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CYCLOTRIVERATRYLENES AND CRYPTOPHANES

ANDRÉ COLLET

Collège de France, Chimie des Interactions moléculaires, E.R. CNRS No. 285, 11, place Marcelin-Berthelot, 75005 Paris, France

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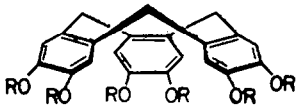
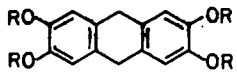
1. INTRODUCTION

The cyclotriveratrylene story begins with a report dated 1915 by Mrs G. M. Robinson,[1] that the acid catalyzed condensation of veratryl alcohol, or of veratrole and formaldehyde, produced in excellent yield a compound (m.p. 227°C) which she considered to be 2,3,6,7-tetramethoxy-9,10-dihydroanthracene, **1a**. This conclusion was based on the fact that the product gave, on nitration, bis(3,4-dimethoxy-6-nitrophenyl)methane, 6-nitroveratric acid, and 4,5-dinitroveratrole, and on

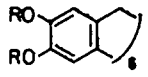
dehydrogenation 2,3,6,7-tetramethoxyanthracene (*in very small yield, however*). In making this proposal, she was doubtless influenced by an earlier, hardly justified claim by Ewins[2] (1909), that piperonyl alcohol or its chloride furnished, under a variety of acidic conditions, a high-melting compound similar in many respects to hers, and then described as being, 'with considerable probability' 2,3,6,7-dimethylenetetraoxy-9,10-dihydroanthracene **2a**.





1a, 2a

1 R = CH_3
2 R,R = CH_2<
3 R = H



1b, 2b

The structures **1a** and **2a** have been widely accepted in the literature up to the 1950s, when, some questions being raised on the dihydroanthracene constitution,[3] the alternative cyclic hexamer formulas **1b** and **2b** were proposed.[4,5] These new assignments were apparently supported by a bundle of chemical data,[6-10] and were substantiated by a determination of the space group and cell dimensions of Robinson's compound by X-rays.[11]

That Robinson's and Ewins' compounds did in fact have the unusual *trimer* structures **1** and **2** was established in 1963–65 by the works of Lindsey,[12,13] Erdtman *et al.*,[14] and Goldup *et al.*,[15] based on molecular weight determinations, re-examination of the earlier X-ray data interpretation, chemistry, mass and NMR spectroscopy.

The name *cyclotriveratrylene* (CTV) was coined by Lindsey for **1**, which was shown[16] at the same time by NMR to adopt this aesthetically pleasant locked crown conformation (C3v) depicted on the stereoformula and later evidenced by single-crystal X-ray crystallography.[17,18] As a consequence of the rigidity of the structure, it was soon recognized that suitably substituted derivatives might be *chiral*. Since the first observation of a weak rotatory power in such a compound by Luttringhaus and Peters[19] in 1966, many optically active cyclotriveratrylenes have been synthesised, mostly at the Collège de France in Paris.

For a long time, Robinson's compound has attracted attention in view of its ability to form crystalline inclusion compounds with small molecules. This property was initially mentioned in 1931 by Bhagwat *et al.*,[20] and was investigated in great detail by Caglioti *et al.* some 25 years later,[21] during the 'hexamer period'. The inclusion compounds of **1** and related host lattices such as *cyclotricatechylene* **3**[22] have been reviewed in 1984,[18] and will only be briefly presented here.

Since the last decade, interest in cyclotriveratrylenes has moved toward the use of the rigid, cone shaped frame for investigations and applications in several fields, including UV and CD spectroscopy, host–guest chemistry, molecular mechanics, liquid crystals etc. These works have been made possible because at the same time new and efficient synthetic routes have been set up for the preparation of a wide range of molecules containing the CTV structural unit.

