.



(175)

However, reaction of carbamate (173) with t-butyllithium at -100°, followed by warming at room temperature, led to the production of a mixture of products, of which dibenzylamine (155) was the major component (71%).

Methyl chloroformate (170), however, reacted with N-(4-methoxybenzyl) dibenzylamine (172) comparatively slowly to give the corresponding methyl carbamate (176) in 79% yield, together with unreacted starting material (Scheme 18). The carbamate (176) was identical to an authentic sample, which was prepared by the action of methyl chloroformate on dibenzylamine. As before, no other carbamates resulting from N-benzyl cleavage were detectable. On basic hydrolysis (potassium hydroxide-methanol), methyl carbamate (176) cleanly gave dibenzylamine (155) in quantitative yield. Interestingly, N-allyldibenzylamine (156) on treatment with methyl chloroformate, rapidly afforded carbamate (177) in high yield, thus demonstrating preferential

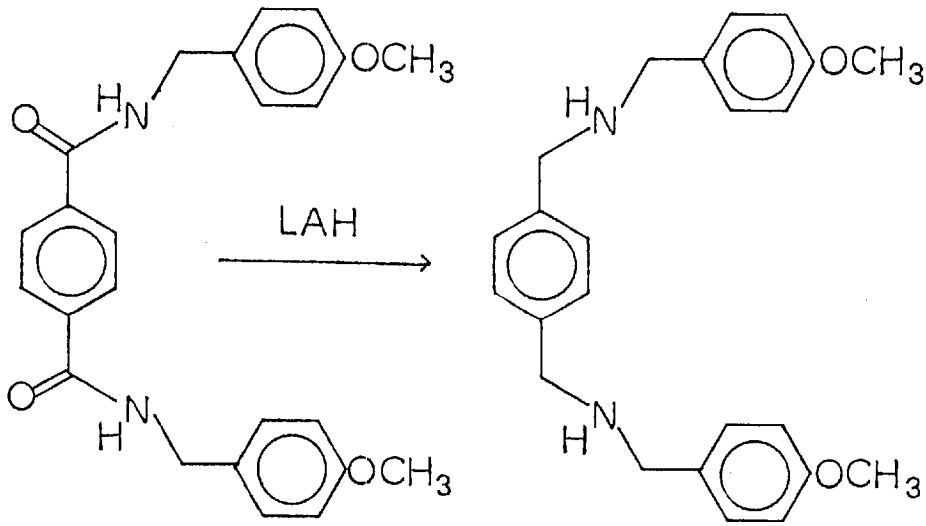


(177)

cleavage of the N-benzyl bond in the presence of an N-allyl bond. On reaction with trimethylsilyl iodide, generated *in situ* by the action of iodine on hexamethyldisilane[128], N-(4-methoxybenzyl)-dibenzylamine (172) gave four major products.

Having established a system which worked reasonably well in the model series, we then turned our attention to the synthesis of the suitably functionalised symmetrical [3.3.3.3] heterocyclophane.

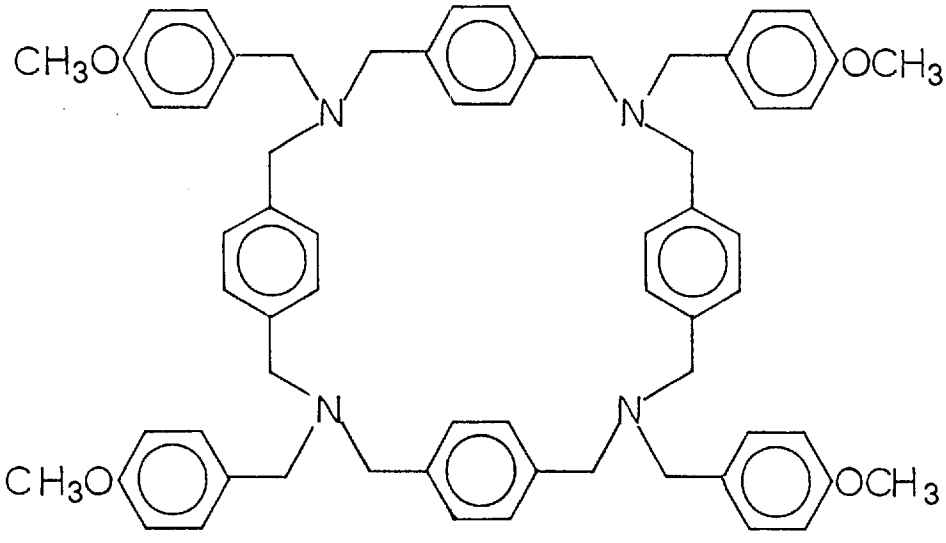
Treatment of 4-methoxybenzoic acid sequentially with thionyl chloride and then ammonia gave 4-methoxybenzamide in 92% yield. Subsequent reduction with lithium aluminium hydride in refluxing tetrahydrofuran then afforded 4-methoxybenzylamine in high yield (87%). Reaction of terephthaloyl chloride (55) with two equivalents of 4-methoxybenzylamine in the presence of triethylamine rapidly and quantitatively gave the analytically pure symmetrical diamide (178).



(178) (179)

Scheme 19

Subsequent reduction with lithium aluminium hydride proceeded smoothly to give symmetrical diamine (179) (Scheme 19), which was microanalysed



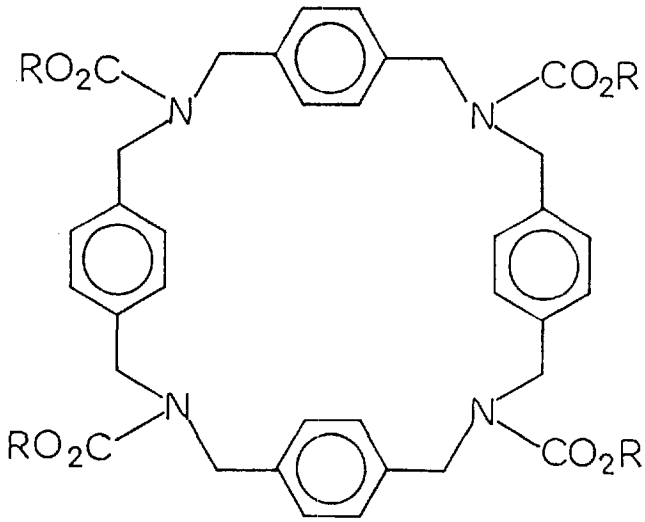
(180)

as its hydrochloride salt.

Cyclisation was effected by reaction between terephthaloyl chloride (55) and the symmetrical diamine (179) under high dilution conditions similar to those of Urushigawa *et al*[61]. Thus, dilute solutions of acid chloride (55) and diamine (179) were slowly added simultaneously to a large volume of rapidly stirred refluxing benzene and triethylamine. Such conditions ensure low concentrations of reactants, thereby optimising cyclisation and minimising linear polymerisation. The crude mixture of polymeric amides obtained in this reaction was then reduced with lithium aluminium hydride. Repeated chromatography on silica of the resulting mixture of polyamines afforded N,N',N'',N'''-tetra-(4-methoxybenzyl)-2,11,20,29-tetraaza[3.3.3.3]paracyclophane (180). The yields for this reaction, using relatively unsophisticated apparatus were of the order of 16-19%. Contrary to the findings of Murakami *et al*[67], who isolated larger homologues in a similar reaction, heterocyclophane (180) was the only detectable macrocyclic product. The proposed structure was entirely supported by analytical and spectral data. In particular, the highly symmetrical structure was evidenced by relatively simple nmr spectra (^{1}H and ^{13}C).

Removal of the 4-methoxybenzyl substituents to furnish the required [3.3.3.3]heterocyclophane (152) proved to be more problematical than expected

from the results of the model system. Thus, treatment of [3.3.3.3] heterocyclophane (180) with methyl chloroformate (170) in dichloromethane solution at reflux for seven days gave rise to a mixture of products, from which the desired product, tetracarbamate (181), was isolated by chromatography in only 61% yield. The other products of the reaction, most plausibly reaction intermediates resulting from incomplete reaction, were not characterised.



(181) R = Me-

(182) R = CCl_3CH_2-

(183) R = CCl_2=CH-

Attempted basic hydrolysis of the tetracarbamate (181) also proceeded extremely slowly, giving an inseparable mixture of polar products. On the other hand, treatment of [3.3.3.3]heterocyclophane (180) with 2,2,2-trichloroethyl chloroformate (167) smoothly gave the corresponding tetracarbamate (182) and 4-methoxybenzyl chloride in excellent yield. The reaction was carried out in refluxing carbon tetrachloride and conveniently monitored by ^1H nmr spectroscopy, which indicated quantitative reaction within seventeen hours. Tetracarbamate (182), however, was resistant to zinc metal reduction under the same conditions employed in the model system. No satisfactory explanation could be found for this phenomenon. Furthermore, the use of activated zinc[129], led to a complex mixture of

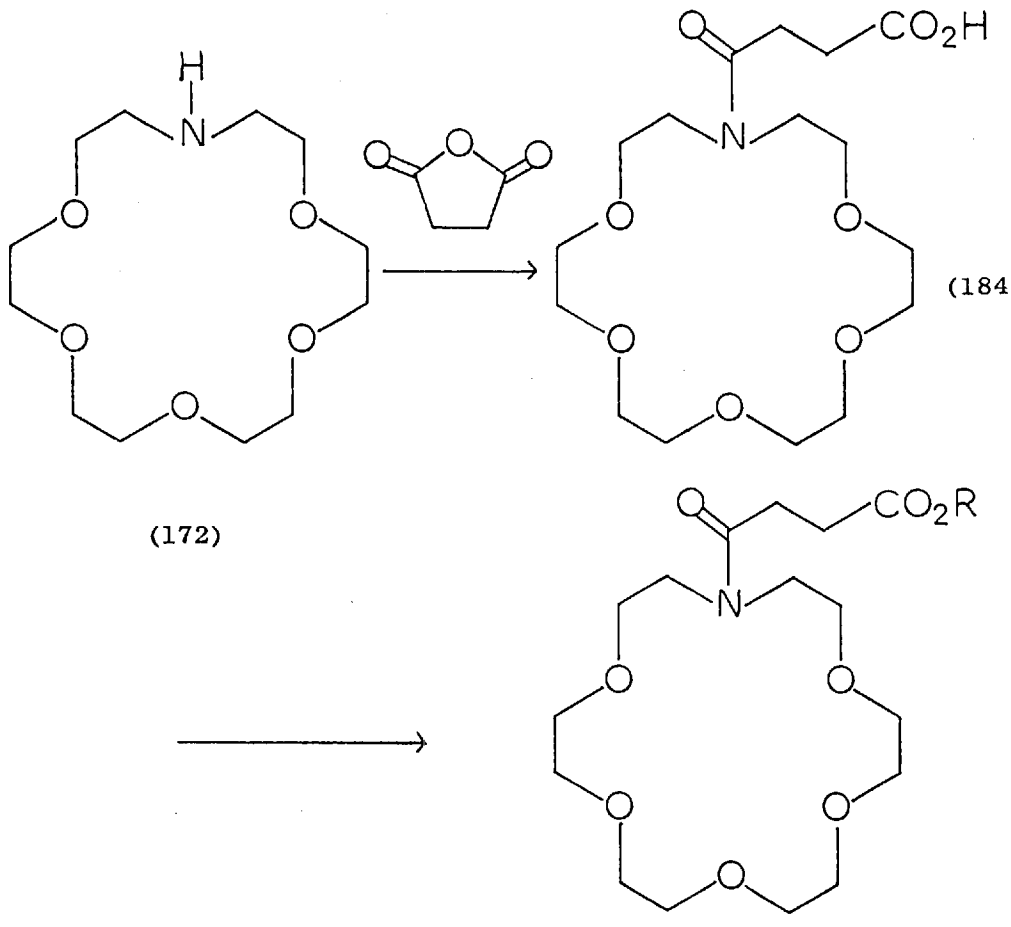
products. Mass spectral analysis indicated the presence of N-methylated derivatives, most plausibly arising from over-reduction. However, this reaction was not investigated further.

Treatment of tetracarbamate (182) with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in refluxing benzene furnished the tetracarbamate derivative (183), by elimination of four equivalents of hydrogen chloride. Although this compound failed to give a satisfactory mass spectrum, the structure was strongly supported by microanalysis and by ^{1}H nmr and ir spectroscopy. Attempts to generate the desired product (152) by treatment sequentially with hydrogen chloride and then ethanol, according to the procedure of Olofson *et al*[126] were unsuccessful.

Hydrolysis of tetracarbamate (182) with potassium hydroxide in aqueous methanol afforded the corresponding tetramethylcarbamate (181) in high yield. The product was identical to the authentic sample. However, on heating with potassium hydroxide in aqueous dioxan at 150° for five days, tetracarbamate (182) was quantitatively hydrolysed to the required [3.3.3.3] heterocyclophane (152). The structure was confirmed by spectral evidence and by accurate mass measurement of the molecular ion in the mass spectrum. In view of the air-sensitivity of this compound, it was further characterised as the hydrochloride salt, which analysed as the dihydrate.

Having successfully prepared [3.3.3.3]heterocyclophane (152), it was therefore necessary to devise a suitable method of selective reaction of one of four identical secondary amine functions. It was reasoned that this might be achieved by the use of a 4-nitrophenyl ester, which might complex within the macrocyclic ring of the substrate and subsequently react to form a mono-amide. Bender[30] and Breslow[40] have used analogous approaches to effect selective monofunctionalisation of the C-3 secondary hydroxyl functions in the cyclodextrin field.

With this aim in mind, the synthesis of the novel 4-nitrophenyl ester (186) was undertaken. Succinic anhydride was chosen as a convenient synthon for the four carbon unit linking together the two binding sites in the target molecule (150). Thus, mono-aza-18-crown-6- (122), on treatment with one equivalent of succinic anhydride in tetrahydrofuran, in the presence of sodium hydride, led to the quantitative formation of the



Scheme 20

(185) R = Ph_2-CH-
(186) R = 4-NO_2.C_6H_4-

carboxylic acid (184) as a polar oil (Scheme 20). Carboxylic acid (184) was fully characterised by conversion to the corresponding benzhydryl ester (185), formed as a chromatographable oil in 80% yield, by treatment with diphenyldiazomethane in dichloromethane solution at room temperature. Sequential treatment of carboxylic acid (184) with sodium hydride and then oxalyl chloride furnished the acid chloride derivative. However, subsequent

reaction with 4-nitrophenol gave rise to a complex mixture of products, from which the desired ester (186) could only be isolated in low yield.

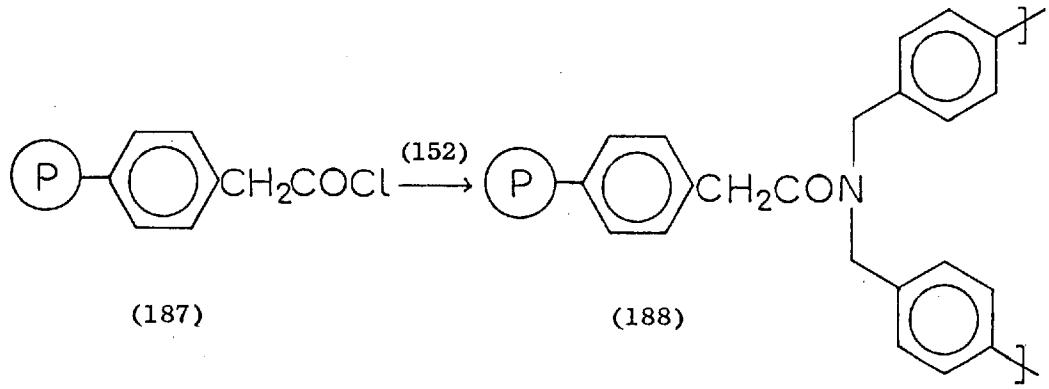
Bodanzky and du Vigneaud have reported[130] the synthesis of 4-nitrophenyl esters of carbobenzoxy amino acids by reaction with 4-nitrophenol in the presence of dicyclohexylcarbodi-imide. Under the same conditons, carboxylic acid (184) gave the desired 4-nitrophenyl ester (186) cleanly and in high yield (93%).

Treatment of the symmetrical [3.3.3.3]heterocyclophane (152) with 4-nitrophenyl ester (186) in dichloromethane at room temperature, however, gave rise to a mixture of inseparable polar products together with unreacted starting material. Significantly, under the same reaction conditions the model compound dibenzylamine (155) failed to react, thus strongly indicating that complexation may have been occurring between the reactants in the former reaction, thereby increasing the reaction rate. No direct spectroscopic evidence, however, was obtained to further support this theory. Methylation of the crude product mixture was effected by treatment with formic acid and paraformaldehyde[131]. Subsequent chromatography on alumina afforded the known[61] permethylated derivative (57, n = 1) as the major product (49.5%) together with a mixture of more polar products. Analysis of the mixture by mass spectroscopy failed to indicate the presence of the required diamide product. The possibility of amide hydrolysis during the methylation step was not discounted.

Hydrophobic binding is strongest in polar media. However, treatment of heterocyclophane (152) with the 4-nitrophenyl ester (186) in aqueous solution at pH 5 was unproductive. A less direct approach was therefore adopted. The reaction between heterocyclophane (152) and 1-naphthoyl chloride was examined under a variety of conditions in both polar and non-polar media, as it was thought that this might also lead to monofunction-

alisation via prior complexation. In the event, complex product mixtures resulted. Furthermore, the absence of the desired monosubstituted product was demonstrated by mass spectral analysis of the product mixtures.

Selective monofunctionalisation of symmetrical long-chain diamines in high yield, using a polymer-supported reagent, has been reported[132]. We reasoned that reaction of the polymer-bound acid chloride (187)[133] with the symmetrical heterocyclophane (152) might lead to selective monofunction-



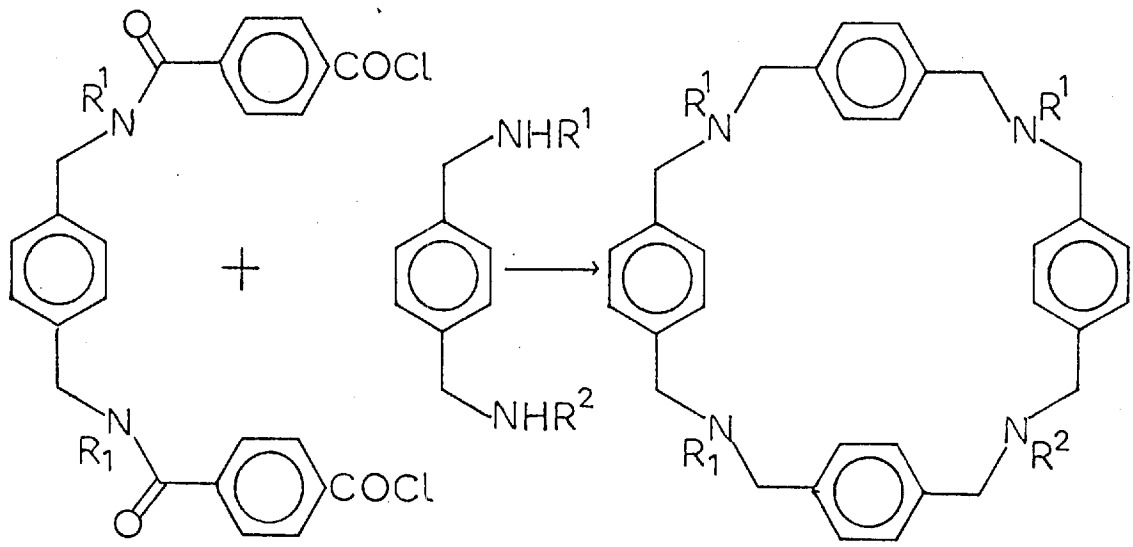
(187) (188)

Scheme 21

alisation to give the polymer-bound intermediate (188), subsequent to methylation and hydrolysis (Scheme 21).

The required polymer-bound acid chloride (187) was prepared in a short synthetic sequence from chloromethylated styrene-divinyl benzene copolymer according to the method of Kusana and Hayatso[133]. However, sequential treatment with heterocyclophane (152) in pyridine, formic acid-paraformaldehyde (reflux, two days) and then potassium hydroxide (dioxan-water, reflux six days) gave only a small amount of heterocyclophane (152). Clearly, the methylation step was unproductive even under the conditions employed. This approach was not examined further.

A consideration of the mechanism for the cyclisation reaction between terephthaloyl chloride (55) and a symmetrical diamine revealed a potentially more direct route to the required unsymmetrically substituted [3.3.3.3]heterocyclophane (191, $R_1 \neq R_2$) which might obviate the need for selective monosubstitution of the symmetrical compound (152). Clearly, several permutations are possible which could give rise to a macrocycle containing four para-substituted aromatic rings. One likely possibility, however, involves initially the reaction between one molecule of symmetrical diamine and two molecules of dicarboxylic acid chloride to afford the corresponding adduct (189).