This review is intended to provide an as exhaustive as possible literature coverage, since the first (or presumably so) papers by Ewins and Robinson, even though the way in which the matter is presented reflects more the current trends in the area, and especially, the work carried out at the Collège de France, than the historical course of the story. Accordingly, the paper contains three major sections; (i) the first one treats the cyclotriveratrylenes themselves, i.e. CTV **1**, its closest derivatives and its analogues (hetero-cyclotriveratrylenes), and discusses their chemistry, physical properties, and some applications; (ii) the second section is devoted to more complex molecules in which the CTV structure furnishes a *cavity*, for inclusion of suitable guest species. The major part of this section deals with the *cryptophanes*.[23] This name designates host molecules made of two CTV units linked in front of one another, and which are probably the most powerful complexing agents known to date for neutral, lipophilic molecules; (iii) the last section describes the chiroptical properties of cyclotriveratrylenes and cryptophanes. The optical activity of these compounds presents what is perhaps one of the most impressive illustrations of the Kuhn–Kirkwood coupled oscillator mechanism (exciton optical activity), a theory introduced to chemists by the pioneering work of S. F. Mason[24] in the 1960s, and recently popularized by Harada and Nakanishi.[25] The aim of the discussion is to show how the circular dichroism (CD) spectra of these complex molecules

can be explained by means of simple concepts, and reveal subtle properties of the benzene chromophore, that had never been observed before.

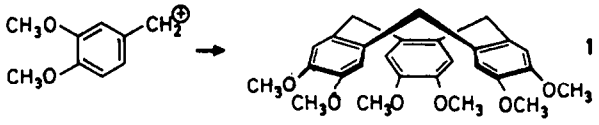
2. CYCLOTRIVERATRYLENES

First we discuss the chemistry, then the confirmations and finally some applications of cyclotriveratrylenes.

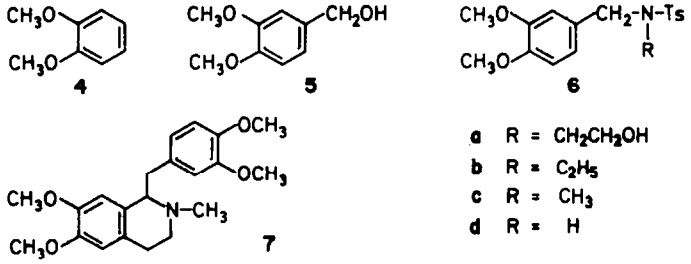
2.1. *Chemistry and Synthetic Methods*

2.1.1. *Cyclotriveratrylene synthesis and mechanistic considerations*

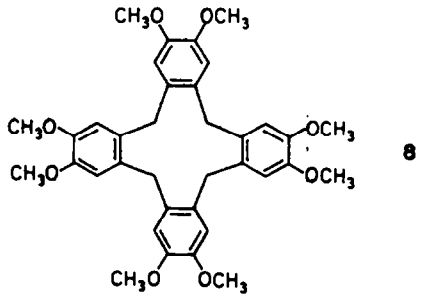
Cyclotriveratrylene, as a wealth of experimental data suggests, appears to be the major condensation product of the veratryl cation, whatever the way in which the latter is generated, from a variety of precursors, under acidic conditions.



Selected procedures for the preparation of **1** are assembled in Table 1. Although veratrole **4** or veratryl alcohol **5** have proven to be the most suitable starting materials (the best procedure being perhaps that of Robinson),[1] alternative syntheses have been reported in which the veratryl cation is generated from *N*-tosyl veratrylamine derivatives **6**.[26,27] These compounds have been (serendipitously) shown to afford **1** in almost quantitative yield, in the presence of perchloric acid.



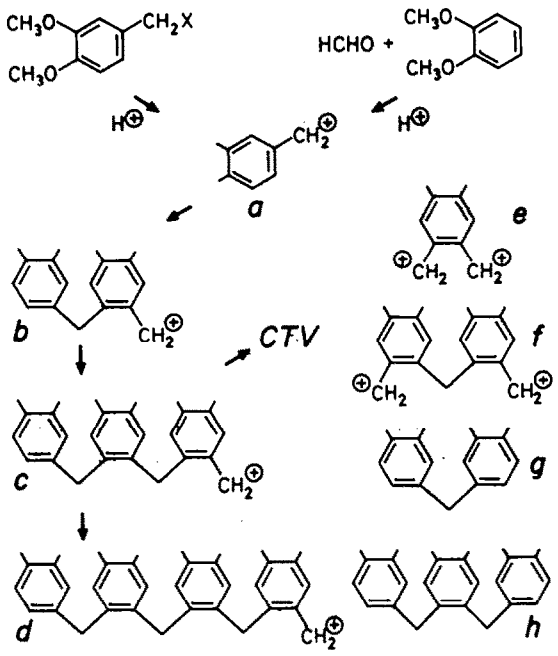
The formation of **1** is usually accompanied by that of the corresponding *tetramer* cyclotetraveratrylene **8** (CTTV),[28,29] and very likely of higher cyclic oligomers, that have neither been isolated nor characterized so far. Although there is a dearth of data, the yields of tetramer **8** in Table 1 suggest that its formation is favoured when the reaction takes place in organic solvents, rather than in aqueous mineral acids.



The strong tendency of the veratryl cation to condense to a cyclic trimer is attested by a number of reports on the unexpected or undesired formation of CTV: as a result of the self-condensation of veratryl chloride on standing in the presence of moisture,[30,31] during the attempted distillation of veratryl alcohol in the presence of traces of nickel,[32] in the oxidation of alkaloid laudanosine **7**,[20,33,34] and, in short, whenever a veratryl group may be involved in a reaction.[93-96]

It is not established whether the ease with which **1** is produced reflects a thermodynamic

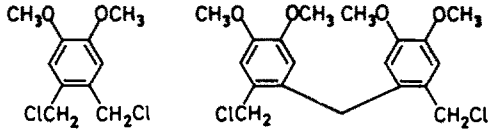
equilibrium favouring the cyclic trimer, or is simply the result of a kinetically controlled process, possibly driven by crystallization. Moreover, different mechanisms can play a role, depending on whether veratrole and formaldehyde, or a veratryl alcohol derivative, are employed as starting materials (Scheme 1). In the latter case, the reaction should proceed stepwise via the mono-, di-, and trimeric cations (**a**), (**b**), and (**c**); then (**c**) can either cyclize to **1** or react with (**a**) to give (**d**), a precursor of tetramer **8** and the higher polymers ((**d**) can also arise from dimerization of (**b**)).



Scheme 1.

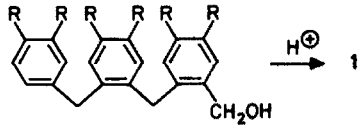
On the other hand, starting from veratrole and formaldehyde, one would also expect the formation of additional species, including (**e**), (**f**), (**g**), and (**h**). Reaction of (**e**) with (**g**), of (**f**) with veratrole, or of (**h**) with formaldehyde, would lead to (**c**) which eventually can cyclize to **1**.

Experimentally, the presence of (**e**) and (**f**) can be inferred from the isolation of the bis-(chloromethyl) derivatives **9** and **10**, during the course of a temperature controlled chloromethylation of veratrole; **10** has been shown to react with veratrole in refluxing acetic acid to give **1**.[13]



9 **10**

The formation of tetramethoxydiphenylmethane (**g**) has been observed at the onset of the same reaction, carried out at $-10°C$.[31] The behaviour of this intermediate has been the object of controversial claims. According to Robinson,[1] (**g**) condenses with formaldehyde in sulphuric acid to give **1**; this finding, which was one of her arguments for the dihydroanthracene structure **1a**, was denied by Lindsey,[13] and subsequently confirmed by Umezawa,[27] and Arcoleo.[35] The formation of **1** from (**g**) requires that the latter be first cleaved back to (**a**) or (**e**), and therefore suggests that some among intermediates (**a**)–(**h**) could be reversibly formed, under certain conditions.



11 R = OCH_3

Compound (**h**) has also been isolated and subsequently transformed into **1**, by reaction with formaldehyde.[4] Finally, the easiness of the cyclization of (**c**) is attested by the fast and quantitative conversion of the benzylic alcohol **11** into **1**, in the presence of perchloric acid at 3°C.[27]

Table 1. Selected procedures for the preparation of CTV (1) and CTTV (8).