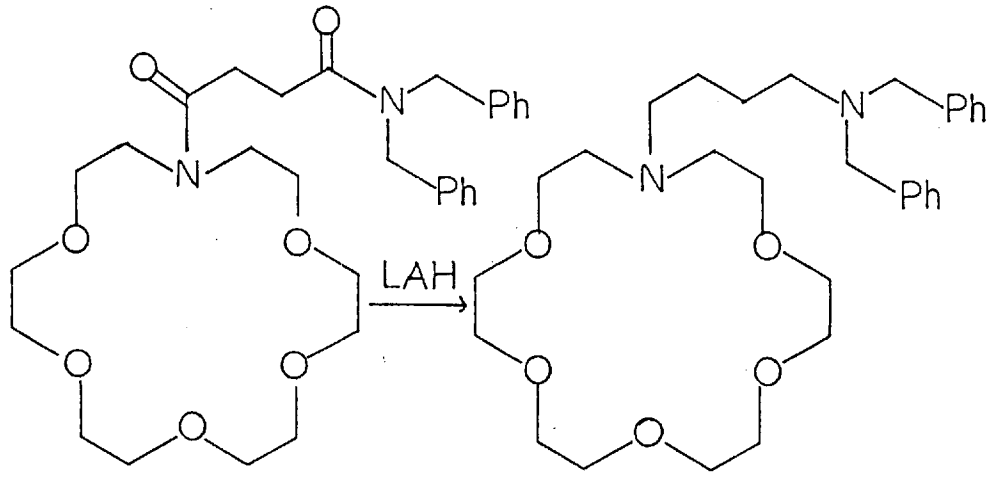


(189) (190) (191)

Scheme 22

Under the high dilution conditions of the cyclisation reaction, this intermediate may then react in a stepwise manner with a second molecule of diamine (190, $R_1 = R_2$) to give, after reduction, the [3.3.3.3]heterocyclophane (191, $R_1 = R_2$) (Scheme 22). It was therefore resolved to synthesise the dicarboxylic acid chloride (189) separately, and then to examine its reaction with an unsymmetrical diamine of the type (190, $R_1 \neq R_2$).

Model experiments indicated that once having successfully prepared the [3.3.3.3]heterocyclophane (191, R_1 = Me, R_2 = H), the remainder of the final product could be assembled readily. Thus, sequential treatment of the carboxylic acid (184) with sodium hydride and then oxalyl chloride gave the corresponding acid chloride derivative, which reacted with dibenzylamine (155) to afford the novel di-amide (192) in 55% yield after



(192) (193)

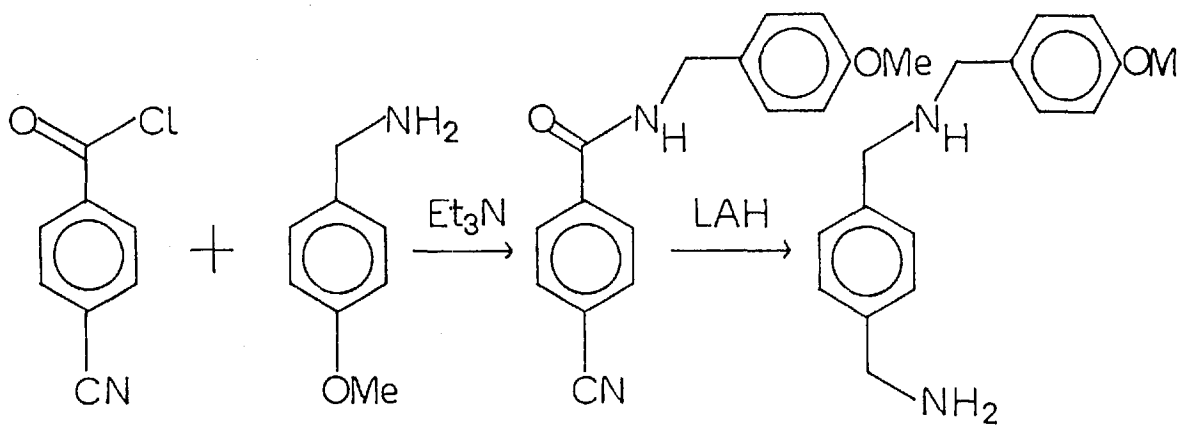
Scheme 23

chromatography (Scheme 23). Subsequent reduction with lithium aluminium hydride in refluxing tetrahydrofuran resulted in the smooth quantitative production of the corresponding diamine (193) as a polar oil. The proposed structure was entirely consistent with the spectral data. Further confirmation was provided by conversion to the crystalline dihydrochloride salt.

The unsymmetrical diamine (197) was chosen for study, as the presence of a 4-methoxybenzyl substituent would aid isolation of the final product and would permit further structural modification if necessary, using the methodology developed earlier. Thus, N-(4-methoxybenzyl)-4-cyanobenzamide (196) was readily prepared by the treatment of 4-methoxybenzylamine with

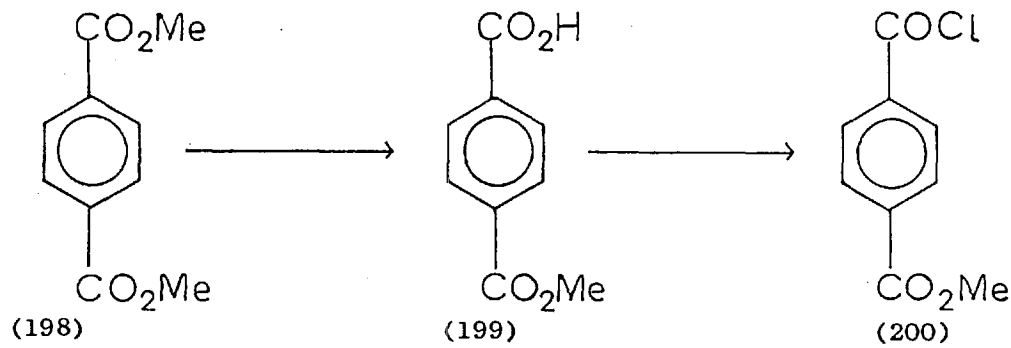
4-cyanobenzoyl chloride (194) (Scheme 24). Subsequent reduction (lithium aluminium hydride, refluxing tetrahydrofuran) afforded the desired unsymmetrical diamine (197) in 91% yield. Diamine (197) was microanalysed as its crystalline di-hydrochloride salt.

Dimethyl terephthalate (198) was prepared in excellent yield by treatment of terephthaloyl chloride (55) with methanol. Careful basic hydrolysis with one equivalent of methanolic potassium hydroxide in toluene gave the monomethyl ester of terephthalic acid (199). Subsequent

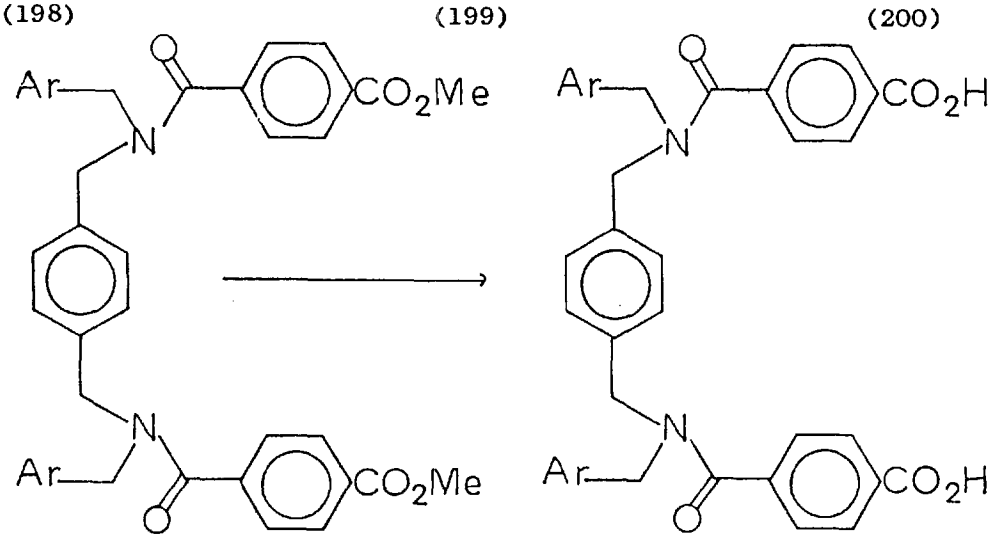


(194) (195) (196) (197)

Scheme 24



(198) (199) (200)



(201) (202)

Scheme 25

conversion to the corresponding acid chloride (200) with thionyl chloride, and then reaction with symmetrical diamine (179) afforded the dimethyl ester (201) in 86% yield after chromatography on silica. Finally basic hydrolysis, followed by acidification, gave the required dicarboxylic acid (202) (Scheme 25).

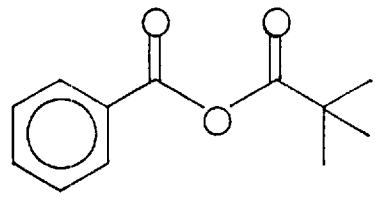
However, problems were encountered in the formation of the corresponding dicarboxylic acid chloride derivative. Treatment with oxalyl chloride in the presence of triethylamine resulted in the formation of acid chloride as evidenced by ir spectroscopy. Subsequent reaction with methanol gave the dimethyl ester (201) in only 70% yield after chromatography. Similarly, the dicarboxylic acid chloride generated by treatment of acid (202) with thionyl chloride in the presence of triethylamine, gave a 65% yield of ester (201). More vigorous conditions resulted in degradation of the amide functions. The reaction of the dicarboxylic acid chloride with symmetrical diamine (179) was studied first as this was expected to result in the production of the previously prepared [3.3.3.3]heterocyclophane (180).

The reaction carried out under high dilution conditions as before, afforded, after reduction, the macrocycle (180) in 6% yield after repeated chromatography on silica. Encouraged by this result, despite the low yield, we then attempted the reaction with the unsymmetrical diamine (197). However, in this case we were unable to isolate any of the required product.

In view of the apparently unsatisfactory formation of the di-acid chloride derivative, and the resulting poor performance in the cyclisation step, it was resolved to examine some alternative activated acid derivatives with the aim of developing a more effective system. The di-imidazolide derivative was readily prepared by treatment of the dicarboxylic acid (202) with 1,1'-carbonyldi-imidazole in the presence of base. These derivatives have found application in the synthesis of esters and amides[134].

However, on reaction with methanol, the corresponding dimethyl ester (201) was isolated in only 59% yield after chromatography. Clearly, there was no advantage to be gained by using this system.

Mixed anhydrides of N-protected amino acids with trimethylacetic acid have been used in peptide synthesis[135]. As a model system, we chose to examine the regioselectivity of the reactions between benzylamine and dibenzylamine with benzoic trimethylacetic anhydride (203). Dibenzylamine reacted with the anhydride (203) at room temperature to give exclusively



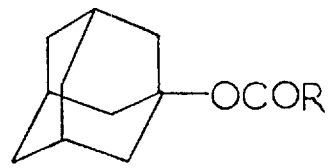
(203)

N,N-dibenzylbenzamide as a result of nucleophilic attack at the less hindered carbonyl function. However, on treatment with benzylamine both N-benzylbenzamide and N-benzyltrimethylacetamide were formed in the ratio 56:44 as determined by ^{1}H nmr spectroscopy. Clearly, the less hindered amine showed little discrimination between the two carbonyl functions.

Undeterred by this result, we resolved to attempt the cyclisation reaction between unsymmetrical diamine (197) and the mixed anhydride of dicarboxylic acid (202) with trimethylacetic acid. Thus, on treatment with trimethylacetyl chloride, in the presence of triethylamine, the dicarboxylic acid (202) gave the corresponding mixed anhydride derivative, as evidenced by ir spectroscopy. Attempted cyclisation with the unsymmetrical diamine (197) under high dilution conditions as before, afforded a mixture of polymeric amides. Subsequent reduction with lithium aluminium hydride in refluxing tetrahydrofuran gave a mixture of products which was separated by chromatography on silica. However, all of the major products were shown to possess tert-butyl groups by ^{1}H nmr spectroscopy, indicating that nucleophilic

attack at the supposedly more hindered trimethylacetyl carbonyl group had predominated.

The reactions between the mixed anhydride (204) and benzylamine and dibenzylamine was also examined. Mixed anhydride (204) was prepared by treatment of 1-adamantyl chloroformate[136] with triethylammonium benzoate. In this case, rapid attack by benzylamine at the less hindered benzoyl carbonyl group predominated, giving N-benzylbenzamide as the major product in 80% yield. Carbamate (205) was also isolated in 16% yield after

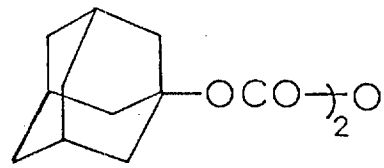


(204) R = PhCO.O-

(205) R = $PhCH_2$.NH-

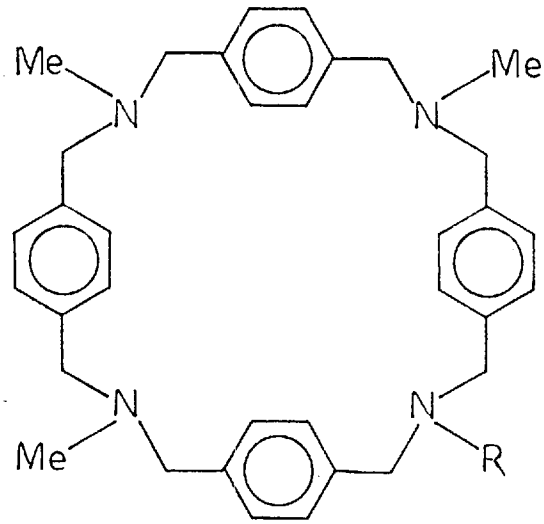
(206) R = $(PhCH_2)_2N$-

chromatography. In direct contrast and quite unexpectedly, dibenzylamine reacted slowly with mixed anhydride (204) to give carbamate (206) as the major product in 88% yield. A small amount of N,N-dibenzylbenzamide was also isolated, contaminated with adamantan-1-ol. Clearly, it is inconceivable that the more hindered amine would preferentially attack the more hindered carbonyl group of mixed anhydride (204). More plausibly, the reaction involves the intermediacy of a carbonic anhydride intermediate (207)



(207)

Other work in this department has recently[137] led to the synthesis of the unsymmetrical [3.3.3.3]heterocyclophane (207) in 9% yield *via* an analogous route. Selective removal of the 4-methoxybenzyl substituent, in the presence of the *N*-methyl groups, using the methodology developed herein is currently underway. One can envisage an even more direct unambiguous route to the required final product (150), *via* the intermediacy of the unsymmetrical [3.3.3.3]heterocyclophane (208). Subsequent oxidation to the corresponding carboxylic acid, and conversion to the acid chloride derivative, should lead directly to the final product on reaction with mono-aza-18-crown-6 (122).

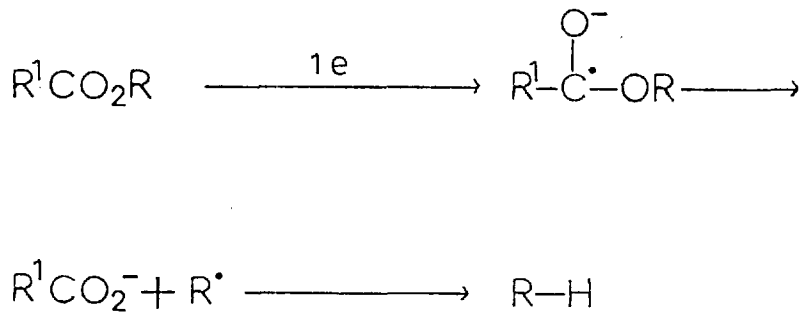


(207) R = 4-MeO.$C_6H_4CH_2$-

(208) R = HO$(CH_2)_4$-

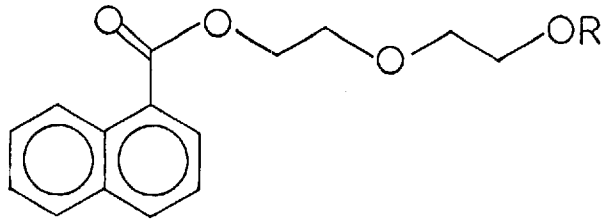
2.3 DISSOLVING METAL REDUCTIONS

The deoxygenation of alcohols and their derivatives to the corresponding alkanes is a synthetically important reaction. The subject has recently been reviewed by Prokopiou[138]. Barton *et al*[139] have demonstrated that selective deoxygenation of sterically hindered alkyl carboxylic esters can be effected in moderate yield by reduction with potassium and 18-crown-6 in t-butylamine. The mechanism was thought to involve the addition of one electron to the substrate, followed by alkyl-oxygen cleavage of the resulting radical anion to give the alkyl radical and the carboxylate anion (Scheme 26). Subsequent reduction to the carbanion and protonation by the solvent gave alkane.



Scheme 26

The concomitant formation of the alcohol component of the ester substrate in these reactions was later shown[140] to result, at least in part, from competitive deacylation of the ester by alkoxide fragments derived from the crown ether under the reaction conditions. Competitive hydrolysis by adventitious water was ruled out. Acylation of the crown ether fragments with 1-naphthoyl chloride gave a complex mixture of products, including esters (209), (210) and (211).

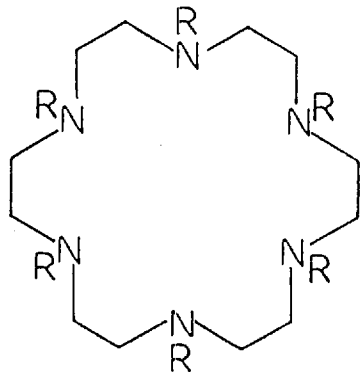


(209) R = H

(210) R = CH_2CH_2OEt

(211) R = $(CH_2CH_2O)_2Et$

It was postulated that a nucleophile-free medium could be obtained by using a nitrogen analogue of 18-crown-6 which would be expected to be less suceptible to cleavage under the reducing conditions. Hexamethyl-hexa-aza-18-crown-6 (213) was therefore prepared by treatment of hexa-aza-18-crown-6 (212)[141] with formic acid and paraformaldehyde[131].



(212) R = H

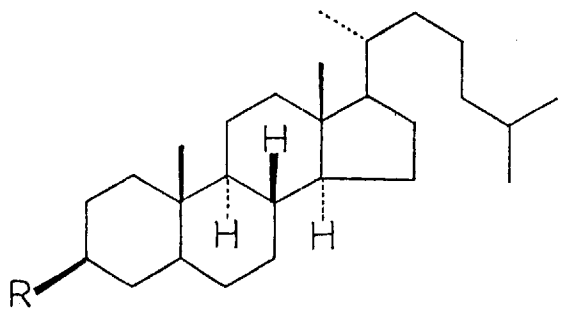
(213) R = Me

The product (213), a colourless, air-sensitive oil was isolated by bulb-to-bulb distillation at reduced pressure in 92% yield. The spectral and analytical data were entirely consistent with the assigned structure.

Preliminary experiments, however, showed that hexamethyl-hexa-aza-

18-crown-6 (213) and potassium metal in dry t-butylamine failed to produce the characteristic dark blue solutions readily available in the presence of 18-crown-6. Clearly, under these conditions the metal was insufficiently soluble to give significant electron concentration. Interestingly, CPK models indicated that the bulky N-methyl groups on alternate nitrogen atoms of the macrocycle (213) effectively obscured both faces of the molecule, possibly disfavouring complexation of the potassium cation. Fortunately, in the presence of sodium-potassium eutectic, an intense dark blue solution was obtained which was stable at room temperature for at least several days.

Having developed a suitable nucleophile-free system, we examined the reduction of a selection of esters (Table 9) (Experimental Section).



(214) R = Me_3CCO_2-

(215) R = H

(216) R = 1-adamantanyl - CO_2-

3β-(2,2-Dimethylpropanoyloxy)-5α-cholestane (214) on reduction gave the deoxygenated product 5α-cholestane (215) in 73% yield and 5α-cholestan-3β-ol (142) in 15% yield. Addition of the ester substrate (214) to the reducing system in one portion led to a reduced yield of deoxygenated product (215) and increased formation of alcohol (142). Strictly anhydrous

conditions were maintained throughout, thus eliminating the possibility that the alcohol was arising through concomitant hydrolysis. Consistent with the results obtained with potassium and 18-crown-6[139,140], reduction of the more hindered adamantane-1-carboxylic ester (216) of 5α-cholestan-3β-ol led to even greater deoxygenation (90%). Even esters of primary alcohols were deoxygenated under these conditions. Thus, octadecan-1-yl acetate (217) gave octadecane (218) (33%) and octadecan-1-ol (219) (61%).

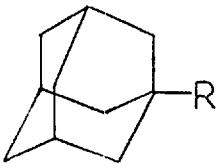
$n\text{-}C_{18}H_{37}OCOR$ $n\text{-}C_{18}H_{38}$ $n\text{-}C_{18}H_{37}OH$

(217) R = CH_3- (218) (219)

(220) R = 1-adamantyl

Greater deoxygenation (49%) was observed when the substrate was added as a solution in t-butylamine instead of tetrahydrofuran. In this case, the reaction mixture was kept at 25° for three days and, on quenching with acetic acid, afforded in addition to the expected products (218) and (219), a small amount of starting material. Formation of the enolate form of the substrate was suggested to explain this phenomenon. The ester was shown to be resistant towards nucleophilic attack by the solvent in a separate experiment. The more hindered adamantane-1-carboxylic ester (220), in keeping with the earlier results, was deoxygenated in 74% yield. Clearly, the reducing system developed herein has greater synthetic potential, and merits further investigation.

On performing the blank experiment, we discovered that the deoxygenation of hindered esters could be realised in high yield with 18-crown-6 in t-butylamine in the presence of the sodium-potassium eutectic. A preliminary study of the effects of temperature variation on the reaction of the adamantane-1-carboxylic ester (216) was carried out (Table 10) (Experimental Section).



(221) R = CO_2H

(222) R = CH_2OH

Clearly, deoxygenation to afford alkane (215) and carboxylic acid (221) is suppressed at low temperatures. These results are consistent with those of Barton *et al* [140] for lithium in ethylamine, who concluded that the radical anion fragmentation reaction had a finite but low activation energy. At low temperatures, competitive two-electron Bouveault-Blanc reduction, giving 1-admantane methanol (222) and 5α-cholestan-3β-ol (142), takes place.