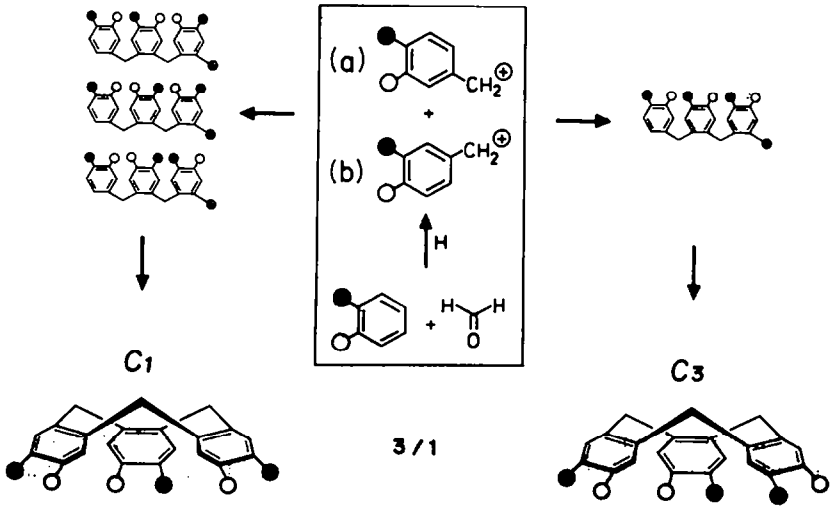
Starting materials	Catalyst	Solvent	Temp.	Isolated yields CTV	CTTV	Refs.
4 + HCHO[a]	70% H_2SO_4	none	r.t.	70		1,15
4 + HCHO[a]	70% H_2SO_4	none	0°C	21		13
4 + HCHO[a]	70% H_2SO_4	none	0°C	ca. 68	ca. 16	28
4 + HCHO[a]	60% $HClO_4$	none	r.t.	70		27
4 + HCHO[b]	6M HCl	none	reflux	"good"		16
4 + HCHO[b]	concd. HCl	none	r.t.	45		36
4 + HCHO[c]	HCl/$ZnCl_2$	none	-10°C	unspecified		30
5	concd. HCl	none	r.t.	unspecified		31
5	H_2SO_4	acetic acid	90°C	68	16	28
5	H_2SO_4	acetic acid	warm	87		13
5	60% $HClO_4$	none	r.t.	35		27
6a-d	60% $HClO_4$	none	r.t.	80-89		26,27
6a	BF_3 ether.	benzene	r.t.	45	26	27
6a	BF_3 ether.	benzene	reflux	35	30	27
6a	TsOH	benzene	reflux	56	21	27

(a) Aqueous HCHO; (b) paraformaldehyde; (c) trioxymethylene (after A. Collet, in "Inclusion compounds", J.L. Atwood, J.E.D. Davies and D.D. MacNicol Eds.; © Academic Press, London, 1984).

2.1.2. *Preparation of analogues and derivatives*

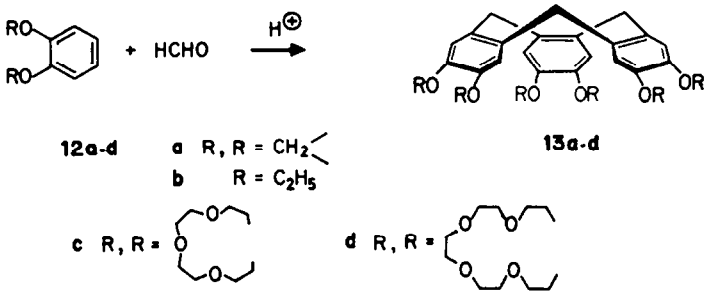
For the preparation of CTV analogues, several general methods can be employed: the 'trimerization route', which itself can be effected in two different ways **A** and **B**, and which resembles Robinson's procedures; the condensation of suitable diphenylmethanes with benzene derivatives; the modification of the CTV ring system, or of the peripheral substituents.

2.1.2.1. *The trimerization route* **A**. The acid catalyzed condensation of aromatic compounds with formaldehyde provides a simple access to CTV analogues. In practice, the scope of this method seems to be restricted to 1,2-disubstituted benzenes bearing two electron donating groups, such as catechol ethers. Moreover, as shown in Scheme 2, the cross condensation of the two regioisomeric



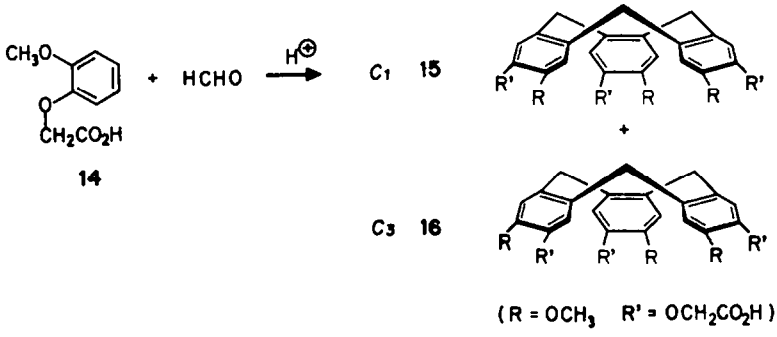
Scheme 2.

benzylic cations (**a**) and (**b**) which are produced initially is expected to end up with a mixture of two racemic trimers having C1 and C3 symmetry, unless the starting material is symmetrical. For instance, methylenedioxybenzene **12a**,[5] 1,2-diethoxybenzene **12b**[10] and the benzo-crown ethers **12c** and **12d**[37] afford the achiral C3v CTV analogues **13a–d**, respectively.



12a-d **a** R, R = CH_2 **b** R = C_2H_5 **c** R, R = **d** R, R = **13a-d**

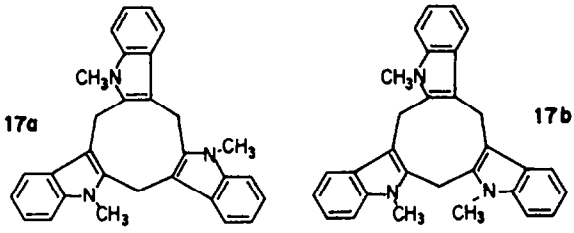
In contrast, the dissymmetrical ether **14** furnishes a mixture of the racemic C1 and C3 isomer **15** and **16** in a statistical 3 : 1 ratio.[38]



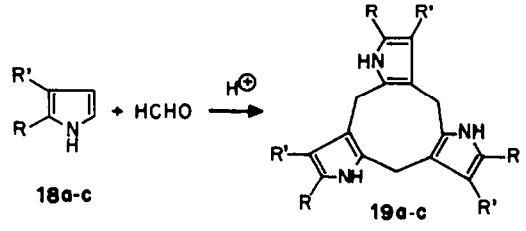
14

(R = OCH_3 R' = OCH_2CO_2H)

The same reaction applied to indole, pyrrole and thiophene derivatives has occasionally been shown to produce *hetero-cyclotriveratrylenes*; *N*-methylindole and formaldehyde thus give a cyclic trimer[39] (m.p. 275°C) in 24% yield, the structure of which may be either **17a** (C3) or **17b** (C1). Under similar conditions, however, indole itself affords a tetramer.



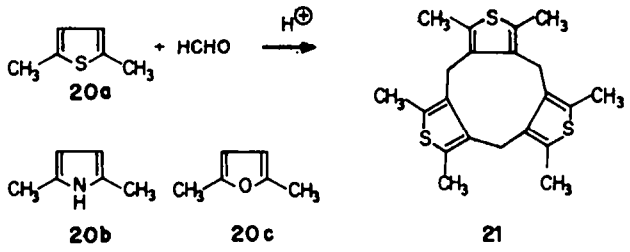
The pyrrole derivatives **18a–c** give in fair to excellent yields the corresponding hetero-CTVs **19a–c**, to which the C3 structure has implicitly been assigned.[40]