CHAPTER 3

EXPERIMENTAL

Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Ultraviolet spectra were recorded on a Unicam SP 800 B ultraviolet spectrophotometer. Infrared spectra were recorded on a Perkin Elmer 298 or 257 grating infrared spectrophotometer. Nmr spectra were recorded on a Varian T60 or a Perkin Elmer R32 spectrometer, using tetramethylsilane as an internal reference. Analytical thin layer chromatography (tlc) was performed on Merck precoated GF_{254} silica or F_{254} (Type E) alumina plates. Preparative layer chromatography (plc) was performed on GF_{254} silica or H (type 60/E) alumina plates. Medium pressure chromatography was carried out on Merck Kieselgel H (type 60) silica or H (type 60/E) alumina.

Solvents were purified as follows: Benzene, toluene - redistilled, sodium dried. Chloroform, dichloromethane, ethyl acetate - redistilled, dried if necessary over 4A molecular sieves. Diethyl ether - redistilled, dried if necessary over sodium wire. Dioxan, tetrahydrofuran - redistilled from potassium/benzophenone ketyl. N,N-Dimethylformamide - redistilled at reduced pressure from 4A molecular sieves onto 4A molecular sieves. Ethanol, methanol - AnalaR reagents. Light petroleum - redistilled b.p. 40-60° fraction. Pyridine - redistilled from potassium hydroxide and stored over 4A molecular sieves. Triethylamine - redistilled from sodium and stored over sodium wire. Reagents were purified according to standard procedures [142].

Organic solutions were routinely dried over anhydrous sodium or magnesium sulphate. Solvents were evaporated at reduced pressure using a rotary evaporator at or below 40° unless otherwise stated.

Microanalyses and mass spectral measurements were carried out by the respective laboratories at Imperial College.

Preparation of D,L,N,N-dibenzylglutamic acid (111)

To a stirred solution of glutamic acid (110) (25.00 g, 0.1699 mol) in 50% aqueous ethanol containing sodium hydroxide (27.18 g, 0.6795 mol), was added benzyl bromide (58.13 g, 0.3398 mol) dropwise over a period of 20 min. The resultant two-phase mixture was heated to reflux for 1 h. Tlc analysis of an aliquot after acidification (silica, n-butanol / acetic acid / water, 8:2:1) indicated the formation of two less polar uv and ninhydrin active products. After heating to reflux for a further 24 h, tlc analysis indicated no further change. Equimolar amounts of benzyl bromide and sodium hydroxide were subsequently added until reaction was complete. The reaction mixture was cooled to room temperature, and excess benzyl bromide removed by separation. The resultant yellow solution was evaporated to half volume *in vacuo* and acidified with dilute hydrochloric acid to give a white gummy precipitate. Crystallisation was induced by the addition of ethanol and storage at 4^{o} overnight. The crystalline solid was filtered at the pump, washed with acetone to remove traces of benzyl alcohol and dried *in vacuo* at R.T. to afford the title compound (111) (38.41 g, 69%), m.p. 200^{o} dec (lit.[99] $211-212^{o}$); ν_{max} 3500-2400 cm^{-1} (-OH str.), 1720 (carboxylic acid C=O str), 1600 (carboxylate C=O str.), 1585, 1240, 1175, 1000, 960, 935, 923, 770, 725, 690; m/e 326 (M^{+}-1) 310, 282, 219, 174, 146, 91.

Preparation of D,L-N,N-dibenzyl-2-aminopentan-1,5-diol (112)

To a vigorously stirred suspension of lithium aluminium hydride (0.5810 g, 15.29 mmol) in dry redistilled tetrahydrofuran (50 ml) at 0^{o} was carefully added, N,N-dibenzyl glutamic acid (111) (2.500 g, 7.645 mmol) in small portions. After the initial exothermic reaction had subsided (approx. 1 h), the resultant green reaction mixture was heated to reflux under an atmosphere of nitrogen. Tlc analysis (silica, ethyl acetate) of an aliquot indicated complete reaction after 90 min. The reaction mixture was cooled to 0^{o} and quenched by the slow dropwise addition of saturated sodium sulphate solution. The resultant precipitate was filtered off at the pump, and leached with diethyl ether (x 3). The combined filtrate was evaporated *in vacuo* to give a colourless oil, which was redissolved in dichloromethane (100 ml), dried (Na_2SO_4), filtered and evaporated to give *the title compound* as a colourless oil which solidified on standing (2.286 g, 99%), m.p. 58-61^{o}; ν_{max} (CH_2Cl_2), 3620 cm^{-1}, 3450, 2935, 2865, 1605, 1500, 1365, 1120, 1070, 1030; ^{1}H nmr ($CDCl_3$) δ 1.55 (4H, m), 2.50 (2H, br.s, exch.D_2O, -OH), 2.90 (1H, m), 3.60 (4H, m), 3.60 (4H, s, aryl-CH_2-), 7.30 (10H, br. s, aryl-H); m/e 299 ($M^{+\cdot}$), 281 ($M^{+\cdot}$ -H_2O), 268 ($M^{+\cdot}$ - CH_2OH), 91 (100). A sample was purified by bulb-to-bulb distillation (Kugelrohr) (176-7^{o}/5 x 10^{-3} mmHg) (Found: C, 76.39; H, 8.53; N, 4.72. $C_{19}H_{25}NO_2$ requires: C, 76.22; H, 8.42; N, 4.68%).

Preparation of D,L-2-aminopentan-1,5-diol (108)

A stirred solution of freshly distilled N,N-dibenzyl-2-aminopentan-1,5-diol (112) (1.3738 g, 4.595 mmol) in absolute ethanol (25 ml) containing trifluoroacetic acid (0.5239 g, 4.595 mmol) was hydrogenated at room temperature and atmospheric pressure in the presence of 10% Pd/C catalyst (500 mg). The theoretical uptake of hydrogen (220 ml) was

absor ed after 72 h. The reaction mixture was filtered through a plug of celite and neutralised by the addition of sodium hydride (1.1 equiv. 100%). When effervescence had ceased, the solution was filtered and evaporated *in vacuo*. Bulb-to-bulb distillation (Kugelrohr apparatus) at reduced pressure gave 2-aminopentan-1,5-diol (108) as a colourless hygroscopic oil (280 mg, 50.8%), b.p. ($120^{o}/10^{-4}$ mmHg); ν_{max} (film) 3300 cm^{-1} (-O-H str., -N-H str.), 2920, 2850 (C-H str.), 1600, 1100 (C-O str.); ^{1}H nmr (CF_3CO_2H) δ_H 1.50 (4H, m, $-\underline{CH}_2-\underline{CH}_2$), 3.20-4.40 (5H, complex m, $O-\underline{CH}_2-$, $C-\underline{H}$); m/e 120 (M^{+} +1), 88 (M^{+} - CH_2OH), 71, 60 (Found: C, 50.69; H, 10.95; N, 11.39. Calc. for $C_5H_{13}NO_2$: C, 50.40; H, 10.99; N, 11.76%).

Preparation of 3,6,9-Tri-oxa-undecan-1,11-diyldi-toluene-4-sulphonate (116)

A solution containing redistilled 3,6,9-trioxa-undecan-1,11-diol (50.0 g, 0.2575 mol) in dry pyridine (450 ml, freshly distilled from potassium hydroxide) was cooled to -5^{o} in an ice/salt bath. Toluene-4-sulphonyl chloride (107.5 g, 0.5150 mol, recrystallised from benzene light petroleum) in dry pyridine (300 ml) was added with vigorous mechanical stirring, at such a rate that the temperature of the reaction mixture remained below 2^{o}. The solution was then stirred at 4^{o} for 18 h and poured over crushed ice (500 g). The resulting aqueous solution was thoroughly extracted with dichloromethane (x 4). The organic layers were combined, dried and evaporated at 25^{o} to give a yellow oil. Column chromatography on silica (Kieselgel 60, eluant ethyl acetate) gave pure 3,6,9-trioxa-undecan-1,11-diyldi-toluene-4-sulphonate (116) as a light yellow oil (96 g, 71%), n_D^{21} 1.5243; ν_{max} (film) 3030 cm^{-1} (w, Ar-H str.), 2960, 2920, 2860 (m, C-H str.), 1600 (m, ArC=C str.), 1355 (s, S=O str.),

1175, 1095 (s, C-O str.); λ_{max}(ε) 222 nm (25100), 255 (890), 260 (1130), 263 (1025), 265 (1050), 271 (950); ^{1}H nmr ($CDCl_3$) δ_H 2.40 (6H, s, aryl-$\underline{CH_3}$), 3.55 (12H, m, -O-$\underline{CH_2}$-C-), 4.10 (4H, m, aryl-O-$\underline{CH_2}$-C-), 7.60 (8H, dq, aryl-$\underline{H}$); m/e 502 ($M^{+\cdot}$), 404, 243, 199, 91.

Attempted preparation of N-(2-hydroxyethyl)-1,4,7,10,13,16-penta-oxa-aza-cyclooctadecane (113)

To a solution containing triethanolamine (117) (1.280 g, 8.610 mmol) in dry tetrahydrofuran (100 ml) under an atmosphere of dry nitrogen, was added potassium tert-butoxide (1.92 g, 17.22 mmol) in one portion. The mixture was stirred at room temperature for 30 min, and then a solution of di-toluene-4-sulphonate (116) (4.50 g, 8.61 mmol) in dry tetrahydrofuran (50 ml) was added dropwise over 60 min, with vigorous stirring. After 24 h, the reaction mixture was heated at reflux for 7 days, filtered and evaporated. The residue was extracted with diethyl ether (x 2) and the ethereal solution dried, filtered and evaporated. Tlc analysis (silica, acetonitrile/water/acetic acid, 6:3:2) indicated a mixture of polar products. Attempts at purification were unsuccessful.

Preparation of N-benzyl-2,2'-dihydroxydiethylamine (120)

Benzyl bromide (63.45 g, 0.37 mol) was added dropwise to a solution of 2,2'-dihydroxydiethylamine (118) (39.00 g, 0.37 mol) in redistilled tetrahydrofuran (250 ml) with vigorous stirring. Stirring was continued for a further 1 h at room temperature under an atmosphere of nitrogen. A solution of sodium hydroxide (15.11 g, 0.38 mol) in water (50 ml) was then added dropwise over a period of 90 min. The reaction mixture was refluxed for a further 6 h, cooled and evaporated *in vacuo*. The residue was

thoroughly extracted with dry tetrahydrofuran (250 ml) and filtered at the pump. The resultant clear solution was re-evaporated to give an oil, which was fractionally distilled at reduced pressure to give the title compound (60.60 g, 83%), b.p. 156-7°/0.9 mmHg, (lit.[103] b.p. 162-4°/1.0 mmHg) n_D^{20} = 1.5352; ν_{max} (film) 3350 cm^{-1} (-OH str.), 3100, 3070, 3040 (Ar-H str.), 2950, 2880, 2820 (C-H str.), 1620, 1580 (ArC=C str.), 1245 (C-N str.),1140 (C-O str.); ^{1}H nmr ($CDCl_3$) δ_H 2.60 (4H,t, -$\underline{CH_2}$-N-, $\underline{J}$ 6Hz), 3.50 (4H, t, -$\underline{CH_2}$-O-, $\underline{J}$ 6Hz), 3.60 (2H, s, aryl-$\underline{CH_2}$-), 4.0 (2H, br.s, exch. D_2O, -O$\underline{H}$), 7.25 (5H, s, aryl-H).

Preparation of N-benzyl-1,4,7,10,13,16-penta-oxa-aza-cyclooctadecane (124)

To a solution of N-benzyl-2,2'-dihydroxydiethylamine (120) (20.00 g, 0.10 mol) in dry redistilled N,N-dimethylformamide (1400 ml) was added sodium hydride (4.93 g, 0.21 mol, 100%) in one portion. The mixture was stirred at room temperature under an atmosphere of dry nitrogen for 48 h. A solution of 3,6,9-trioxatridecan-1,11-diyldi-toluene-4-sulphonate (116) (53.57 g, 0.10 mol) in dry redistilled N,N-dimethylformamide (280 ml) was then added dropwise over a period of 3 h, with vigorous stirring. After a further 48 h, the reaction mixture was quenched by the careful addition of water (10 ml) and the solvent removed *in vacuo*. The residue was thoroughly extracted with diethyl ether (x 2) and the organic extracts filtered, dried and evaporated to give a brown oil. Column chromatography (Grade 1 alumina (200 g), eluant diethyl ether) followed by fractional distillation gave the title compound as a light yellow oil (16.99 g, 47%), b.p. 150-2°, 10^{-4} mmHg; (lit. b.p. 190°/0.3 mmHg); ν_{max} (film) 3060 cm^{-1}, 3030 (Ar-H str.), 2925, 2860 (C-H str.), 1605 (Ar-C=C str.), 1125 (C-O str.), 730, 700; ^{1}H nmr ($CDCl_3$) δ_H 2.75 (4H, t, -N-$\underline{CH_2}$-, $\underline{J}$ 6Hz), 3.70 (22H, m, -O-$\underline{CH_2}$- and aryl-$\underline{CH_2}$-), 7.25 (5H, br. s, aryl-$\underline{H}$); m/e 353 (M^+), 206, 149, 120, 91 (100%). A sample was converted to its corresponding *picrate derivative*,

m.p. 77.5-79° (Found: C, 49.91; H, 6.07; N, 9.30. $C_{25}H_{34}N_4O_{12}.H_2O$ requires C, 49.98; H, 6.05; N, 9.33%). In separate experiments, dry tetrahydrofuran was used as solvent without detrimentally affecting the yield.

Preparation of 1,4,7,10,13,16-penta-oxa-aza-cyclooctadecane (122)

N-Benzyl-1,4,7,10,13,16-penta-oxa-aza-cyclooctadecane (124) (5.00 g, 14.16 mmol) was dissolved in ethanol (90 ml) and acetic acid (10 ml) and hydrogenated at atmospheric pressure and ambient temperature in the presence of 10% Pd/C catalyst (400 mg). The theoretical uptake of hydrogen (345 ml) was absorbed in 30 min. The reaction mixture was filtered through celite, and evaporated to dryness. The residue was redissolved in water (25 ml) and the aqueous solution basified, and extracted with dichloromethane (x 3). The combined organic extracts were dried, filtered and evaporated to give a white solid (3.32 g, 89%) which was purified by recrystallisation from acetonitrile at -40°, m.p. 50.5-51.5° (lit. 48-51°); ν_{max} 3340 cm^{-1} (N-H str.) 2900 (C-H str.), 1460, 1380, 1350, 1290, 1250, 1110 (C-O str.); ^1H nmr ($CDCl_3$) δ_H 2.20 (1H, br.s, exch. D_2O, N-H), 2.80 (4H, t, $-CH_2-N$, J 5Hz), 3.70 (20H, complex m, $-CH_2-O-$); m/e 263 (M^+) 248, 233, 232, 220, 205, 189, 176, 150 (Found: C,54.54; H, 9.43; N, 5.21. Calc. for $C_{12}H_{25}NO_5$ C, 54.73; H, 9.57; N, 5.32%). A sample was converted to its corresponding *picrate derivative*, m.p. 89.5-90° (Found: C, 42.15; H, 5.79; N, 10.90. $C_{18}H_{28}N_4O_{12}H_2O$ requires: C, 42.35; H, 5.92; N, 10.98%).

Preparation of N-(toluene-4-sulphonyl)-1,4,7,10,13,16-penta-oxa-aza-cyclooctadecane (125)

To a solution of 1,4,7,10,13,16-penta-oxa-aza-cyclooctadecane (122) (263 mg, 1 mmol) in dry pyridine (4 ml) at 0° was added toluene-4-sulphonyl

chloride (190.6 mg, 1 mmol) portionwise. The reaction mixture was allowed to warm up to room temperature and stirred overnight (18 h). Tlc analysis (silica, acetonitrile/water/acetic acid, 6:3:2) indicated complete reaction. The reaction mixture was diluted with dichloromethane to 25 ml, and washed with cold dilute hydrochloric acid (25 ml). The aqueous phases were re-extracted with dichloromethane. The organic phases were combined, dried and evaporated to give a yellow oil (460 mg). Chromatography on alumina (Alumina H, 20 g, eluant dichloromethane/ethyl acetate) gave the title compound as a colourless oil, homogeneous by tlc (330 mg, 79%); ν_{max} (CH_2Cl_2) 2860 cm^{-1} (C-H str.), 1600, 1100, (C-O str.), 995; ^1H nmr ($CDCl_3$) δ_H 2.40 (3H, br. s, aryl-$\underline{CH_3}$), 3.47-3.63 (24H, m), 7.2-8.0 (4H, m, aryl-$\underline{H}$); m/e 417 (M^+), 360, 286, 262, 198, 155.

Preparation of N,N-di-(2-hydroxyethyl)toluene-4-sulphonamide (121)

Sulphonamide (121) was prepared according to the method of Eisleb[105] m.p. 99-101° (lit.[105] 100-101°); ν_{max} (Nujol) 3220 cm^{-1}, 1595, 1325, 1150, 1075, 890, 875, 820, 660, 640, 630, 610; ^1H nmr ($CDCl_3$) δ_H 2.57 (3H, br. s, aryl-$\underline{CH_3}$), 3.22 (4H, m, -$\underline{CH_2}$-N), 3.8 (6H, m), 7.2-7.8 (4H, m, aryl-$\underline{H}$); m/e 259 (M^+), 241 (M^+-H_2O), 228, 210, 198, 155, 106, 91, 86.

Preparation of N-(toluene-4'-sulphonyl)-1,4,7,10,13,16-penta-oxa-aza-cyclooctadecane (125)

A solution of N,N-di-(2-hydroxyethyl)toluene-4-sulphonamide) (12.95, 0.05 mol) in dry redistilled tetrahydrofuran (100 ml) was slowly added at room temperature to a stirred suspension of sodium hydride (2.60 g, 0.15 mol) in tetrahydrofuran (350 ml) under an atmosphere of nitrogen over a period of 90 min. After a further 2.5 h, a solution of 3,6,9-trioxa-

undeca-1,11-diyldi-toluene-4-sulphonate (116) (25.10 g, 0.05 g) in tetrahydrofuran (100 ml) was added dropwise. The reaction mixture was stirred for 48 h and then quenched by the careful dropwise addition of water (500 ml). The tetrahydrofuran was removed *in vacuo*, and the resultant aqueous solution was extracted with chloroform (x 3). The combined organic phases were dried, filtered and evaporated to give an oil. Chromatography on silica (Kieselgel 60) afforded the title compound as a colourless oil, homogeneous by tlc (silica, acetonitrile/water/acetic acid, 6:3:2) (10.30 g, 46%). The spectral datawere identical to the authentic sample.

Reduction of N-(toluene-4'-sulphonyl)-1,4,7,10,13,16-penta-oxa-aza-cyclooctadecane (125)

(1) To a solution of N-(toluene-4-sulphonyl)-1,4,7,10,13,16-penta-oxa-aza-cyclooctadecane (125) (2.00 g, 5.31 mmol) in dry redistilled tetrahydrofuran (20 ml) under nitrogen was added lithium aluminium hydride (250 mg, 6.56 mmol). The solution was heated to reflux with stirring. Tlc analysis of an aliquot after 48 h (silica, acetonitrile/water/acetic acid 6:3:2), indicated the formation of a mixture of products including 1,4,7,10,13,16-penta-oxa-aza-cyclooctadecane (122). The reaction mixture was cooled to room temperature and quenched by the addition of saturated sodium sulphate solution dropwise with vigorous stirring. Filtration and evaporation yielded a brown oil. Attempts to isolate (122) (by distillation at reduced pressure or crystallisation) were unsuccessful.

(2) To a solution of N-(toluene-4-sulphonyl)-1,4,7,10,13,16-penta-oxa-aza-cyclooctadecane (125) (5.60 g, 13.43 mmol) in liquid ammonia (50 ml) and tetrahydrofuran (50 ml) was added sodium (800 mg, 34.78 mmol). Tlc analysis (silica, acetonitrile/water/acetic acid, 6:3:2) indicated completion within 10 min. The reaction was quenched with ammonium chloride

and the ammonia was evaporated overnight. The resultant solution was evaporated to dryness, and the residue partitioned between water and dichloromethane. The organic phase was dried, filtered and evaporated to afford a mixture, with crown (122) as the major component. Attempts to isolate crown (122) were unsuccessful.

Attempted preparation of N-(2-hydroxyethyl)-1,4,7,10,13,16-penta-oxa-aza-cyclooctadecane (113)

1,4,7,10,13,16-Penta-oxa-aza-cyclooctadecane (122) (500 mg, 1.90 mmol) and ethylene oxide (1.50 g, 34.09 mmol) were heated together in a sealed tube for 18 h. The brown contents of the tube were extracted into dichloromethane and then partitioned with dilute hydrochloric acid. The aqueous phase was extracted with dichloromethane until almost colourless, basified, and then re-extracted with dichloromethane (x 3). The organic layers were combined, dried and evaporated to give a yellow oil (1.33 g). Attempts at further purification were unsuccessful.

In another experiment, a solution containing 1,4,7,10,13,16-penta-oxa-aza-cyclooctadecane (122) (200 mg, 0.76 mmol), sodium hydride (22 mg, 0.92 mmol), imidazole (5 mg, 0.07 mmol) and ethylene oxide (40 mg, 0.90 mmol) in tetrahydrofuran (10 ml) were stirred overnight. Tlc analysis (silica, eluant acetonitrile/water/acetic acid, 6:3:2) indicated negligible reaction. The solution was cooled to 0^{o} and further ethylene oxide (0.45 ml, excess) added. Tlc analysis indicated slight reaction after 1.5 h.