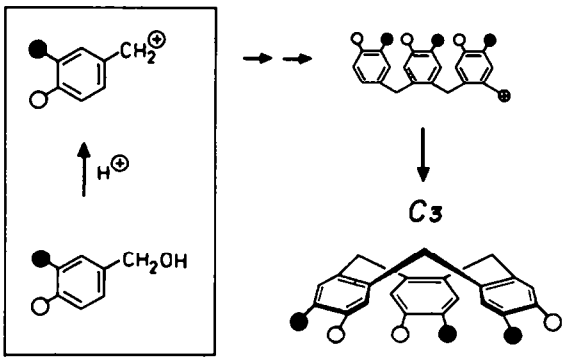
18a-c **19a-c**

	R	R'
a	CH_3	$CO_2C(CH_3)_3$
b	CH_3	$CO_2CH_2C_6H_5$
c	CO_2CH_3	H

Similarly, 2,5-dimethylthiophene **20a** and formaldehyde condense in refluxing acetic acid in the presence of zinc chloride and 'a little' mineral acid to the trimer **21** (42%) and a small quantity of the tetramer.[41] Contrariwise, 2,5-dimethylpyrrole **20b** and 2,5-dimethylfuran **20c** under similar treatment only afford intractable tars.

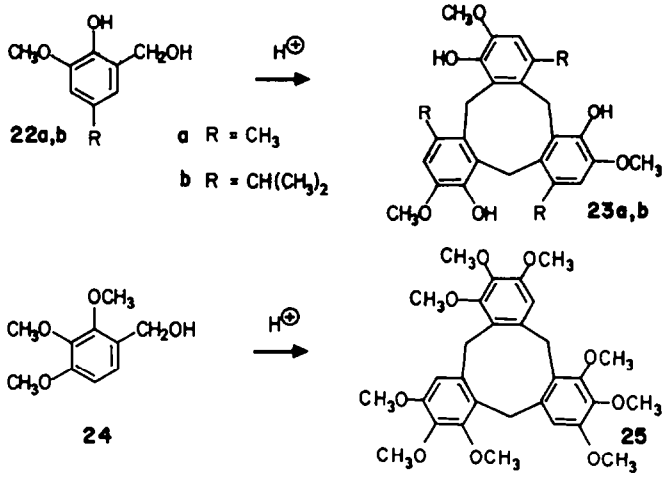


2.1.2.2. *The trimerization route* **B**. The utilization of suitable benzyl alcohols as starting materials has the advantage that a *single* benzylic cation is generated in the first step (Scheme 3), eventually leading to the formation of a single CTV analogue having C3 symmetry.



Scheme 3.

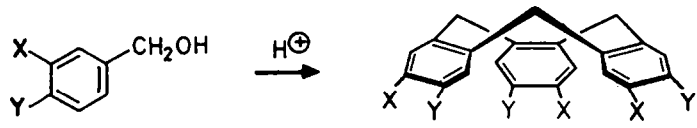
Although this method has been applied mostly to 3,4-disubstituted benzyl alcohols, it also works with trisubstituted derivatives such as **22a,b**[42] and **24**[43,45] which on reaction with acids give the corresponding C3 trimers **23a,b** and **25**, respectively.



Experimental data for the trimerization of 3,4-disubstituted benzyl alcohols are assembled in Table 2. In these reactions, one of the benzene apexes in *ortho* to the CH_2OH group must be activated toward electrophilic attack, which requires that a strongly electron donating group be present in *para* to this position (X in Table 2). The effect of the substituents on the trimerization yield is not always easily predictable, however. For instance, vanillyl alcohol (entry (2) of Table 2) affords tars under the conditions where its allyl ether (entry 7) is converted to the trimer **32** in 55% yield.[46,47] Nevertheless, the importance of having a strongly electron donating X substituent is evidenced by comparing the behaviour of 4-bromo-3-methoxybenzyl alcohol with that of its regioisomer in which the bromine atom occupies the 3-position (entries 9 and 10); only the former can be converted to the cyclic trimer **34**.[48] The observation that 3-methoxybenzyl alcohol (entry 11)

only affords a small yield of trimer **35** means that the Y substituent also plays a role in the reaction, perhaps by protecting this position toward undesired electrophilic attacks, leading to polymeric by-products.[49]