Preparation of ethyl 2-(1,4,7,10,13,16-penta-oxa-aza-cyclooctadecyl)acetate (126)

1,4,7,10,13,16-Penta-oxa-aza-cyclooctadecane (122) (500 mg, 1.90 mmol)

was added in one portion to a solution containing ethyl bromoacetate (317.5 mg, 1.90 mmol) and ethyldi-iso-propylamine (246 mg, 1.90 mmol) in dry freshly distilled tetrahydrofuran (10 ml). The resulting solution was stirred at room temperature under an atmosphere of dry nitrogen for two days, when tlc analysis (silica, eluant acetonitrile/water/acetic acid 6:3:2) indicated complete reaction. The reaction mixture was filtered and evaporated *in vacuo*. The oily residue was redissolved in dichloromethane and washed with water. The organic layer was separated, dried and evaporated. Bulb-to-bulb distillation of the residue gave the title compound as a colourless oil in analytically pure condition (616.8 mg, 93%); bath temperature ($155^{o}/10^{-5}$ mmHg); ν_{max} (film) 2950-2850 cm^{-1} (C-H str.), 1735 (s, ester C=O str.), 1100 (s, C-O str.); ^{1}H nmr ($CDCl_3$) δ_H 1.25 (3H, t, J 8Hz, $-C\underline{H}_3$), 2.90 (4H, t, J 8Hz, $N-C\underline{H}_2$), 3.55 (2H, s, $N-CH_2-CO-$), 3.70 (20H, m, $-O-C\underline{H}_2-C$), 4.20 (2H, q, J 8Hz, $O-C\underline{H}_2C$); m/e 349 (M^+), 276 ($M^+ - CO_2Et$); 246, 188, 100 (Found: C, 55.08; H, 8.84; N, 3.90. $C_{16}H_{31}NO_7$ requires: C, 55.00; H, 8.94; N, 4.01%).

Preparation of N-(2-hydroxyethyl)-1,4,7,10,13,16-penta-oxa-aza-cyclooctadecane (113)

To a solution of ethyl ester (126) (100 mg, 0.29 mmol) in dry tetrahydrofuran (10 ml), was added lithium aluminium hydride (50 mg, 1.32 mmol). The solution was stirred at room temperature under an atmosphere of dry nitrogen. Tlc analysis (silica, acetonitrile/water/acetic acid, 6:3:2) of an aliquot indicated quantitative conversion to a single more polar product. The reaction mixture was quenched by the careful addition of saturated sodium sulphate solution, filtered and evaporated to afford a colourless oil. Bulb-to-bulb distillation ($150/10^{-4}$ mmHg) gave slightly impure alcohol (113) as a colourless oil (85 mg, 97%), ν_{max} (film) 3340

cm^{-1} (O-H str.), 2880, 1355, 1300, 1250, 1100 (C-O str.), 945; ^1H nmr ($CDCl_3$) δ_H 2.77 (6H, t, J 6Hz, N-$\underline{CH_2}$-), 3.67 (25 H, m); m/e 320 (imp.) 308 (M^+ + H), 307 (M^+), 306 (M^+ - H), 276, 246, 232, 188, 158, 100.

Preparation of 4(5)-hydroxymethylimidazole picrate

4(5)-Hydroxymethylimidazole picrate (34.9 g, 50%) was prepared from fructose (36.00 g) according to the procedure of Totter and Darby[111], m.p. 204-5° from water (lit.[111] 204°); ν_{max} (Nujol) 3300 cm^{-1}, 3140, 1635. 1555, 1350, 1280, 1030; ^1H nmr (d_6-DMSO) δ_H 4.60 (2H, s, -$\underline{CH_2}$-O-), 6.90 (3H, br s, D_2O exch.), 7.50 (1H, s, aryl-$\underline{H}$), 8.60 (2H, s, aryl-$\underline{H}$).

Preparation of 4(5)-hydroxymethylimidazole hydrochloride

4(5)-Hydroxymethylimidazole hydrochloride was prepared from the corresponding picrate derivative (94%) m.p. 107-9° from absolute alcohol (lit.[111] 107-9°).

Attempted preparation of 4(5)-imidazolylmethyl 2-(1,4,7,10,13,16)-pentaoxa-aza-cyclooctadecyl)-acetate (129)

Anhydrous toluene-4-sulphonic acid (33 mg, 0.19 mmol) was added to a solution of the ethyl ester (126) (61.5 mg, 0.18 mmol) in dry redistilled dioxan (5 ml), and the mixture stirred under dry nitrogen until homogeneous. 4(5)-Hydroxymethylimidazole hydrochloride (28 mg, 0.178 mmol was then added in one portion and the resultant mixture heated overnight at 140° under reflux with stirring. Tlc analysis (silica, eluant acetonitrile/water/acetic acid, 6:3:2) indicated the presence of starting material only. The solvent was removed *in vacuo*, and the residue heated overnight

at 140°/0.5 mmHg. Tlc analysis indicated slight formation of a more polar product.

Preparation of 4(5)-imidazolylmethyl 2-chloroacetate hydrochloride (130)

To a solution of 4(5)-hydroxymethylimidazole hydrochloride (100 mg, 0.74 mmol) in dry N,N-dimethylformamide (2 ml) at room temperature, was added sodium hydrogencarbonate (62.5 mg, 0.74 mmol) in one portion. The solution was stirred until effervescence had ceased and then filtered from sodium chloride. The resultant clear yellow solution was cooled with vigorous stirring to -30° and chloroacetyl chloride (56 µl, 0.74 mmol) added dropwise via syringe over 5 min. After 30 min, the temperature was allowed to rise to room temperature, and stirring was continued overnight (16 h). The solvent was removed *in vacuo*, and the solid residue recrystallised from absolute ethanol to give *4(5)-imidazolylmethyl 2-chloroacetate hydrochloride* (130) as colourless prisms. (107 mg, 76%); m.p. 140-142° ν_{max} (Nujol) 3160, 3100, 1750 (ester C=O str.), 1635, 1530, 1405, 1320, 1185, 1170, 965, 925; ^{1}H nmr (D_2O) δ_H 4.20 (2H, s, -$\underline{CH_2}$-Cl), 5.20 (2H, s, -$\underline{CH_2}$-O-), 7.50 (1H, m, aryl-$\underline{H}$), 8.70 (1H, m, aryl-$\underline{H}$); m/e 174 (M^+ - HCl), 97 (100) (M^+ -HCl-$COCH_2Cl$), 81 (Found: C, 34.37; H, 3.46; N, 13.10. $C_6H_7ClN_2O_2HCl$ requires C, 34.31; H, 3.36; N, 13.34%).

Attempted preparation of 4(5)-imidazolylmethyl 2-(1,4,7,10,13,16-pentaoxa-aza-cyclooctadecyl)acetate (129)

To a stirred solution of 4(5)-imidazolylmethyl 2-chloroacetate hydrochloride (130) (47 mg, 0.22 mmol) in dry N,N-dimethylformamide (2 ml) was added di-iso-propylethylamine (65 mg, 0.50 mmol). The resulting solution was stirred at room temperature under an atmosphere of nitrogen

for 30 min. 1,4,7,10,13,16-penta-oxa-aza-cyclooctadecane (122) (69 mg, 0.26 mmol) was then added in one portion. Tlc analysis (silica, acetonitrile/water/acetic acid, 6:3:2) of the reaction mixture after 24 h indicated the presence of four more polar products in addition to the starting material. In another experiment, sodium iodide (40 mg, 0.26 mmol) was added to a solution of chloroacetate (130) (53 mg, 0.25 mmol) in dry N,N-dimethylformamide (0.5 ml). After stirring for 30 min, 1,4,7,10,13,16-penta-oxa-aza-cyclooctadecane (122) (66 mg, 0.25 mmol) and di-iso-propylethylamine (87 µl, 0.50 mmol) were added. The solvent was removed *in vacuo*, and the residue chromatographed on alumina (plc, Alumina H, methanol) to give a yellow oil (68 mg), shown to be a mixture by tlc analysis (silica, acetonitrile/water/acetic acid, 6:3:2); ν_{max} ($CHCl_3$) 3400 cm^{-1}, 1735, 1600, 1450, 1355, 1100; ^1H nmr ($CDCl_3$) δ_H 2.60 (t), 2.80 (t), 3.05 (s), 3.70 (m), 7.00 (s), 7.70 (s); m/e 406, 336, 304, 290, 264.

Attempted preparation of N-(2-carboxymethyl)-1,4,7,10,13,16-penta-oxa-aza cyclooctadecane (131)

To a suspension of potassium tert-butoxide (0.96 g, 8.61 mmol) in dry tetrahydrofuran (45 ml) under an atmosphere of dry nitrogen was added bicine (132) (0.46 g, 2.87 mmol). The mixture was stirred at room temperature for 30 min, and then a solution of ditosylate (116) (1.50 g, 2.87 mmol) in dry tetrahydrofuran (30 ml) was added dropwise over 15 min. The mixture was heated at reflux for 7 h, cooled, filtered and evaporated to give an oil. Chromatography on silica (Kieselgel 60, eluant ethyl acetate) afforded an unidentified crystalline solid (20 mg), m.p. 136-140° from $CHCl_3$; ν_{max} 1725 cm^{-1}, 1095; m/e 469, 368.

Preparation of potassium 2-(1,4,7,10,13,16-penta-oxa-aza-cyclooctadecyl)-acetate

To a solution of the freshly distilled ethyl ester (126) (349 mg, 1 mmol) in dry redistilled tetrahydrofuran (3 ml) was added a solution of potassium hydroxide in water (1 ml of a 1M solution), and the resultant solution was stirred at room temperature for 2 h. Tlc analysis (silica acetonitrile/water/acetic acid, 6:3:2) indicated complete reaction. The reaction mixture was evaporated to dryness, and the residue stored *in vacuo* over phosphorus pentoxide to give the salt (359 mg, 100%) m.p. 132.5-134°; ν_{max} (CH_2Cl_2) 3320 cm^{-1}, 1603 (carboxylate C=O str.), 1380, 1355, 1100 (C-O str.), 950; ^1H nmr ($CDCl_3$) δ_H 2.67 (4H, m, N-CH_2-), 3.05 (2H, s, N-$\underline{CH_2}$-CO), 3.65 (20H, m, O-$\underline{CH_2}$-) (Found: C, 44.56; H, 7.28; N, 3.70; $C_{14}H_{26}KNO_7H_2O$ requires: C, 44.55; H, 7.47; N, 3.71%).

Attempted preparation of 4(5)-Imidazolylmethyl 2-(1,4,7,10,13,16-penta-oxa-aza-cyclooctadecyl)acetate (129)

To a stirred solution of the dried potassium salt (359 mg, 1.00 mmol) in dry dichloromethane (10 ml) under an atmosphere of dry argon was added oxalyl chloride (88 µl) dropwise via syringe at 0°. The temperature was raised to 25° and stirring continued for 60 min (ν_{max} 1760 cm^{-1}). The solution was added to a solution of 4(5)-hydroxymethylimidazole (127) (98 mg,1.00 mmol) in dry N,N-dimethylformamide (3 ml) at 0°C. After 45 min the temperature was raised to 25°. Tlc analysis (silica, eluant acetonitrile/water/acetic acid, 6:3:1) after 100 h indicated the formation of a single product. The solvent was removed *in vacuo* at 25° to give a green oil. The residue was taken up in dichloromethane, filtered and evaporated. Tlc analysis indicated extensive decomposition.

Preparation of ethyl 3-thiaheptanoate (136)

To a solution of n-butanethiol (135) (5.00 g, 55.5 mmol) in dry tetrahydrofuran (25 ml) was added sodium hydride (1.33 g, 55.5 mmol, 100%) and imidazole (20 mg) in one portion. The suspension was stirred vigorously at room temperature under an atmosphere of dry nitrogen until the reaction had reached completion. To the resultant white suspension was added a solution of ethyl bromoacetate (9.25 g, 55.5 mmol) in dry tetrahydrofuran (25 ml) dropwise over a period of 10 min. The mixture was stirred at room temperature for a further two days, and then filtered and evaporated *in vacuo* to give a light yellow liquid. Fractional distillation gave unreacted ethyl bromoacetate (2.06 g, 22%) and *ethyl 3-thiaheptanoate (136)* (6.30 g, 65%) b.p. (78^{o}/3 mmHg); ν_{max} (film) 2960 cm^{-1}, 2935, 2880, 1740 (ester C=O str.), 1470, 1370, 1270, 1130, 1035; ^{1}H nmr ($CDCl_3$) δ_H 0.92 (3H, t, -$\underline{CH}_3$, $\underline{J}$ 7 Hz), 1.30 (3H, t, -$\underline{CH}_3$, $\underline{J}$ 8 Hz), 1.50 (4H, m, -$\underline{CH}_2$-), 2.67 (2H, t, -$\underline{CH}_2$-S-, $\underline{J}$ 7 Hz), 3.22 (2H, s, -$\underline{CH}_2$-S-), 4.20, (2H, q, -O-$\underline{CH}_2$-, $\underline{J}$ 8 Hz); m/e 176 ($M^{+\cdot}$), 120, 103, 88 (100), 61 (Found: C, 54.72; H, 9.41. $C_8H_{16}O_2S$ requires: C, 54.51; H, 9.15%).

Preparation of N-(3-thiaheptanoyl)pyrrolidine (137)

A solution of ethyl 3-thiaheptanoate (136) (1.00 , 5.68 mmol) in freshly distilled pyrrolidine (10 ml) was heated to reflux under an atmosphere of nitrogen. The disappearance of ester (136) was monitored by tlc analysis, which indicated quantitative conversion to a single more polar product within 4 h. The reaction mixture was allowed to cool, and the excess pyrrolidine removed *in vacuo*. The residue was purified by bulb-to-bulb distillation to afford *the title compound* as a colourless liquid (1.08 g, 94%). Bath temperature 80^{o}/0.25 mmHg; ν_{max} (film) 2960 cm^{-1}

2880, (C-H str.), 1640 (amide C=O str.), 1435, 730 (C-S str.); ^{1}H nmr ($CDCl_3$) δ_H 0.90-2.10 (11 H, complex M, -$\underline{CH_2}$), 2.70 (2H, t, $\underline{J}$ 7 Hz, -S-$\underline{CH_2}$-), 3.30 (2H, s, -CO$\underline{CH_2}$S-), 3.60 (4H, m, -$\underline{CH_2}$-N); m/e 201 (M^+), 187, 117, 84 (100) (Found: C, 59.62; H, 9.65; N, 7.04. $C_{10}H_{19}NOS$ requires: C, 59.66; H, 9.51; N, 6.96%).

Preparation of N-(3-thiaheptanyl)pyrrolidine (138)

(a) To a stirred suspension of lithium aluminium hydride (59 mg, 1.54 mmol) in dry redistilled tetrahydrofuran (2.5 ml), at room temperature under an atmosphere of nitrogen, was added dropwise a solution of N-(3-thiaheptanoyl) pyrrolidine (137) (250 mg, 1.54 mmol) in tetrahydrofuran (4 ml). After 18 h, the reaction mixture was quenched by the dropwise addition of saturated sodium sulphate solution. After filtration and evaporation, the residue was partitioned between dichloromethane and dilute hydrochloric acid. The aqueous phase was basified and extracted with dichloromethane. The combined organic phases were dried, filtered and evaporated to yield *the title compound* as a brown oil which was purified by bulb-to-bulb distillation (100 mg, 43%), b.p. 110°/10 mmHg; ν_{max} (film) 2940 cm^{-1}, 2780, 1460, 1380, 1355, 1300, 1230, 1150, 1125, 880, 750; ^{1}H nmr (90 mHz) ($CDCl_3$) δ_H 0.92 (3H, t, $\underline{J}$ 6 Hz, -$\underline{CH_3}$), 1.4-2.0 (8H, m), 2.6 (10 H, m); m/e 187 (M^+), 187 (M^+), 117, 84 (Found: C, 64.08; H, 11.30; N, 7.46. $C_{10}H_{21}NS$ requires: C, 64.11; H, 11.30; N, 7.48%).

(b) Diborane solution (0.85 ml of a 2.2 M solution in tetrahydrofuran) was added dropwise to a solution of N-(3-thiaheptanoyl)pyrrolidine (137) (250 mg, 1.24 mmol) in dry tetrahydrofuran (5 ml) at 0° under an atmosphere of nitrogen. The solution was refluxed for 4h, cooled and quenched by the careful addition of 25% hydrochloric acid (4 ml). The resultant suspension was refluxed for a further 1 h, basified with sodium hydroxide and

extracted thoroughly with dichloromethane. The combined organic layers were dried and evaporated to give a red oil. Bulb-to-bulb distillation at reduced pressure (110°/10 mmHg) afforded pure aminosulphide (138) (196.6 mg, 84%).

Preparation of N-(3-thiaheptanyl)pyrrolidine S-oxide trifluoroacetate (134)

A solution containing N-(3-thiaheptanyl)pyrrolidine (138) (374 mg, 2 mmol) and trifluoroacetic acid (228 mg, 2 mmol) in dry dichloromethane (20 ml) was cooled to -78°. A stream of ozonised oxygen was bubbled through the solution until a permanent blue colouration indicated saturation (5-10 min). Nitrogen was bubbled through the solution at -78° until the blue colour was discharged and the temperature allowed to rise to room temperature. Tlc analysis (silica, eluant acetonitrile/water/acetic acid, 6:3:2) indicated quantitative conversion to a single more polar product. The dichloromethane solution was dried (Na_2SO_4), filtered and evaporated at 25° to yield *the title compound* as a colourless oil (628.5 mg, 94%); ν_{max} (film) 3450 cm^{-1}, 2970, 2940, 2880, 2720, 2600, 2480, 1675, 1465, 1420, 1180, 1130, 1035 (S=O str.), 830, 720; ^1H nmr ($CDCl_3$) δ_H 0.85 (3H, t, J 6Hz, $-CH_3$), 1.50 (4H, m), 1.90 (4H, m), 2.60 (4H, t, J 7 Hz), 3.30 (6H, m) (Found: C, 42.96; H, 6.67; N, 4.03. $C_{12}H_{22}F_3NSH_2O$ requires C, 42.97; H, 6.61; N, 4.17%).

Preparation of 3-thiaheptanoic acid (141)

To a solution of ethyl 3-thiaheptanoate (136) (4.00 g, 22.72 mmol) in redistilled tetrahydrofuran (20 ml) under an atmosphere of nitrogen at room temperature, was added dropwise a solution of sodium hydroxide (1.09 g, 1.2 equiv.) in water (10 ml). The solution was stirred vigorously for 2 h

until clear. Tlc analysis indicated complete reaction. The tetrahydrofuran was removed *in vacuo*, (the residue redissolved in water (10 ml) and the pH adjusted to 2.5 by addition of dilute hydrochloric acid. The resultant cloudy solution was extracted thoroughly with dichloromethane (x 3). The combined organic phases were washed with water (x 1) and brine (x 1), dried filtered and evaporated to give *3-thiaheptanoic acid* (3.36 g). Bulb-to-bulb distillation ($100^{o}/1.25$ mmHg) afforded pure acid (141) as a colourless oil (3.20 g, 95%); ν_{max} (film) 3500-2500 cm^{-1}; 1715 (carboxylic acid C=O str.), 1470, 1425, 1300, 1195, 1140, 925; ^{1}H nmr ($CDCl_3$) δ_H 0.92 (3H, t, $-\underline{CH_3}$ J 7 Hz), 1.55 (4H, m, $-\underline{CH_2}-$), 2.65 (2H, t, $-\underline{CH_2}-S-$, J 7 Hz), 3.26 (2H, s, $-\underline{CH_2}-S-$), 11.90 (1H, s, D_2O exch. $CO_2\underline{H}$); m/e 148 ($M^{+\cdot}$), 89 ($S^{n}Bu^{+}$) (Found: C, 48.81; H, 8.22. $C_6H_{12}SO_2$ requires: C, 48.62; H, 8.16%).

Preparation of N-(3-thiaheptanoyl)-1,4,7,10,13,16-penta-oxa-aza-cyclooctadecane (139)

To a stirred solution of 3-thiaheptanoic acid (141) (250 mg, 1.69 mmol) in dichloromethane (5 ml) under an atmosphere of dry nitrogen was added sodium hydride (45 mg, 1.86 mmol) in one portion. The suspension was stirred at room temperature until effervescence was complete (1 h). Oxalyl chloride (193 µl, 1.3 equiv.) was then added dropwise via syringe, and stirring continued for a further 90 min. Ir analysis indicated complete formation of acid chloride (ν_{max} 1790 cm^{-1}). The resultant solution was added dropwise via syringe to a cooled(0^{o}) solution of 1,4,7,10,13,16-penta-oxa-aza-cyclooctadecane (122)(350 mg, 1.33 mmol) and triethylamine (140 mg, 1.39 mmol) in dichloromethane (5 ml). The brown reaction mixture was diluted with dichloromethane, washed with water (x 1), dried, filtered and evaporated to give a yellow oil. Column chromatography on basic alumina (30 g, eluant 4% methanol in diethyl ether) afforded *the title compound* as yellow oil (446 mg, 85%); ν_{max} 2900 cm^{-1}, 1640 (amide C=O str.), 1450,

1355, 1300, 1110 (C-O str.) 945; ^{1}H nmr ($CDCl_3$), δ_H 0.90 (3H, t, J 6Hz), 1.50 (4H, m, $-\underline{CH_2}-$), 2.67 (2H, t, $-\underline{CH_2}-S$, J 8 Hz), 3.38 (2H, s, $S-\underline{CH_2}-CO$), 3.67 (24H, m); m/e 393 (M^{+}) 364, 350, 336, 319, 305, 262 (Found: C, 55.08; H, 9.12; N, 3.52. $C_{18}H_{35}NO_6S$ requires: C, 54.93; H, 8.96; N, 3.56%).

Preparation of N-(3-thiaheptanyl)-1,4,7,10,13,16-penta-oxa-aza-cyclooctadecane (140)

To a stirred solution of amide (139) (109 mg, 0.25 mmol) in dry redistilled tetrahydrofuran (4 ml) under an atmosphere of nitrogen at room temperature was added diborane in tetrahydrofuran (0.25 ml of a 2.2M solution) dropwise via syringe. The reaction mixture was refluxed overnight (18 h). Tlc analysis (silica, acetonitrile/water/acetic acid, 6:3:2) of an aliquot indicated quantitative conversion to a single more polar product. The reaction mixture was cooled to 0° and 20% hydrochloric acid (5 ml) added. After refluxing for 1 h, the reaction mixture was recooled to 25°, and basified with sodium hydroxide. The aqueous solution was extracted with dichloromethane (x 3) and the combined organic phases dried, filtered and evaporated. Chromatography of the residue on alumina (Alumina H, 10 g, eluant dichloromethane) afforded *the title compound* as an homogeneous oil (99 mg, 94%); ν_{max} (CH_2Cl_2) 2875 cm^{-1}, 1355, 1115 (C-O str.), 990, 945, 840; ^{1}H nmr (90 MHz) ($CDCl_3$) δ_H 0.92 (3H, t, J 6Hz), 1.50 (4H, m), 2.70 (10 H, m), 3.70 (20 H, m, $-\underline{CH_2}-O-$); m/e 379 (M^{+}), 290 ($M^{+}-S^{n}Bu$), 276 (100) ($M^{+} -CH_2-S^{n}Bu$) (Found: C, 56.75; H, 10.17; N, 3.69. $C_{18}H_{37}NO_5S$ requires: C, 56.96; H, 9.83; N, 3.69%).

Model oxidation reactions

The results are summarised in Table 8.

TABLE 8

Entry	Substrate (mmol)	Oxidising Systems (mmol)[a]	T° (t)	Product (%)	Notes
1	(142) (3.0)	DMSO (3.0), TFA (1.5) Py (3.0), DCC (9.0)	25 (72h)	5α-cholestanone(143) (36%)	*c,e*
2	(142) (1.0)	DMSO (1.0), TFAA(1.0) Et_3N (2 ml)	-65 (2 h)	5α-cholestanone(143) (73%)	*b,f*
3	(142) (0.25)	(134) (0.25), TFA (0.25) TFAA (0.25), DEA (0.5 ml)	-40 (1 h)	5α-cholestanone(143) (29%)	*b,g*
4	(142) (1.0)	NCS (1.0), DMS(1.0) DEA (1.0)	-20 (2 h)	5α-cholestanone(143) (50%)	*d,h*
5	(142) (1.0)	(138) (1.0), NCS (1.0) TFA (1.0), DEA (2.0)	-20 (2 h)	N.R.	*d,i*
6	(142) (1.0)	(138) (1.0), TFA (1.0) NCS (1.0)	-20) (2 h)	complex mixture	*d,j*
7	(142) (0.70)	(134) (0.70), $(COCl)_2$ (0.70), DEA (1.41)	-78 (2 h)	5α-cholestanone(143) (25%)	*b,k*
8	(142) (0.98)	(134) (0.98), $(COCl)_2$ (1.96), DEA (2.93)	-10	complex mixture	*b,k*
9	(144) (1.0)	DMSO (1.0),$(COCl)_2$ (1.0), DEA (1.0) CH_2Cl_2	-60° 15min	N.R.	*b,l*
10	(145) (1.0)	18-crown-6 (1.0),DMSO (1.0), $(COCl)_2$ (1.0), DEA (1.0) CH_2Cl_2	-60° 30min	P	*b,m*

/continued...

TABLE 8/continued...

Entry	Substrate (mmol)	Oxidising System (mmol)	T° (t)	Product (%)	Note
11	(145) (1.0)	(a) DMSO (1.0)$(COCl)_2$ (1.0), 18-crown-6 (1.0), DEA (1.0) CH_2Cl_2	-60 30min	P	*b,n*
		(b) PhCOCl/DEA			
12	(145) (1.0)	(a) $(COCl)_2$ (1.0), DMSO (1.0), 18-crown-6- (1 mmol)	-60 5min	P	*b,o*
		(b) PhCOCl/Et_3N			

a Reactions carried out under dry nitrogen in dry solvents and quenched by the addition of di-isopropylethylamine (DEA) or triethylamine (TEA) Work up consisted of washing with water, drying and evaporating, followed by chromatography on silica (Kieselgel H), if necessary.

b Solvent dichloromethane.

c Solvent benzene.

d Solvent toluene.

e Dicyclohexyl carbodi-imide (DCC) added to alcohol (142), dimethyl sulphoxide (DMSO), trifluoroacetic acid (TFA), pyridine (py).

f Trifluoroacetic anhydride (TFAA) added to alcohol (142), DMSO.

g TFAA added to alcohol (142), TFA, sulphoxide (144).

h Dimethylsulphide (DMS), N-chlorosuccinimide (NCS) added to alcohol (142).

i TFA, sulphide (145), NCS added to alcohol (142).

j Sulphide (145), TFA added to NCS, resulting solution added to alcohol (142).

k Oxalyl chloride added to sulphoxide (144) and alcohol (142).

l Oxalyl chloride added to DMSO and alcohol (146).

m Oxalyl chloride added to alcohol (147),

DMSO, 18-crown-6.

n To DMSO was added (1) Oxalyl chloride, (2) alcohol (147), 18-crown-6, (3) DEA, (4) benzoyl chloride, DEA.

o DMSO, alcohol (147), 18-crown-6 were added to oxalyl chloride, then DEA followed by benzoyl chloride, TEA.

p No identifiable products.

Attempted preparation of 2,11,20,29-tetraaza[3.3.3.3]paracyclophane (152)

To a stirred solution of dry triethylamine (2.75 ml, 19.70 mmol) in dry redistilled benzene (500 ml) at reflux under an atmosphere of nitrogen were added, simultaneously, solutions (500 ml) of terephthaloyl chloride (55) (2.00 g, 9.85 mmol) and 1,4-xylylene diamine (154) (1.34 g, 9.85 mmol), dropwise over a period of 24 h. After 48 h, the precipitate was filtered off, washed with dichloromethane and then extracted (soxholet) for 72 h with hot methanol. The resultant solution was evaporated to dryness to give a white solid (1.00 g), ν_{max} 3280 cm^{-1}, 1635. Attempted reduction of a sample (200 mg) with lithium aluminium hydride (300 mg) afforded a mixture of polar products (tlc analysis) from which the desired compound could not be isolated.

Preparation of N-allyldibenzylamine (156)

To a stirred solution of dibenzylamine (4.937 g, 25 mmol) and allyl bromide (3.63 g, 30 mmol) in dry redistilled tetrahydrofuran (40 ml), was added sodium hydride (720 mg, 30 mmol). The reaction mixture was heated to reflux under an atmosphere of nitrogen for 12 h. Water (20 ml) was carefully added to the solution and the tetrahydrofuran removed *in vacuo*. The aqueous residue was extracted with dichloromethane (x 3). The combined organic phases were dried, filtered and evaporated to give an oil (5.30 g). Medium pressure chromatography on silica (Kieselgel H, 30 g, eluant dichloromethane-light petroleum) yielded *the title compound* as a colourless oil (5.05 g, 85%), ν_{max} (film) 3090 cm^{-1}, 3065, 3030, 2980, 2795, 1650 (C=C str.), 1610, 1497, 1465, 917, 740, 695; ^{1}H nmr ($CDCl_3$) δ_H 3.03 (2H, d, J 6Hz), 3.57 (4H, br s), 5.20 (2H, m), 5.90 (1H, m), 7.30(10H, br s, aryl-H); m/e 237 ($M^{+\cdot}$), 210, 160, 146, 91 (100) (Found: C, 85.76; H, 8.16; N, 5.80. $C_{17}H_{19}N$ requires: C, 86.03; H, 8.07; N, 5.90%).

Ozonolysis of N-allyldibenzylamine (156)

Ozonised oxygen was passed through a solution of N-allyldibenzylamine (156) (1.198 g, 5.06 mmol) in 20% hydrochloric acid (5 ml) at room temperature. Tlc analysis of aliquots after basification and extraction into diethyl ether indicated the formation of several more polar products. After 72 h, hydrogen peroxide (5 ml, 30% aqueous solution) was added, and the reaction mixture stirred overnight until homogeneous. The solvent was removed *in vacuo* at 100° to give an oil which crystallised from methanol-diethyl ether (0.85 g), m.p. > 200°; ν_{max} 3500-2500 cm^{-1}, 2410, 1750, 1575, 1230, 1125, 985, 745, 700 (Found: C, 69.50; H, 6.79; N, 5.94). A portion (500 mg) was dissolved in water, basified and extracted into dichloromethane. Drying, filtration and evaporation gave dibenzylamine (157)

as a colourless oil (270 mg); ^{1}H nmr ($CDCl_3$) δ_H 1.57 (1H, br, s), 3.67 (4H, br, s), 7.23 (10H, br, s, aryl-H), which was converted into the known N-(toluene-4-sulphonyl) derivative (89%), m.p. 77-8° (lit.[143] 78°).

Preparation of N,N'-diallylterephthalamide (159)

To a solution containing sodium hydroxide (3.94 g, 0.10 mol) and allylamine (10.0 g, 0.18 mol) in water (100 ml) and tetrahydrofuran (50 ml) was added freshly distilled terephthaloyl chloride (10 g, 0.05 mol) in small portions. After an initial exothermic reaction had subsided (30 min) the reaction mixture was stirred for a further 30 min. Filtration and recrystallisation from ethanol afforded the *title compound* (11.92 g, 99%), m.p. 205°; ν_{max} (Nujol) 3300 cm^{-1}, 1635, 1550, 1295, 1165, 995, 920, 860; ^{1}H nmr (d_6-DMSO) δ_H 4.0 (4H, m), 5.23 (4H, m), 5.6-6.2 (2H, m), 7.97 (4H, br s, aryl-H); m/e 244 (M^+), 188 (base), 104, 76 (Found: C, 68.92; H, 6.66; N, 11.49. $C_{14}H_{16}N_2O_2$ requires: C, 68.83; H, 6.60; N, 11.47%).

Reduction of N,N'-diallylterephthalamide (159)

To a stirred suspension of N,N'-diallylterephthalamide (159) (20.0 g, 0.08 mol) in dry redistilled tetrahydrofuran (600 ml) was added lithium aluminium hydride (6 g, excess) in small portions. After refluxing for 7 d, the reaction was quenched by the dropwise addition of saturated sodium sulphate at 0°. Filtration and evaporation *in vacuo* gave an oil (20.0 g); ν_{max} (film) 3300 cm^{-1}, 1647, 1455, 1095, 1060, 915; ^{1}H nmr ($CDCl_3$) δ_H 0.90 (t, 3H, J 6Hz), 1.45 (2H, br. s, D_2O exch), 1.3-1.8 (2H, m), 3.22 (2H, d, 6Hz), 3.92 (4H, br. s), 5.0-5.4 (2H, m), 5.7-6.2 (1H, m), 7.22 (4H, br. s, aryl-H), m/e 220, 218, 216, 191, 189, 160, 162, 120. A sample was converted to the ditosylate salt (Found: C, 59.71; H, 6.98; N, 5.08.

$C_{28}H_{38}N_2O_6S_2$ requires: C, 59.76; H, 6.81; N, 4.98%).

Preparation of N,N'-diallyl-N,N'-dibenzylterephthalamide (162)

To a solution of N,N'-diallylterephthalamide (159) (1.22 g, 5 mmol) in dry N,N'-dimethylformamide (10 ml) under nitrogen at room temperature was added sodium hydride (255 mg, 11.09 mmol) in one portion, and imidazole (10 mg). After stirring for 45 min, benzyl bromide (1.20 ml, 10.08 mmol) was added dropwise *via* syringe. The reaction mixture was stirred for 90 min, and then more sodium hydride (2 equiv.) and benzyl bromide (1 equiv.) were added. After a further 2 h, the reaction mixture was quenched by the careful addition of water (25 ml). A white precipitate formed which was filtered off, washed with cold diethyl ether, and then recrystallised from ethyl acetate to afford *the title compound* as a white crystalline solid (1.81 g, 85%), m.p. 140-141° from ethyl acetate; ν_{max} (CH_2Cl_2) 1635 cm^{-1} (amide C=O str.), 1515, 1500, 1410, 1150, 1080, 985, 850; ^1H nmr ($CDCl_3$) δ_H 3.83 (4H, m), 4.60 (4H, br. s), 5.25 (4H, m), 5.4-5.8 (2H, m), 7.27 (10H, br. s, aryl-H), 7.45 (4H, s, aryl-H); m/e 424 (M^+), 383, 333, 278, 105, 91 (Found: C, 79.11; H, 6.72; N, 6.52. $C_{28}H_{28}N_2O_2$ requires: C, 79.22; H, 6.65; N, 6.60%).

Reduction of N,N'-diallyl-N,N'-dibenzylterephthalamide(162)

Phosgene was bubbled through a solution of diamide (162) (424 mg, 1 mmol) in dry dichloromethane at 0°. Ir analysis showed completion of reaction after 4.5 h (ν_{max} 1670 cm^{-1}). The solvent was removed *in vacuo* at 0°, and the residue redissolved in dry tetrahydrofuran (30 ml). Lithium aluminium hydride (100 mg, 2.63 mmol) was added in one portion, and the mixture heated at reflux under an atmosphere of dry nitrogen for 12 h.

Saturated sodium sulphate solution was then added drop-wise at 0^{o} with vigorous stirring. The reaction mixture was filtered and evaporated, and the residue chromatographed on silica (plc, Kieselgel H, diethyl ether) to give *inter alia* N,N'-diallyl-N,N'-dibenzyl-1,4-xylylene diamine (163) (66 mg, 16%) as a colourless oil; ν_{max} 2800 cm^{-1}, 1645 (C=C str.), 1605; ^{1}H nmr ($CDCl_3$) δ_H 3.03 (4H, d, J 6Hz), 3.53 (8H, br. s), 5.0-5.4 (4H, m), 5.5-6.1 (2H, m), 7.23 (14H, br. s, aryl-H); m/e 396 ($M^{+\cdot}$), 369, 305, 250, 160, 146, 91, 88.

Preparation of N,N-dibenzyl-4-methoxybenzamide (171)

To a stirred solution containing 4-methoxybenzoyl chloride (3.40 g, 20 mmol) and di-iso-propylethylamine (5.16 g, 40 mmol) in dry tetrahydrofuran (20 ml) was added dibenzylammonium toluene-4-sulphonate (7.38 g, 20 mmol) in small portions. After the initial exothermic reaction had subsided (5 min), ir analysis indicated completion. The solvent was removed *in vacuo*, and the solid residue extracted with water (25 ml). The crude product (6.30 g) was filtered off and recrystallised from methanol-water to afford *the title compound* (171) (5.65 g, 85%), m.p. 119-120°; ν_{max} (Nujol) 1630 cm^{-1} (amide C=O str.), 1605, 1300, 1250, 1170; ^{1}H nmr ($CDCl_3$) δ_H 3.80 (3H, s, -OMe), 4.57 (4H, br s, aryl-CH_2-), 6.70-7.60 (14H, m, aryl-H),; m/e 331 ($M^{+\cdot}$), 254 ($M^{+\cdot}$ - $PhCH_2$), 240, 135 (100) (Found: C, 79.56; H, 6.40; N, 4.18. $C_{22}H_{21}NO_2$ requires: C, 79.73; H, 6.39; N, 4.23%).

Preparation of N-(4-methoxybenzyl)dibenzylamine(172)

To a stirred solution of N,N-dibenzyl-4-methoxybenzamide (171) (1.00 g, 3.16 mmol) in dry redistilled tetrahydrofuran (20 ml) was added

lithium aluminium hydride (200 mg, 5.26 mmol) in small portions. After the initial exothermic reaction had subsided (15 min) the reaction mixture was refluxed under nitrogen for a further 6 h. Ir analysis of an aliquot indicated completion. The reaction mixture was cooled to 0^{o} and saturated sodium sulphate solution added dropwise with vigorous stirring. Filtration and evaporation of the solvent *in vacuo* gave an oil which was chromatographed on silica (Kieselgel H, 25 g, eluant light petroleum-dichloromethane) to give *the title compound* as a colourless oil (940 mg, 98%); ν_{max} (film) 3090 cm^{-1}, 3070, 3035, 2930, 2820, 2800, 1620, 1580, 1515, 1497, 1457, 1370, 1305, 1250, 1170, 1037, 810, 745, 697; ^{1}H nmr ($CDCl_3$) δ_H 3.45 (2H, s, aryl-C<u>H</u>$_2$-), 3.50 (4H, s, aryl-C<u>H</u>$_2$-), 3.70 (3H, s, -O<u>Me</u>), 6.80-7.50 (14H, m, aryl-<u>H</u>); m/e 317 (M^{+}), 240, 226, 210, 196, 121, (100). A sample was purified by plc (Kieselgel-H, eluant dichloromethane) (Found: C, 83.52; H, 7.48; N, 4.58. $C_{22}H_{23}NO$ requires: C, 83.24; H, 7.30; N, 4.41%).

<u>Preparation of 2,2,2-trichloroethyl chloroformate (167)</u>

Phosgene was bubbled through a stirred solution of 2,2,2-trichloroethanol (20 g, 0.13 mol) and <u>N</u>,<u>N</u>-dimethylaniline (16.22 g, 0.13 mol) in dichloromethane (25 ml) at 0^{o} until a weight increase of 30 g had been attained (30 min). The solution was allowed to warm up to room temperature overnight (15 h). The excess phosgene was removed *in vacuo* and the resultant phosgene-free solution diluted with dichloromethane and washed quickly with cold water (x 1). The aqueous phase was re-extracted with dichloromethane (x 1) and the combined organic extracts dried, filtered and evaporated to give a green liquid. Distillation gave 2,2,2-trichloroethyl chloroformate (167) as a colourless liquid (19.1 g, 67%), b.p. (175 765 mmHg) (lit.[125] b.p. 171-2^{o}/760 mmHg); ν_{max} 3025 cm^{-1}, 2970, 1790 (C=O str.), 1605, 1450, 1375, 1280, 1150, 1060, 800, 720, 680; ^{1}H nmr

($CDCl_3$) δ_H 4.37 (s).

Preparation of N-(2,2,2-trichloroethoxycarbonyl)dibenzylamine(173)

To a stirred solution containing dibenzylammonium toluene-4-sulphonate (369 mg, 1 mmol) and triethylamine (205 mg, 2.03 mmol) in dichloromethane (20 ml) at room temperature was added 2,2,2-trichloroethyl chloroformate (150 µl, 1.09 mmol) dropwise via syringe. Tlc analysis (silica, eluant dichloromethane) of the reaction mixture indicated complete reaction within 5 min. The solvent was removed *in vacuo*, and the residue chromatographed on silica (Kieselgel H, 12 g, eluant light petroleum-dichloromethane) to afford *the title compound* as a colourless oil (350 mg, 94%); ν_{max} (film) 3100 cm^{-1}, 3075, 3040, 2960, 1725 (carbamate C=O str.), 1500, 1460, 1430, 1230, 1125, 700; ^1H nmr ($CDCl_3$) δ_H 4.52 (4H, br. s, aryl-$C\underline{H}_2$), 4.90 (2H, s, -$C\underline{H}_2$-O), 7.35 (10H, br s, aryl-$\underline{H}$); m/e 375, 373, 371 ($M^{+\cdot}$), 335, 293, 287, 245, 239, 231, 150, 106, 91. A sample was purified by bulb-to-bulb distillation ($150^o/2.5 \times 10^{-2}$ mmHg) (Found: C, 54.46; H, 4.62; N, 3.85. $C_{17}H_{16}Cl_3NO_2$ requires: C, 54.79; H, 4.33; N, 3.76%).

Reduction of N-(2,2,2-trichloroethoxycarbonyl)dibenzylamine

To a stirred solution of N-(2,2,2-trichloroethoxycarbonyl)dibenzylamine (173) (46 mg, 0.12 mmol) in 10% aqueous acetic acid (10 ml) was added zinc dust (200 mg, excess) in one portion. The resulting suspension was stirred at room temperature under an atmosphere of argon. After 24 h, the reaction mixture was filtered through celite, and the resulting solution evaporated *in vacuo*. The residue was treated with benzoyl chloride (1 ml) in 0.1 M potassium hydroxide (10 ml) and the mixture shaken until clear. The reaction mixture was extracted with dichloromethane (x 2) and the combined

organic phases dried, filtered and evaporated. The residue was chromatographed (plc, Kieselgel-H, eluant dichloromethane) to afford N,N-dibenzylbenzamide (29 mg, 78%), m.p. 110-112° (lit.,[144] 112-112.8°); ν_{max} 1630 cm^{-1} (amide C=O str.), ^1H nmr ($CDCl_3$) δ_H 4.55 (4H, br.s, aryl-CH_2-), 7.05-7.55 (15H, m, aryl-H).

Reduction of N-(2,2,2-trichloroethoxycarbonyl)dibenzylamine (173)

To a stirred solution of N-(2,2,2-trichloroethoxycarbonyl)dibenzylamine (173) (357 mg, 0.96 mmol) in methanol (20 ml) was added zinc dust (500 mg, excess). The resulting mixture was heated at reflux under an atmosphere of argon. Tlc analysis (silica, eluant dichloromethane) indicated completion after 2.5 h. The reaction mixture was filtered through celite, and then evaporated *in vacuo*. The residue was partitioned between dilute hydrochloric acid and dichloromethane. The aqueous layer was basified and extracted with dichloromethane. The combined organic phases were dried, filtered and evaporated to give dibenzylamine (142 mg, 75%) as a colourless oil. ^1H nmr ($CDCl_3$) δ_H 1.85 (1H, br.s, N-H), 3.95 (4H, br.s, aryl-CH_2), 7.27 (10H, br.s, aryl-H).

Reaction of N-(2,2,2-trichloroethoxycarbonyl)dibenzylamine (173) with t-butyllithium

To a stirred solution of N-(2,2,2-trichloroethoxycarbonyl)dibenzylamine (173) (110 mg, 0.30 mmol) in dry tetrahydrofuran at -100° under an atmosphere of dry argon was added a solution of t-butyllithium (1 ml, approx. 5-fold excess). The solution was stirred at -100° for 2.5 h, and then allowed to warm up to 25°. Tlc analysis (silica, eluant dichlo-

romethane) of the reaction mixture indicated complete reaction. After evaporation *in vacuo*, the residue was taken up in dilute hydrochloric acid and extracted with dichloromethane (x 2). The aqueous phase was basified and then re-extracted with dichloromethane (x 2). The combined organic phases were dried, filtered and evaporated to give dibenzylamine as a colourless oil (41 mg, 71%).

Reaction of N-(4-methoxybenzyl)dibenzylamine(172) with 2,2,2-trichloroethyl chloroformate

To a solution of N-(4-methoxybenzyl)dibenzylamine(172) (142 mg, 0.45 mmol) in dry benzene (5 ml) was added 2,2,2-trichloroethyl chloroformate (75 µl, 0.54 mmol) dropwise via syringe. The solution was heated to reflux overnight under an atmosphere of dry argon. The solvent was removed in *vacuo*, and the residue chromatographed on silica (Kieselgel-H, 10 g, eluant light petroleum-dichloromethane) to afford N-(2,2,2-trichloroethoxy)-dibenzylamine (173) (100 mg, 96%) as a colourless oil. The spectral data were identical to an authentic sample.

Preparation of N-(methoxycarbonyl)dibenzylamine (176)

To a stirred suspension of dibenzylammonium toluene-4-sulphonate (369 mg, 1 mmol) in dichloromethane (10 ml) was added triethylamine (202 mg, 2 mmol). Methyl chloroformate (1 ml, excess) was added dropwise with stirring at room temperature. Tlc analysis (silica, eluant dichloromethane) indicated complete conversion to a single product within 2 min. The solution was washed with water (x 2), dried, filtered and evaporated. The residue was chromatographed on silica (Kieselgel H, 15 g, eluant

dichloromethane) to afford *the title compound* (176) as an homogeneous oil (249 mg, 97%); ν_{max} (film) 3030 cm^{-1}, 2950, 1690, 1600, 1450, 1405, 1235, 1115, 950, 770, 755, 700; ^1H nmr ($CDCl_3$) δ_H 3.75 (3H, s, -OMe), 4.38 (4H, br. s, aryl-CH_2-), 7.18 (10H, br. s, aryl-H); m/e 255 ($M^{+\cdot}$), 164 ($M^{+\cdot}$ - $PhCH_2$), 121, 91 (100). A sample was re-purified by plc on silica (Kieselgel H, eluant dichloromethane) (Found: C, 75.21; H, 6.81; N, 5.52. $C_{16}H_{17}NO_2$ requires: C, 75.27; H, 6.71; N, 5.49%).

Hydrolysis of N-(methoxycarbonyl)dibenzylamine (176)

To a solution of N-(methoxycarbonyl)dibenzylamine (176) (196 mg, 0.77 mmol) in methanol (25 ml) was added powdered potassium hydroxide (260 mg, excess). The reaction mixture was heated to reflux under an atmosphere of argon. Tlc analysis indicated completion after 48 h. The solvent was evaporated, and the residue partitioned between water and dichloromethane. The aqueous phase was re-extracted with dichloromethane (x 2), and the combined organic extracts dried, filtered and evaporated to give dibenzylamine (144 mg, 94%) as a colourless oil.

Reaction of N-(4-methoxybenzyl)dibenzylamine (172) with methyl chloroformate

A solution of N-(4-methoxybenzyl)dibenzylamine (172) (323 mg, 1.02 mmol) in dry dichloromethane (5 ml) was treated with a solution of methyl chloroformate (100 mg, 1.02 mmol) in dichloromethane (1 ml). The resulting solution was stirred at room temperature under nitrogen. After 48 h, tlc analysis (silica, eluant dichloromethane) indicated the presence of starting material only. The solvent was removed *in vacuo* and replaced with methyl chloroformate (5 ml). After 72 h, tlc indicated the formation of a more polar product. The solvent was removed *in vacuo*, and the residue

separated by medium pressure chromatography on silica (Kieselgel H, 15 g, eluant dichloromethane-light petroleum) to give unreacted starting material (172) (85 mg) and N-(methoxycarbonyl)-dibenzylamine (176) (150 mg, 78% based on converted starting material), spectral data identical to an authentic sample. No other carbamates were detectable.

Reaction of N-allyldibenzylamine (156) with methyl chloroformate

To a solution of N-allyldibenzylamine (156) (115 mg, 0.49 mmol) in dichloromethane (1 ml) were added freshly distilled methyl chloroformate (1 ml) and ethyldi-iso-propylamine (100 µl). The reaction mixture was stirred at room temperature, under an atmosphere of dry argon. After 19.5 h, tlc analysis (silica, eluant dichloromethane) indicated the quantitative formation of a single product. The solvent was removed *in vacuo*, and the residue chromatographed on silica (plc, eluant dichloromethane) to afford N-*allyl*-N-*benzylmethoxycarbonylamine* (177) as a colourless oil (107 mg, 100%), ν_{max} (CH_2Cl_2) 2950,1700 cm^{-1} (C=O str. carbamate); 1405, 1335, 900; ^1H nmr ($CDCl_3$) δ_H 3.75 (5H, m, O-C<u>H</u>$_3$, N-C<u>H</u>$_2$), 4.43 (2H, br s, aryl-C<u>H</u>$_2$), 4.9-5.3 (2H, m), 5.5-6.0 (1H, m), 7.25 (5H, br s, aryl-<u>H</u>); m/e 205 ($M^{+\cdot}$), 164 ($M^{+\cdot}$-allyl), 146, 121, 114, 91 (100) (Found: C, 70.08; H, 7.54; N, 6.80. $C_{12}H_{15}NO_2$ requires: C, 70.22; H, 7.37; N, 6.82%).

Reaction of N-(4-methoxybenzyl)dibenzylamine (172) with trimethylsilyl iodide

To a stirred solution of hexamethyldisilane (91 mg, 0.62 mmol) and iodine (158 mg, 0.62 mmol) in dichloromethane (5 ml) under an atmosphere of argon was added a solution of N-(4-methoxybenzyl)dibenzylamine (172) (358 mg, 1.13 mmol) in dichloromethane (2 ml) over 5 min, and the reac-

tion mixture was heated to reflux. After 30 min, tlc analysis (silica, eluant dichloromethane) indicated the formation of four major products.

Preparation of 4-methoxybenzoyl chloride

4-Methoxybenzoic acid (50.00 g, 0.33 mmol) was refluxed with thionyl chloride (50 ml) for 90 min. The excess thionyl chloride was removed by distillation, and the residue distilled at reduced pressure to furnish the title compound as an oil which solidified on standing (52.00 g, 93%), b.p. 170° (40 mmHg (lit.[145] 160-4°/35 mmHg); ν_{max} 1773 cm^{-1}, 1740.

Preparation of 4-methoxybenzamide

A solution of 4-methoxybenzoyl chloride (27.00 g, 0.16 mmol) in dry tetrahydrofuran (50 ml) was added dropwise to aqueous ammonia solution (100 ml, '880') at 0° with vigorous stirring. A white precipitate formed immediately. Stirring was continued for a further 3 h at room temperature, then the precipitate was filtered, washed (cold water) and dried *in vacuo* (23.90 g, 99%), m.p. 161-3° from water (lit.[145] 163°); ν_{max} 1640 cm^{-1}, 1620, 1575, 1250.

Preparation of 4-methoxybenzylammonium chloride

To a vigorously stirred suspension of 4-methoxybenzamide (8.50 g, 57.43 mmol) in dry redistilled tetrahydrofuran (250 ml) was carefully added lithium aluminium hydride (2.50 g, 65.79 mmol) portionwise. The reaction mixture was refluxed for 5 h and more lithium aluminium hydride (500 mg) added. After 24 h, the reaction mixture was cooled to 0° and quenched by the dropwise addition of saturated sodium sulphate solution.

Filtration and evaporation of the solvent afforded crude 4-methoxybenzylamine which was converted to the corresponding hydrochloride salt and recrystallised from methanol-diethyl ether (8.70 g, 87%), m.p. 240° (lit.[146] 240-1°).

Preparation of N,N'-di-(4-methoxybenzyl)terephthalamide (178)

To a stirred suspension of freshly distilled terephthaloyl chloride (55) (4.11 g, 2023 mmol) and 4-methoxybenzylammonium chloride (7.00 g, 40.46 mmol) in dry dichloromethane (200 ml) was added triethylamine (12 ml, excess) dropwise at room temperature. An immediate exothermic reaction took place and a white precipitate formed. The reaction mixture was stirred for a further 15 min, and then filtered at the pump. The solid was washed thoroughly with dichloromethane and hot methanol to afford analytically pure N,N'-*di(4-methoxybenzyl)terephthalamide* (178) (7.37 mg, 98%), m.p. 246-7°; ν_{max} (Nujol) 3300 cm^{-1} (N-H str.), 1630 (amide C=O str.), 1550, 1515, 1320, 1300, 1260, 1235, 1180, 1030, 815, 690; ^1H nmr (CF_3CO_2H) δ_{II} 4.17 (6H, s, -OMe), 4.72 (4H, m, aryl-CH_2), 7.17 (8H, m,aryl-H), 7.90 (4H, br. s, aryl-H); m/e 404 (M^+), 283, 268, 241, 136, 121 (Found: C, 71.11; H, 5.95; N, 6.75. $C_{24}H_{24}N_2O_4$ requires: C, 71.27; H, 5.98; N, 6.93%).

Preparation of N,N'-di(4-methoxybenzyl)-1,4-xylylenediamine (179)

To a stirred suspension of N,N'-di-(4-methoxybenzyl)terephthalamide (178) (3.00 g, 8.07 mmol) in dry redistilled tetrahydrofuran (40 ml) under an atmosphere of nitrogen at room temperature, was added lithium aluminium hydride (920 mg, 24.21 mmol) in small portions. After the initial exothermic reaction had ceased, the reaction mixture was heated to reflux. Ir analysis of an aliquot indicated complete reaction within

18 h. The reaction mixture was cooled to 0° and saturated sodium sulphate solution added dropwise with vigorous stirring. Filtration and evaporation gave a colourless oil which was redissolved in dichloromethane, dried filtered and evaporated to give the title compound (179) as a colourless oil which solidified on standing (2.91 g, 96%), ν_{max} (film) 3310 cm^{-1} (N-H str.), 3000, 2905, 2815, 1615 (Ar C=C str.); 1580, 1510, 1445, 1300, 1240, 1175, 1100, 1030; ^{1}H nmr ($CDCl_3$) δ_H 1.68 (2H, br s, D_2O exch., N-H), 3.68 (4H, s), 3.73 (10H, 2 s), 6.70-7.40 (12H, m, aryl-H); m/e 376 ($M^{+\cdot}$) 255, 241, 121 (100). The corresponding *hydrochloride salt* was prepared m.p. subl. > 250°C (Found: C, 64.14; H, 6.76; N, 6.15. $C_{24}H_{28}N_2O_2.2HCl$ requires: C, 64.14; H, 6.73; N, 6.23%).

Preparation of N,N',N'',N'''-tetra-(4-methoxybenzyl)-2,11,20,29-tetra-aza [3.3.3.3]paracyclophane (180)

To a rapidly stirred refluxing solution of triethylamine (50 ml, excess) in dry benzene (2.5 l) under an atmosphere of dry argon were simultaneously added over 24 h a solution of terephthaloyl chloride (55) (5.40 g, 26.60 mmol) in dry benzene (1 l) and a solution of N,N'-di(4-methoxybenzyl)-1,4-xylylene diamine (179) (10.00 g, 26.00 mmol) in dry benzene (1 l). After refluxing for a further 24 h, the solvent and excess triethylamine were removed by distillation, and the residue partitioned between dichloromethane and dilute hydrochloric acid. The aqueous phase was re-extracted with dichloromethane (x 1) and the combined organic phases dried, filtered and evaporated to give a solid (15 g), ν_{max} 1640 cm^{-1} (amide C=O str.); ^{1}H nmr ($CDCl_3$), δ_H 3.88 (s), 4.3-4.9 (m), 6.8-7.7 (m).

The solid was suspended in dry tetrahydrofuran (500 ml) and lithium aluminium hydride (2.50 g, 65.79 mmol) added in small portions. After heating at reflux for 48 h under an atmosphere of dry nitrogen with

vigorous stirring, the reaction mixture was cooled to 0° and quenched with saturated sodium sulphate. Filtration and evaporation gave a white foam, which was chromatographed twice on silica (Kieselgel H, 30 g, eluant dichloromethane) to afford *the title compound* (180) as a white solid (2.36 g, 18.6%); m.p. 207-8° from light petroleum-dichloromethane; ν_{max} (CH_2Cl_2) 2930 cm^{-1}, 2810, 1610, 1510, 1365, 1170, 1120, 1105, 1035, 975, 830; ^1H nmr (250 MHz) ($CDCl_3$) δ_H 3.38 (16H, br. s, aryl-C<u>H</u>$_2$-), 3.50 (8H, br s, aryl-C<u>H</u>$_2$), 3.77 (12H, s, O<u>Me</u>), 6.86 (8H, d, <u>J</u> 9 Hz, aryl-<u>H</u>), 7.35 (8H, d, <u>J</u> 9 Hz, aryl-<u>H</u>), 7.38 (16H, s, aryl-<u>H</u>); ^{13}C nmr (62.9 MHz) ($CDCl_3$), δ_C 158.64, 139.04, 131.78, 130.00, 128.23, 113.64, 58.06, 57.36, 55.26; m/e 956 ($M^{+\cdot}$), 836, ($M^{+\cdot}$ - 4-MeO-C_6H_4-CH_2), 714 ($M^{+\cdot}$ - 2(4-MeO-C_6H_4-CH_2-), 612, 596, 478, 388, 357, 343, 268, 238, 182, 121 (100%) (Found: C, 80.26; H, 7.26; N, 5.77. $C_{64}H_{68}N_4O_4$ requires: C, 80.30; H, 7.16; N, 5.85%).

<u>Preparation of</u> N,N',N",N"'-<u>tetra-(methoxycarbonyl)-2,11,20,29-tetra-aza [3.3.3.3]paracyclophane (181)</u>

To a stirred solution of N,N',N",N"'-tetra-(4-methoxybenzyl)-2,11,20,29-tetra-aza[3.3.3.3]paracyclophane (180) (144.5 mg, 0.15 mmol) in dry dichloromethane (2.5 ml) was added freshly distilled methyl chloroformate (0.5 ml, excess), and the reaction mixture was heated to reflux under an atmosphere of dry nitrogen. Tlc analysis (silica, eluant dichloromethane-diethyl ether 9:1) indicated the formation of a complex mixture of products. After 7 d, the solvent was removed *in vacuo*, and the residue separated by plc (Kieselgel H, eluant dichloromethane-diethyl ether 3:1) to afford *the title compound* (181) as the major product (65.7 mg, 61%), ν_{max} (CH_2Cl) 1700 cm^{-1} (carbamate C=O str.), 1405, 1225, 1125, 900; ^1H nmr ($CDCl_3$) δ_H 3.80 (12H, s, -O<u>Me</u>), 4.30 (16H, br. s, aryl-C<u>H</u>$_2$-), 6.90

(16H, br.s, aryl-H); m/e 708 ($M^{+\cdot}$), 649, 633, 603, 530, 394, 355, 353, 105, 91 (Found: m/e 708.3139; $C_{40}H_{44}N_4O_8$ requires: m/e 708.3159).

Preparation of N,N',N",N"'-tetra-(2,2,2-trichloroethoxycarbonyl)-2,11,20,29-tetra-aza[3.3.3.3]paracyclophane (182)

To a stirred solution of paracyclophane (180) (1.00 g, 0.05 mmol) in dry carbon tetrachloride (25 ml) at room temperature was added freshly distilled 2,2,2-trichloroethyl chloroformate (1.10 ml, 7.99 mmol) dropwise via syringe. The resulting solution was heated to reflux under an atmosphere of dry nitrogen. ^{1}H nmr analysis of the reaction mixture indicated quantitative reaction within 17 h. The solvent was removed *in vacuo* and the residue chromatographed on silica (Kieselgel H, 20 g, eluant dichloromethane-diethyl ether) to afford *the title compound* (182) as a white foam (1.117 g, 91%), ν_{max} (CH_2Cl_2) 2940 cm^{-1}, 1705 (carbamate C=O str.), 1510, 1350, 1210, 1120, 1060, 840; ^{1}H nmr (250 MHz) ($CDCl_3$) δ_H 4.38 (16H, br. s, aryl-CH_2-), 4.86 (8H, s, -CH_2-CCl_3), 6.95 (16H, s, aryl-H); ^{13}C nmr (62.9 MHz) ($CDCl_3$) δ_C 154.76; 136.15, 128.36, 75.52, 50.82, 50.40; m/e ($M^{+\cdot}$) centred around 1178, 1023, 994, 979, 960, 926, 876, 845, 686, 672, 584. (Found: C, 44.97; H, 3.50; N, 4.44. $C_{44}H_{40}Cl_{12}N_4O_8$ requires C, 44.85; H, 3.42; N, 4.76%).

Preparation of N,N',N",N"'-tetra-(2,2-dichloroethenoxycarbonyl)-2,11,20,29-tetra-aza[3.3.3.3]paracyclophane (183)

To a stirred solution of N,N',N",N"'-tetra(2,2,2-trichloroethoxycarbonyl)-2,11,20,29-tetra-aza[3.3.3.3]paracyclophane (182) (239 mg, 0.20 mmol) in dry benzene (5 ml) was added 1,5-diazabicyclo[5.4.0]undec-5-ene

(152 µl, 1.01 mmol) dropwise *via* syringe. The solution was heated at reflux overnight (18 h) and the solvent removed *in vacuo*. The residue was chromatographed on silica (Kieselgel H, 12 g, eluant dichloromethane-diethyl ether, 19:1) to afford *the title compound* (183) (187 mg, 90%) as a colourless glass; ν_{max} (CH_2Cl_2) 3100 cm^{-1}, 2930, 2790, 1735 (carbamate, C=O str.), 1655, 1620, 1520, 1405, 1370, 1355, 1205, 1150, 1050, 930; ^1H nmr (90 MHz) ($CDCl_3$), δ_H 4.40 (16H, br. s, aryl-C<u>H</u>$_2$-), 7.00 (16H, br. s, aryl-<u>H</u>) 7.70 (4H, s) (Found: C, 51.30; H, 3.71; N, 5.38. $C_{44}H_{36}N_4Cl_8O_8$ requires C, 51.19; H, 3.51; N, 5.43%).

<u>Attempted deprotection of heterocyclophane (183)</u>

Heterocyclophane (183) (62 mg, 0.06 mmol) was dissolved dry dichloromethane (25 ml) and the resultant solution saturated with hydrogen chloride at room temperature. The solvent was removed *in vacuo*, and the residue dissolved in absolute ethanol (25 ml) and heated at 50° for 30 min. The ethanol was evaporated and the residue partitioned between dichloromethane and water. The organic phase was separated, dried, filtered and evaporated to give unreacted starting material (55 mg).

<u>Attempted hydrolysis of N,N',N",N"' -tetra-((2,2,2-trichloroethoxy)carbonyl) -2,11,20,29-tetra-aza[3.3.3.3]paracyclophane (182)</u>

To a solution of paracyclophane (182) (80 mg, 0.068 mmol) in methanol (10 ml) was added powdered potassium hydroxide (1 g). After heating the solution of reflux for 48 h, the solvent was removed *in vacuo*, and the residue partitioned between water and dichloromethane. The aqueous phase was re-extracted with dichloromethane (x 1) and the combined organic phase dried, filtered and evaporated to give <u>N</u>,<u>N'</u>,<u>N"</u>,<u>N"'</u>-tetra-(methoxycarbonyl)-

-2,11,20,29-tetra-aza[3.3.3.3]paracyclophane (181) (45 mg, 93.6%).

Attempted reduction of N,N',N'',N'''-tetra-((2,2,2-trichloroethoxy)carbonyl)-2,11,20,29-tetra-aza[3.3.3.3]paracyclophane (182)

To a solution containing carbamate (182) (263 mg, 0.22 mmol) in methanol (30 ml) was added zinc dust (1 g) in one portion. The mixture was heated at reflux under argon for 2.5 d, filtered through celite and evaporated to give unreacted starting material (242 mg).

In another experiment, a mixture of carbamate (182) (46 mg, 0.04 mmol), zinc dust (55 mg), acetic acid (0.5 ml), tetrahydrofuran (2 ml) was stirred at room temperature for 15 h. The usual work up gave an oil (45 mg). ^{1}H nmr ($CDCl_3$) indicated ca. 30% reaction.

Preparation of 2,11,20,29-tetra-aza[3.3.3.3]paracyclophane (152)

To a stirred solution of N,N',N'',N'''-tetra((2,2,2-trichloroethoxy)carbonyl)-2,11,20,29-tetra-aza[3.3.3.3]paracyclophane (182) (500 mg, 0.42 mmol) in redistilled dioxan (15 ml) was added a solution of potassium hydroxide (1 g, large excess) in water (5 ml). The two-phase mixture was heated to reflux with vigorous stirring under an atmosphere of nitrogen for 5 d. Tlc analysis (silica, eluant methanol) of the reaction mixture indicated the presence of a single product. The reaction mixture was cooled to 50° and the bulk of the solvent removed *in vacuo*. The residue was partitioned between water and dichloromethane. The combined organic phases were dried, filtered and evaporated *in vacuo* to give *th title compound* (152) (197 mg, 97%) as a colourless crytalline solid, m.p. 142-3°; ν_{max} 3320 cm^{-1}, 2910, 2810, 1600, 1505, 1345,

1205, 980, 700; ^{1}H nmr ($CDCl_3$) δ_H 1.60 (4H, br. s, N-H), 3.67 (16H, s, ary-CH_2), 7.05 (16H, s, aryl-H); m/e 476 (M^+) 355, 121, 104, 91 (Found: m/e 476.2934; $C_{32}H_{36}N_4$ requires: m/e 476.2940) Heterocyclophane (152) was further characterised as the *tetrahydrochloride salt*, m.p. > 300°C, ν_{max} 3700-3100 cm^{-1} (Found: C, 58.70; H, 6.52; N, 8.38. $C_{32}H_{36}N_4.4HCl.2H_2O$ requires: C, 58.34; H, 6.74; N, 8.51%).

Preparation of N-(3-carboxypropanoyl)-1,4,7,10,13,16-pentaoxa-aza-cyclo-octadecane (184)

To a stirred solution of 1,4,7,10,13,16-pentaoxa-aza-cyclooctadecane (122) (528 mg, 2 mmol) in dry redistilled tetrahydrofuran (10 ml) at ambient temperature under an atmosphere of argon, was added sodium hydride (80 mg, excess 100%) in one portion and imidazole (10 mg). After hydrogen evolution had ceased (30 min), succinic anhydride (20 mg, 2 mmol) was added. After a further brisk effervescence, tlc analysis (silica, eluant acetonitrile/water/acetic acid 6:3:2) indicated quantitative formation of a single less-polar product. The reaction mixture was quenched by the careful dropwise addition of water (1 ml). The solvent was removed *in vacuo*, and the residue dissolved in water. Acidification with dilute hydrochloric acid and extraction with dichloromethane (x 3), followed by drying of the combined organic phases and evaporation afforded the title compound (184) as a colourless oil (695 mg, 95%), ν_{max} (film) 1745 cm^{-1}, 1645, ^{1}H nmr ($CDCl_3$), δ_H 2.73 (4H, br. s, -CH_2-CO), 3.70 (24H, m, -CH_2O-, -CH_2-N-); 10.00 (1H, br s, CO_2H); m/e 363 (M^+), 346, 320, 262, 232. The acid (184) was further characterised by conversion to the benzylhydryl ester (185).

Preparation of N-{2-[(1,1-diphenylmethyloxy)carbonyl]ethylcarbonyl}-1,4,7,

10,13,16-pentaoxa-aza-cyclooctadecane (185)

To a stirred solution of carboxylic acid (184) (157 mg, 0.43 mmol) in dichloromethane (5 ml) under nitrogen at ambient temperature was added diphenyldiazomethane (85 mg, slight excess) in one portion. After 4 h, tlc analysis (silica, eluant acetonitrile/water/acetic acid, 6:3:2) indicated complete loss of starting material. The solvent was removed *in vacuo*, and the residue chromatographed on silica (plc, kieselgel H, eluant methanol:diethyl ether, 9:1) to yield *the title compound* (185) as a colourless oil (183 mg, 80%), ν_{max} (film) 3070 cm^{-1}, 3040, 2875, 1740 (ester C=O str.), 1645 (amide C=O str.), 1455, 1355, 1250, 1250, 1120 (C-O str.), 990, 735, 705; ^1H nmr ($CDCl_3$) δ_H 2.75 (4H, t, J 6 Hz CO-CH_2-CH_2-CO), 3.60-3.7 (24H, m, -CH_2-O-), 6.90 (1H, s, $CHPh_2$), 7.33 (10H, br. s, aryl-H), m/e 529 ($M^{+\cdot}$), 469, 410, 368, 362, 354 (Found: C, 65.77; H, 7.42; N, 2.64. $C_{29}H_{39}NO_8$ requires: C, 65.78; H, 7.53; N, 2.70%).

Preparation of N-{2-[(4-nitrophenyloxy)carbonyl]ethylcarbonyl}-1,4,7,10,13,16-penta-oxa-aza-cyclooctadecane (186)

To a stirred solution of carboxylic acid (184) (500 mg, 1.38 mmol) and 4-nitrophenol (192 mg, 1.38 mmol) in dry redistilled ethylacetate (5 ml) at 0° under an atmosphere of argon, was added dicyclohexylcarbodiimide (284 mg, 1.38 mmol) in one portion. A white precipitate began to form immediately. After 1 h, stirring was stopped and the reaction mixture stored at 4°C overnight. Tlc analysis (silica, acetonitrile/water/acetic acid, 6:3:2) indicated complete reaction. After careful filtration, the yellow solution was diluted further with cold ethyl acetate (25 ml) and washed with cold 5% sodium hydrogencarbonate solution (x 1) and water (x 3). The organic phase was dried, filtered and evaporated *in vacuo* at 25° to give *the title compound* (186) as an homogeneous yellow oil

(620 mg, 93%). A sample was purified by chromatography on silica (plc, Kieselgel H, acetonitrile-diethyl ether, 3:7), ν_{max} (film) 3120 cm^{-1}, 3080, 1770 (ester C=O str.), 1650 (amide C=O str.), 1595, 1525, 1495, 1350, 1300, 1120 (C-O str.) 940, 750; ^1H nmr ($CDCl_3$) δ_H 2.88 (4H, br. s, $-\underline{CH}_2-CO-$), 3.67 (24H, m, $-\underline{CH}_2O-$), 7.32 (2H, d, J 9Hz, aryl-H), 8.25 (2H, d, J 9 Hz, aryl-H); m/e 346 ($M^{\cdot+}$ - 4-$OC_6H_4NO_2$), 282, 242, 224, 186, 166, 156, 149, 139, 99 (Found: C, 54.69; H, 6.92; N, 5.89. $C_{22}H_{32}N_2O_{10}$ requires C, 54.54; H, 6.66; N, 5.78%).

Reaction of 2,11,20,29-tetra-aza[3.3.3.3]paracyclophane (152) with 4-nitrophenyl ester (186)

To a solution of heterocyclophane (152) (49 mg, 0.10 mmol) in dichloromethane (1 ml) was added a solution of 4-nitrophenyl ester (186) (48 mg, 0.99 mmol) in dichloromethane (2 ml). After stirring at room temperature for 72 h, ir analysis of the reaction mixture indicated completed reaction. Tlc analysis (silica, eluant acetonitrile/water/acetic acid, 6:3:2) indicated the presence of starting heterocyclophane (152) in addition to several slightly less polar products. The reaction mixture was diluted with dichloromethane and partitioned with 10% hydrochloric acid. The aqueous phase was basified and extracted with dichloromethane (x 3) and the combined organic phases were dried, filtered and evaporated to give an oil (52 mg); ν_{max} 1635 cm^{-1}. After dissolution in formic acid (10 ml, 90%) paraformaldehyde (100 mg, excess) was added in one portion and the stirred mixture heated at reflux under an atmosphere of argon for 48 h. The excess formic acid was removed by distillation, and the residue redissolved in water, basified and extracted with dichloromethane (x 3). The organic phases were combined, dried, filtered and evaporated to give an oil. Chromatography on alumina (Alumina H, 10 g, eluant dichloro-

methane-diethyl ether-methanol) to give in order of increasing polarity, N,N',N",N"'-tetramethyl-tetra-aza[3.3.3.3]paracyclophane (57, n = 1) (27 mg, 49%); m.p. 195-196° (lit.[61] 196-198.5°); ν_{max} (CH_2Cl_2), 2930 cm^{-1}, 2885, 2790, 1615, 1515, 1365, 1125, 1100, 1030, 1020, 980, 875; ^1H nmr (90 MHz) ($CDCl_3$) δ_H 2.14 (12H, s, N-Me), 3.15 (16H, s, aryl-CH_2), 7.21 (16H, s, aryl-H) ; m/e 532 ($M^{+\cdot}$), 517, 502, 482, 427, 397, 370, 296, 294, 266, 237, 161, 133, 118, 105, 91; and an inseparable mixture of more polar products (40 mg).

Reaction of 4-nitrophenyl ester (186) with dibenzylamine

To a stirred solution containing dibenzylammonium toluene-4-sulphonate (76 mg, 0.2 mmol) and triethylamine (58 µl, 0.41 mmol) in dichloromethane (1 ml) at room temperature, was added a solution of 4-nitrophenyl ester (186) (99.2 mg, 0.21 mmol) in dichloromethane (4 ml). The solution was stirred for 3.5 d, diluted with dichloromethane and then washed with dilute hydrochloric acid (x 1). The aqueous phase was re-extracted with dichloromethane (x 1) and the combined organic phase dried, filtered and evaporated to give unreacted 4-nitrophenyl ester (186) (90 mg) as the sole component.

Preparation of N-(N'N'-dibenzyl-3-carboxamidopropanoyl)-1,4,7,10,13,16-penta-oxa-aza-cyclooctadecane (192)

To a stirred solution of carboxylic acid (184) (363 mg, 1 mmol) in dry dichloromethane (5 ml) under nitrogen, was added sodium hydride (48 mg, 2 mmol) in one portion. After stirring at room temperature for 1 h, oxalyl chloride (100 µl, 1.1 mmol) was added dropwise via syringe, and stirring continued for a further 1 h. The solvent and excess oxalyl chloride

were removed *in vacuo*, and the residue extracted into dichloromethane (5 ml), and added dropwise via syringe to an ice-cooled solution of dibenzylamine (197 mg, 1 mmol) and triethylamine (105 mg, 1.04 mmol) in dichloromethane (10 ml). The reaction mixture was stirred at 0^{o} for 45 min, and then allowed to warm to room temperature overnight. The solution was diluted to 25 ml and washed successively with 10% sodium hydrogencarbonate solution (x 1), dilute hydrochloric acid (x1) and water (x1). The organic phase was dried, filtered, evaporated and chromatographed on silica (plc, Kieselgel H, diethyl ether-methanol, 9:1) to yield *the title compound* (192) as an homogeneous colourless oil (300 mg, 55%); ν_{max} (CH_2Cl_2) 3690 cm^{-1}, 1640 (amide C=O str.), 1115 (C-O str.); ^{1}H nmr ($CDCl_3$) δ_H 2.80 (4H, m, $-\underline{CH}_2-CO-$), 3.67 (24H, m, $-\underline{CH}_2-O-$, $-\underline{CH}_2-N-$), 4.57 (4H, br. s, aryl-$\underline{CH}_2-$), 7.27 (10H, br. s, aryl-$\underline{H}$); m/e 542 ($M^{+\cdot}$) 346, 280 (100), 196, 91 (Found: C, 64.08; H, 7.72; N, 4.69. $C_{30}H_{42}N_2O_7 \cdot H_2O$ requires: C, 64.27; H, 7.91; N, 4.99%).

Preparation of N-(N',N'-dibenzyl-4-butanyl)-1,4,7,10,13,16-penta-oxa-aza cyclooctadecane (193)

To a solution of diamide (192) (146 mg, 0.27 mmol) in dry redistilled tetrahydrofuran was added lithium aluminium hydride (500 mg, excess) in small portions. Brisk effervescence occurred and a green colour developed immediately. The reaction mixture was heated to reflux under an atmosphere of nitrogen. Tlc analysis (silica, eluant acetonitrile/water/acetic acid 6:3:2) of an aliquot indicated the complete loss of starting material within 45 min, and the formation of a single more polar product. The reaction mixture was refluxed overnight resulting in no further charge. The reaction was quenched by the careful dropwise addition of saturated sodium sulphate solution to the vigorously stirred reaction mixture at 0^{o}. Filtration and evaporation yielded a colourless oil, which was

redissolved in dichloromethane. The organic phase was dried, filtered, evaporated *in vacuo* and chromatographed on alumina (plc, alumina H, diethyl ether-methanol, 9:1) to afford *the title compound* (193) as a colourless oil (127 mg, 92%); ν_{max} (CH_2Cl_2) 2860 cm^{-1} (C-H str.), 1605 (Ar C=C str.), 1355, 1115 (C-O str.); ^1H nmr ($CDCl_3$) δ_H 1.42 (4H, m, -CH_2-CH_2-), 2.20-2.83 (8H, m, N-CH_2-), 3.50 (4H, s, aryl-CH_2-), 3.60 (20H, m, -CH_2O-), 7.20 (10H, br. s, aryl-H); m/e 514 ($M^{+\cdot}$), 423 (100), 278, 160. Diamine (193) was further characterised as the corresponding *hydrochloride salt* (Found: C, 55.81; H, 8.53; N, 4.33. $C_{30}H_{48}N_2O_5Cl_2 \cdot 3H_2O$ requires: C, 56.13; H, 8.48; N, 4.37%).

Preparation of N-(4-methoxybenzyl)-4-cyanobenzamide (196)

A suspension of 4-cyanobenzoic acid (1.27 g, 8.65 mmol) was heated with freshly distilled thionyl chloride (5 ml) until a clear solution was obtained (60 min). The excess thionyl chloride was removed *in vacuo* to give crude 4-cyanobenzoyl chloride (194) as a white solid (1.43 g, ν_{max} 1780 cm^{-1},1740). To a partial solution of 4-cyanobenzoyl chloride (1.43 g, 8.65 mmol) and 4-methoxybenzylammonium chloride (1.50 g, 8.65 mmol) in dichloromethane (25 ml) was added a solution of triethylamine (1.75 g, 17.29 mmol) in dichloromethane (5 ml) dropwise over a period of 10 min. Ir analysis of the reaction mixture indicated complete reaction within 60 min. The reaction mixture was diluted with dichloromethane and washed with dilute hydrochloric acid. The organic phase was dried, filtered and evaporated to give a solid residue which was recrystallised from hot methanol-water to yield *the title compound* (196) as colourless needles (1.80 g, 78%), m.p. 138-9°; ν_{max} ($CHCl_3$) 3440 (N-H str.), 2235 (C≡N str.), 1660 (amide C=O str.), 1610; ^1H nmr ($CDCl_3$) δ_H 3.73 (3H, s, -OMe), 4.48 (2H, d, aryl-CH_2-), 6.7-8.0 (8H, m, aryl-

H); m/e 266 ($M^{+\cdot}$), 136, 130 (100), 121 (Found: C, 72.08; H, 5.32; N, 10.56. $C_{16}H_{14}N_2O_2$ requires: C, 72.17; H, 5.30; N, 10.52%).

Preparation of N-(4-methoxybenzyl)-1,4-xylylene diamine (197)

To a stirred suspension of N-(4-methoxybenzyl)-4-cyanobenzamide (196) (266 mg, 1 mmol) in dry redistilled tetrahydrofuran (40 ml) under an atmosphere of nitrogen at room temperature, was added lithium aluminium hydride (250 mg, excess) portion-wise. After the initial exothermic reaction had subsided, the reaction mixture was heated to reflux. Analysis of an aliquot (ir, tlc) indicated complete reaction within 2 d. The reaction mixture was cooled to 0^{o}, and saturated sodium sulphate solution added dropwise with vigorous stirring. After filtration, the resultant solution was evaporated to dryness *in vacuo*, redissolved in dichloromethane dried, filtered and evaporated to give an oil. Bulb-to-bulb distillation at reduced pressure afforded the title compound as a colourless oil (233 mg, 91%). Bath temperature 130^{o}/0.2 mmHg; ν_{max} (film) 3300 cm^{-1} (-N-H str.), 3010, 2920, 2840, 1610, 1505, 1245, 1030, 815; ^{1}H nmr ($CDCl_3$), δ_H 1.72 (3H, br. s, D_2O exch., N-H), 3.85 (6H, m, aryl-CH_2-), 6.8-7.2 (8H, m, aryl-H); m/e 256 ($M^{+\cdot}$), 241, 213, 193, 136, 106, 91.

A sample was converted to the corresponding *hydrochloride salt*, m.p. dec. 275^{o} (Found: C, 58.11; H, 6.78; N, 8.28. $C_{16}H_{20}N_2O.2HCl$ requires: C, 58.36; H, 6.73; N, 8.51%).

Preparation of dimethyl terephthalate (198)

To methanol (150 ml) was added freshly distilled terephthaloyl chloride (25.00 g, 0.12 mol) portion-wise with shaking. After the initial

exothermic reaction had subsided (5 min), the reaction mixture was heated to reflux for 90 min. The excess methanol was removed *in vacuo*, and the solid residue recrystallised from diethyl-ether to afford the title compound (22.50 g, 94%), m.p. 141-2° (lit.[147] 140-1°); ν_{max} 1720 cm^{-1} (ester C=O str.); ^{1}H mr ($CDCl_3$) δ_H 3.95 (6H, s, -OMe); 8.15 (4H, s, aryl-H); m/e 194 ($M^{+\cdot}$), 163, 135, 103.

Preparation of methyl terephthalate (199)

Dimethyl terephthalate (198) (10.00 g, 0.05 mmol) was heated in toluene (85 ml) to produce a clear solution. The solution was allowed to cool slightly and a solution of potassium hydroxide (3.41 g, 85%) in methanol (50 ml) was added slowly over 15 min with vigorous stirring. An immediate white precipitate formed. The reaction mixture was then refluxed with stirring for a further 15 min, cooled to room temperature and filtered. The solid was washed with small portions of toluene and methanol, and then redissolved in water (50 ml). Dilute hydrochloric acid was added dropwise with stirring at 0° to give the title compound as a colourless solid which was dried overnight *in vacuo* (9.30 g, 99%), m.p. 220-221° (lit.[147] 220-222.5°, ν_{max} 1730 cm^{-1}, 1700); m/e 180, 149 (100), 121.

Preparation of N,N'-di(4-methoxybenzyl)-N,N'-di(4-methoxycarbonylbenzoyl)-1,4-xylylene diamine (201)

A suspension of methyl terephthalate (199) (1.50 g, 8.34 mmol) in thionyl chloride (5 ml) was heated until a clear solution was obtained (90 min). The excess thionyl chloride was removed *in vacuo* to give a white solid residue (1.65 g) ν_{max} 1790 cm^{-1}, 1750). The residue was redissolved

in dry dichloromethane (25 ml) and N,N'-di-(4-methoxybenzyl)-1,4-xylylene diamine dihydrochloride (1.85 g, 4.17 mmol) was added in one portion with stirring. Dry redistilled triethylamine (5 ml, excess) was added dropwise at room temperature. Ir analysis of the reaction mixture indicated complete reaction within 60 min. The reaction mixture was diluted to 100 ml with dichloromethane, and then washed successively with dilute hydrochloric acid (x 1) and water (x 1). The organic phase was dried, filtered and evaporated to give an oil. Medium pressure chromatography on silica (Kieselgel, 20 g, eluant dichloromethane-diethyl ether) afforded *the title compound* (201) as a white foam (2.53 g, 86%), ν_{max} (CH_2Cl_2) 3100-2970 cm^{-1}, 1720 (ester C=O str.), 1630 (amide C=O str.), 1600, 1510, 1400, 1110; ^1H nmr ($CDCl_3$), δ_H 3.77 (6H, s, $-CO_2\underline{Me}$), 3.87 (6H, s, $-O\underline{Me}$), 4.30-4.80 (8H, m, aryl-$\underline{CH_2}$-), 6.80-8.30 (20H, m, aryl-$\underline{H}$); m/e 669 (M^+ - OMe), 578, 537, 403, 298, 163, 121 (Found: C, 71.72; H, 5.94; N, 3.75. $C_{42}H_{40}N_2O_8$ requires: C, 71.98; H, 5.75; N, 3.99%).

Preparation of N,N'-Di-(4-carboxybenzoyl)-N,N'-di-(4-methoxybenzyl)-1,4-xylylene diamine (202)

Diester (201) (2.52 g, 3.60 mmol) was dissolved in hot methanol (50 ml) and a solution of sodium hydroxide (288 mg, 7.20 mmol) in water (10 ml) added dropwise over a period of 5 min. The resulting solution was refluxed under an atmosphere of nitrogen for 3 h. Analysis of an aliquot of the reaction mixture (tlc, ir) indicated completion of reaction. The methanol was removed *in vacuo*, and the yellow residue diluted with water (200 ml). The aqueous solution was washed with dichloromethane (x 1), treated with charcoal and then filtered through a plug of celite. Acidification with dilute hydrochloric acid gave a white precipitate, which was filtered at the pump, washed with water, and then dried overnight

in vacuo. Recrystallisation (dichloromethane-light petroleum) gave *the title compound* as a white amorphous solid (1.60 g, 66%), m.p. 208-9°; ν_{max} (Nujol) 3500-2500 cm^{-1} (-O-H str.), 1720 (carboxylic acid C=O str.), 1610 (amide C=O str.), 1512, 1250, 1175; ^1H nmr ($CDCl_3$) δ_H 3.60 (6H, s, -OMe), 4.2-4.7 (8H, m, aryl-CH_2-), 6.75-8.30 (20H, m, aryl-H); m/e 470, 356, 286, 250, 207, 192, 178, 166, 149, 135, 121 (Found: C, 71.48; H, 5.46; N, 4.16. $C_{40}H_{36}N_2O_8$ requires C, 71.42; H, 5.39; N, 4.16%).

Formation and methanol quench of diacid chloride of dicarboxylic acid (202) - 1

To a stirred solution of diacid (202) (200 mg, 0.30 mmol) and triethylamine (60 mg, 0.60 mmol) in dry dichloromethane (5 ml) at room temperature was added freshly distilled oxalyl chloride (104 µl, 1.20 mmol) dropwise via syringe. After 30 min, the solvent and excess oxalyl chloride was removed *in vacuo* and the residue (ν_{max} 1775 cm^{-1}, 1735, 1630) redissolved in methanol (10 ml). Tlc analysis (silica, diethyl ether) indicated completion within 2 h. The methanol was evaporated, and the residue chromatographed on silica (Kieselgel H, 12 g, eluant dichloromethane-diethyl ether) to afford the diester (201) (145 mg, 70%).

Formation and quench of diacid chloride of dicarboxylic acid (202) - 2

To a stirred solution of diacid (202) (200 mg, 0.30 mmol) and triethylamine (64 mg, 0.63 mmol) in dry dichloromethane (5 ml) at room temperature, was added thionyl chloride (100 mg, 0.75 mmol). Ir analysis indicated complete reaction within 5 min (ν_{max} 1775 cm^{-1}, 1735, 1630). The addition of more thionyl chloride (100 mg, 0.75 mmol) after 60 min and

(60 mg, 0.45 mmol) after a further 90 min, produced no change. The solvent and excess thionyl chloride were removed *in vacuo* and replaced with methanol (10 ml). After 18 h, the methanol was evaporated and the residue chromatographed as before to give the diester (29) (135 mg, 65%).

Preparation of N,N',N'',N'''-tetra(4-methoxybenzyl)-2,11,20,29-tetra-aza-[3.3.3.3]paracyclophane (180)

To a stirred solution of diacid (202) (672 mg, 1.00 mmol) and triethylamine (210 mg, 2.07 mmol) in dry dichloromethane (25 ml) at room temperature, was added oxalyl chloride (183 µl, 2.10 mmol) dropwise via syringe. After 30 min, the solvent and excess oxalyl chloride were removed *in vacuo* and the residue (ν_{max} 1775 cm^{-1}, 1735, 1630) redissolved in dry dichloromethane (25 ml) and sodium-dried benzene (75 ml). The resulting solution and another solution containing N,N'-di(4-methoxybenzyl)-1,4-xylylenediamine (179) (344 mg, 1 mmol) in sodium-dried benzene (100 ml) were added simultaneously overnight to a stirred, refluxing solution of triethylamine (5 ml, excess) in benzene (200 ml) under argon. The benzene and excess triethylamine were removed by distillation and the residue partitioned between dichloromethane and dilute hydrochloric acid. The aqueous phase was re-extracted with dichloromethane (x 1) and the combined organic phases dried, filtered and evaporated to give a solid residue (460 mg). The residue was redissolved in dry tetrahydrofuran (10 ml) and lithium aluminium hydride (500 mg, 13.16 mmol) added in one portion. After heating at reflux for 48 h, the reaction mixture was quenched with saturated sodium sulphate solution, filtered and evaporated to give a yellow foam. Chromatography twice on silica (Kieselgel H, 12 g, eluant dichloromethane) afforded the title compound (58 mg, 6%), identical to an authentic sample.

Attempted preparation of N,N',N''-tri-(4-methoxybenzyl)-2,11,20,29-tetra-aza[3.3.3.3]paracyclophane

To a rapidly stirred refluxing solution of dry triethylamine (10 ml, excess) in dry benzene (100 ml) were slowly added simultanesouly, solutions containing the diacid chloride derivative of dicarboxylic acid (202) (165 mg, 0.22 mmol) in benzene (25 ml) and diamine (197) (57 mg, 0.22 mg) in dry benzene (25 ml). After 18 h, the benzene and excess triethylamine were removed by distillation and the residue was redissolved in dichloromethane and then washed with 10% hydrochloric acid (x 1). The aqueous phase was re-extracted with dichloromethane (x 1) and the combined organic phases dried, filtered and evaporated to give an oil (167 mg); ν_{max} 1615 cm^{-1}, ^1H nmr ($CDCl_3$) δ 3.78 (s), 4.17-4.83 (m), 6.67-7.5 (m). The oil was dissolved in dry tetrahydrofuran and lithium aluminium hydride (200 mg) added in one portion. After refluxing under nitrogen for 48 h, the reaction mixture was quenched with saturated sodium sulphate solution, filtered and evaporated to give an oil (51 mg). Tlc analysis (silica, eluant methanol-diethyl ether, 1:1) indicated a complex mixture of products. Chromatography on silica, (plc, Kieselgel H, eluant methanol-diethyl ether) failed to give the title compound. Repeated attempts were similarly unsuccessful.

Preparation of N-(trimethylsilyl)imidazole

Freshly distilled hexamethyldisilazane (32.9 g, 204 mmol), imidazole (18.0 g, 264 mmol) and concentrated sulphuric acid (2 drops) were refluxed together under an atmosphere of dry argon for 3 h. Distillation at reduced pressure gave the title compound (26.32 g, 92%) b.p. 94^o/113 mmHg (lit.[148] 91^o/12 mmHg); ν_{max} (film) 1445 cm^{-1}, 1255, 1165, 1060, 935, 840, 750, 660; ^1H nmr ($CDCl_3$) δ_H 0.00 (9H, s, $\underline{Me}_3Si$), 6.75 (2H, m, aryl-

H), 7.28 (1H, m, aryl-H).

Preparation of 1,1'-carbonyldiimidazole[134]

To a stirred solution of N-(trimethylsilyl)imidazole (12.34 g, 87.98 mmol) in dry benzene (50 ml) at 0° was added a solution of phosgene (4.4 g, 44.4 mmol) in dry benzene (50 ml) dropwise over a period of 90 min. The solvent was removed *in vacuo* at 20° to afford crude 1,1'-carbonyldiimidazole as a white solid which was used without further purification (6.99 g, 98%); ν_{max} (CH_2Cl_2) 1760 cm^{-1}, 1390, 1095, 1025, 870.

Preparation and methanol quench of di-imidazolide of N,N'-di-(4-methoxybenzyl)-N,N'-(4-carboxybenzoyl)-1,4-xylylenediamine (202)

To a stirred solution of freshly prepared 1,1'-carbonyldiimidazole (162 mg, 1 mmol) in dry dichloromethane (10 ml) at room temperature, was added a solution containing dicarboxylic acid (202) (335 mg, 0.50 mmol) and triethylamine (105 mg, 1.04 mmol) dropwise over 10 min. Ir analysis of the reaction mixture indicated completion within 45 min; ν_{max} 1715 cm^{-1}, 1635. The solvent was removed *in vacuo*, and the residue redissolved in methanol (10 ml). After 17 h, the methanol was evaporated and the residue chromatographed on silica (Kieselgel H, 12 g, eluant dichloromethane-diethyl ether) to afford the dimethyl ester (201) (206 mg, 59%).

Preparation of benzoic trimethylacetic anhydride(203)

Triethylamine (1.01 g, 10 mmol) was added to a suspension of benzoic acid (1.22 g, 10 mmol) in dry toluene (30 ml). To the resultant solution was added trimethylacetyl chloride (1.21 g, 10 mmol) dropwise at room

temperature with rapid stirring. An immediate exothermic reaction took place and a white precipitate formed. Ir analysis of the reaction mixture indicated completion within 15 min. The mixture was filtered and the solvent evaporated *in vacuo* to give the title compound as a colourless liquid which was used without further purification (2.00 g, 99%), ν_{max} (film) 1800 cm^{-1}, 1730; ^{1}H nmr ($CDCl_3$) δ_H 1.35 (9H, s, $-CMe_3$), 7.60 (3H, m, aryl-H), 8.10 (2H, m, aryl-H).

Reaction of benzoic trimethylacetic anhydride (203) with dibenzylamine

To a stirred solution of dibenzylammonium toluene-4-sulphonate (362 mg, 1 mmol) and dry triethylamine (500 mg, excess) in dichloromethane (10 ml) at room temperature, was added a solution of benzoic trimethylacetic anhydride (203) (206 mg, 1 mmol) in dichloromethane (2 ml). Tlc analysis (silica, eluant dichloromethane) indicated completion within 4 h with the formation of a single product. The solvent was removed *in vacuo* and the residue chromatographed on silica (Kieselgel H, 15 g, eluant dichloromethane) to give N,N-dibenzylbenzamide as a colourless oil which crystallised from methanol-water (260 mg, 86%) m.p. 110-110° (lit.[144] 112-112.8°); ν_{max} (Nujol) 1630 cm^{-1} (amide C=O str.); ^{1}H nmr ($CDCl_3$) δ_H 4.55 (4H, br. s, aryl-CH_2-), 7.05-7.55 (15H, m, aryl-H).

Reaction of benzoic trimethylacetic anhydride (203) with benzylamine

To a stirred solution of benzoic acid (122 mg, 1 mmol) and triethylamine (205 mg, 2.03 mmol) in dichloromethane (10 ml) at room temperature, was added trimethylacetyl chloride (123 µl, 1 mmol) dropwise via syringe. Tlc analysis (silica, eluant dichloromethane) of the reaction mixture showed complete reaction within 5 min. Benzylamine (109 µl, 1 mmol)

was then added dropwise over 5 min. Tlc analysis indicated completion after 20 min. The solvent was removed *in vacuo* and the residue chromatographed on silica (Kieselgel H, 12 g, eluant dichloromethane-diethyl ether) to give an inseparable mixture (230 mg) of N-benzyl-benzamide and N-benzyl-trimethylacetamide (Ratio 56:44 by ^{1}H nmr).

Attempted preparation of N,N',N''-tri-(4-methoxybenzyl)-2,11,20,29-tetraaza[3.3.3.3]paracyclophane

To a stirred solution containing dicarboxylic acid (202) (200 mg, 0.30 mmol) and dry triethylamine (66 mg, 0.65 mmol) in dry dichloromethane (5 ml) at room temperature was added freshly distilled trimethylacetyl chloride (73 µl, 0.60 mmol) dropwise via syringe over 5 min. Ir analysis of the reaction mixture indicated completion within 5 min, ν_{max} 1800 cm^{-1}, 1725, 1630, 1610. The dichloromethane was removed *in vacuo* at 25°, and the residue redissolved in sodium-dried benzene (50 ml). The resulting solution and another solution containing N-(4-methoxybenzylamine)-1,4-xylylenediamine (179) (76 mg, 0.30 mmol) in sodium-dried benzene (50 ml), were simultaneously added dropwise over 6 h to a refluxing solution of triethylamine (1.00 g, excess) in benzene (100 ml) under an atmosphere of dry argon. After a further 12 h, the solvent was removed by distillation to give a foam, which was partitioned between water and dichloromethane. The aqueous phase was re-extracted with dichloromethane (x 2) and the combined organic phases dried, filtered and evaporated to give a yellow oil (200 mg); ν_{max} 1625 cm^{-1}. Tlc analysis (silica, eluant ethyl acetate) indicated a complex product mixture. The oil was redissolved in dry tetrahydrofuran (20 ml) and lithium aluminium hydride (200 mg, 5.26 mmol) added in one portion. The mixture was heated at reflux with stirring for 3 d. The reaction was quenched with saturated

sodium sulphate solution at 0^{o}, filtered and evaporated to give an oil which was chromatographed on silica (plc, Kieselgel H, eluant diethyl ether) to give a mixture of products which did not include the desired heterocyclophane (mass spectral evidence).

Preparation of 1-benzoyloxycarbonyloxyadamantane (204)

A solution containing benzoic acid (681 mg, 5.58 mmol) and triethylamine (563 mg, 5.57 mmol) in dichloromethane (10 ml) was added dropwise over 5 min to a stirred solution of 1-admantanyl chloroformate (1.28 g, 5.58 mmol) in dichloromethane (20 ml). After 5 min, tlc analysis (silica, eluant dichloromethane) indicated completion. The solvent was removed *in vacuo* and the residue rapidly chromatographed on silica (Kieselgel H, 20 g, eluant light petroleum-dichloromethane) to afford the title compound (1.11 g, 63%); ν_{max} (Nujol) 1810 cm^{-1}, 1750, 1190, 1170, 1030, 1015, 865, 700; ^{1}H nmr ($CDCl_3$) δ_H 1.75 (6H, m), 2.22 (9H, m), 7.50-8.30 (5H, m, aryl-H); m/e 300 ($M^{+\cdot}$), 256, 238, 198, 158, 152, 135, 105, 91.

Reaction of 1-benzoyloxycarbonyloxyadamantane (204) with benzylamine

To a stirred solution of 1-benzoyloxycarbonyloxyadamantane (204) (265 mg, 0.88 mmol) in dichloromethane (10 ml) at room temperature, was added freshly distilled benzylamine (96 µl, 0.88 mmol) dropwise via syringe over 2 min. Tlc analysis (silica, eluant dichloromethane) of the reaction mixture showed completion within 20 min. The solvent was removed *in vacuo*, and the residue chromatographed on silica (Kieselgel H, 12 g, eluant dichloromethane-diethyl ether) to give N-benzylbenzamide (149 mg, 80%), m.p. 104-106° (lit.[149] 105-6°); ν_{max} 3450 cm^{-1}, 1660 (amide C=O str.), 1510, 1480; and *N-(1-adamantanoxycarbonyl)benzylamine* (205) (40 mg,

16%); m.p. 115-116°; ν_{max} (CH_2Cl_2) 3450 cm^{-1} (-N-H str.), 2910, 2850, 1700 (carbamate C=O str.), 1500, 950; ^1H nmr ($CDCl_3$) δ_H 1.67 (6H, m), 2.13 (9H, m), 4.27 (2H, d, J 6-Hz, aryl-CH_2-), 7.30 (5H, br s, aryl-H); m/e 285 ($M^{+\cdot}$), 241, 224, 184, 150, 135, A sample was purified by plc (Kieselgel H, eluant dichloromethane) (Found: C, 75.63; H, 8.24; N, 4.86. $C_{18}H_{23}NO_2$ requires: C, 75.76; H, 8.12; N, 4.91%).

Reaction of 1-benzoyloxycarbonyloxyadamantane (204) with dibenzylamine

To a stirred solution of 1-benzoyloxycarbonyloxyadamantane (204) (257 mg, 0.86 mmol) in dichloromethane (10 ml) at room temperature, was added a solution containing dibenzylammonium toluene-4-sulphonate (317 mg 0.86 mmol) and triethylamine (87 mg, 0.86 mmol) in dichloromethane (5 ml) dropwise over 5 min. Tlc analysis (silica, eluant dichloromethane) of the reaction mixture indicated complete loss of starting material within 3 d. The solvent was removed *in vacuo*, and the residue chromatographed on silica (Kieselgel H, 15 g, eluant dichloromethane-diethyl ether) to give N-*(1-adamantanoxycarbonyl)dibenzylamine* (206) (283 mg, 88%) as a clear oil which solidified on standing, m.p. 76-77° from methanol-dichloromethane; ν_{max} (film) 2910, 2850, 1685 (carbamate C=O str.), 1450, 1410, 1230, 730, 700; ^1H nmr ($CDCl_3$) δ_H 1.67 (6H, m), 2.17 (9H, m), 4.40 (4H, br. s, aryl-CH_2), 7.30 (10H, br. s, aryl-H); m/e 375 ($M^{+\cdot}$), 327, 275, 240, 135; (Found: C, 80.21; H, 7.89; N, 3.84. $C_{25}H_{29}NO_2$ requires: C, 79.96; H, 7.78; N, 3.73%); and N,N-dibenzylbenzamide contaminated with adamantan-1-ol.

Preparation of 1,4,7,10,13,16-hexamethyl-1,4,7,10,13,16-hexa-aza-cyclooctadecane (213)

To a solution of 1,4,7,10,13,16-hexa-aza-cyclooctadecane (212) (1.00 g,

3.88 mmol) in formic acid (10 ml, 90%) at room temperature, was added paraformaldehyde (2.49 g, 5-fold excess) in one portion. The stirred suspension was heated to reflux under an atmosphere of nitrogen. After 72 h, the bulk of the excess formic acid was removed by distillation at atmospheric pressure. The residue was diluted with water, and the resultant solution basified (potassium hydroxide solution) and extracted with dichloromethane (x 3). The organic extracts were combined, dried, filtered and evaporated *in vacuo* to give an oily residue. Bulb-to-bulb distillation at reduced pressure gave *the title compound* (213) as a colourless oil which darkened on prolonged exposure to the atmosphere (1.22 g, 92%); bath temperature $140^{o}/2 \times 10^{-2}$ mmHg; ν_{max} (film) 2950 cm^{-1}, 2820, 2790, 14 1460, 1305, 1120, 1040; ^{1}H nmr ($CDCl_3$) δ_H 2.30 (18H, s, N-Me), 2.57 (24H, s, N-CH_2-CH_2-N-); m/e 343 ($M^{+\cdot}$ + 1), 298, 286, 272, 254, 241, 229, 215, 196, 184, 158, 113 (100) (Found: C, 62.88; H, 12.64; N, 24.41. $C_{18}H_{42}N_6$ requires C, 63.11; H, 12.36; N, 24.53%).

General procedure for sodium-potassium eutectic/hexamethyl-hexa-aza-18-crown-6/t-butylamine reductions

To a solution of 1,4,7,10,13,16-hexamethyl-1,4,7,10,13,16-hexa-aza-cyclooctadecane (213) in dry t-butylamine (freshly distilled from 4Å molecular sieves) under an atmosphere of dry argon at 25^{o} were added small pieces of freshly cut oil-free potassium and sodium, and stirring was commenced until formation of sodium-potassium eutectic (t_1 min) and a blue solution (t_2 min) had occurred. A solution of ester substrate in dry tetrahydrofuran (freshly distilled from molten potassium/benzophenone ketyl or dry t-butylamine was then added dropwise at such a rate as to maintain a blue solution (t_3 min). After addition was complete, the dropping funnel was washed through with more solvent (1 ml), and the residue partitioned between water (50 ml) and diethyl ether (50 ml). The

TABLE 9

Substrate (mmol)	Reducing System (mmol)		T^{o}	t_1	t_2	t_3	Products (%)	Notes
(214) (1.0399) in THF (2)	(213)	(2.518)	25	5	8	120	(215) (73)[a] (142) (15)[b]	
	K	(8.769)						
	Na	(2.609)						
	t-butylamine	(10)						
(214) (1.0339) in THF (2)	(213)	(0.0507)	25	45	95	-	(215) (55.8)[a] (142)(32)[b]	*d*
	K	(9.077)						
	Na	(2.913)						
	t-butylamine	(10)						
(216) (0.4000) in THF (2)	(213)	(1.009)	25	40	71	-	(215) (90)[a] (142)(5.8)[b]	
	K	(8.590)						
	Na	(2.913)						
	t-butylamine	(10)						
(217) (0.4000) in THF (2)	(213)	(0.9737)	25	120	180	120	(218) (33)[c] (219)(60.7)[c]	
	K	(8.590)						
	Na	(2.783)						
	t-butylamine	(10)						

Table 9/continued...

TABLE 9/continued...

Substrate (mmol)	Reducing System (mmol)		T^{o}	t_1	t_2	t_3	Products (%)	Notes
(217) (0.400) in t-butlamine (2)	(213)	(0.9942)	25	65	150	-	(218) (49)[c] (219) (34)[c]	e,f
	K	(8.205)						
	Na	(2.826)						
	t-butylamine	(10)						
(220) (0.400) in t-butylamine (2)	(213)	(0.9795)	25	60	75	75	(218) (73.6)[c] (219)(24)[c]	
	K	(8.769)						
	Na	(3.696)						
	t-butylamine	(10)						

a Recrystallised from dichloromethane-methanol

b Recrystallised from ethanol

c After chromatography

d Substrate added in one portion

e Reaction kept at 25^{o} for 3 d, and quenched with 10% aqueous acetic acid -78^{o}

f Recovered starting material

aqueous phase was re-extracted with diethyl ether (1 x 50 ml), and the combined organic layers dried, filtered and evaporated to dryness. The residue was separated by chromatography on silica (Kieselgel H, 15 g, eluant light petroleum-dichloromethane-diethyl ether mixture) and the crystalline products recrystallised once. The aqueous phase was acidified to pH 1 with dilute hydrochloric acid, extracted with diethyl ether, and the combined organic layers dried, filtered and evaporated to give the acid component (see Table 9).

General procedure for sodium-potassium eutectic/18-crown-6/t-butylamine reductions

To freshly distilled t-butylamine (10 ml) under an atmosphere of dry argon at 25°, were added small pieces of freshly cut oil-free potassium (1.1 g, 28.21 mmol) and sodium (0.2 g, 8.70 mmol). Stirring was commenced until formation of the sodium-potassium eutectic was complete and then dry 18-crown-6 (1.4 g, 5.34 mmol) was added in one portion. The resultant blue solution was adjusted to the required (internal) temperature and then a solution of ester (216), in dry tetrahydrofuran (3 ml), was added dropwise at such a rate as to maintain a blue solution (ca. 30 min). After addition was complete, the reaction was quenched by the careful addition of methanol (2 ml). The reaction mixture was worked up as before, and thenseparated by chromatography on silica (Kieselgel H, 15 g, eluant light petroleum-dichloromethane-diethyl ether mixtures) (see Table 10).

TABLE 10

T (^{o}C)	Yield (%) (215)	(142)[a]	(221)[a]	(222)
46	78	20	-	95
25	57	26	13	81
3	59	33	13	78
-48	51	46	23	61
-78[b]	9	88	trace	64

[a] Yield estimated by ^{1}H nmr spectroscopy

[b] Temperature held at -78^{o} for 30 min, then allowed to rise to 25^{o}.

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