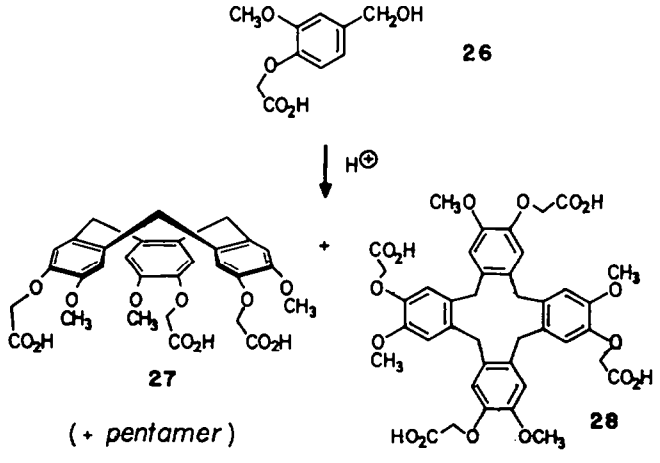
Table 2. Trimerization of 3,4-disubstituted benzyl alcohols



Entry	X	Y	Formula	Yield	Refs.
(1)	OCH_3	OCH_3	1	ca. 70%	
(2)	OCH_3	OH	29	0	46
(3)	OCH_3	OC_2H_5	30	51	50
(4)	OCH_3	OCH_2CO_2H	27	45	51
(5)	OCH_2CO_2H	OCH_3	27	42	38
(6)	OCH_3	$OCH_2CH_2OCH_2CO_2H$	31	40	52
(7)	OCH_3	$OCH_2CH{=}CH_2$	32	55	46,47
(8)	OC_2H_5	$OCH_2CH{=}CH_2$	33	15	50
(9)	OCH_3	Br	34	25-40	48,49,53
(10)	Br	OCH_3	34	0	48
(11)	OCH_3	H	35	6.5	49

The apparent absence of C1 trimers in the condensation products of substituted benzyl alcohols supports the validity of the sequence depicted in Scheme 3, and provides interesting information with regard to the extent to which the various steps in the mechanism discussed in Section 2.1.1 above might be reversible. The results certainly indicate that the stepwise condensation (**a**) → (**b**) → (**c**) → C3-trimer (Schemes 1 and 3) is faster than the cleavage and equilibration of the intermediates and/or of the final products. The use of suitable benzyl alcohols, rather than the condensation of aromatic compounds with formaldehyde, is therefore recommended for the regiospecific preparation of C3 cyclotriveratrylenes by the trimerization route.

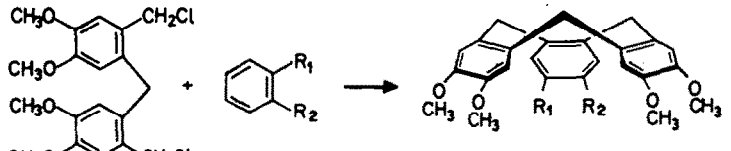
The amount of higher cyclic oligomers formed in addition to the trimer in the reactions described in Table 2 is generally unknown or unspecified, except in one case, the trimerization of **26** to **27**, for which a detailed study has been carried out.[38] When the reaction is effected in 65% aqueous perchloric acid, without added organic solvent, trimer **27** is isolated in 45% yield, with only minor amounts of the corresponding tetramer **28** and pentamer. When, to the mineral acid, is added a



small volume of acetic acid (1 : 5) 32%, 9% and 1% of trimer, tetramer and pentamer, respectively, are obtained. These figures become 28%, 20% and 7% for a 3 : 4 ratio of acetic acid/perchloric acid. The organic solvent therefore tends to increase the yield of higher cyclic oligomers, perhaps by increasing the solubility of the trimer, which generally crystallizes out during the reaction. Incidentally, the C4 tetracarboxylic acid **28**, which is available in fair yield from **26**, is a potentially useful material for the design of new host compounds.

Some of the C3 cyclotriveratrylenes of Table 2 may be obtained in large quantities and lend themselves well to subsequent transformations (see 2.1.2.5). This is especially true for the tris(*O*-allyl) ether **32**, one of the most useful intermediates in CTV chemistry.[46,47]

2.1.2.3. *The diphenylmethane route.* The condensation of diphenylmethane **10** with 1,2-disubstituted benzenes to give trimers of structures **36a–c** was originally described by Lindsey.[13] The chiral analogue **37** was obtained by this method and was resolved by chromatography over cellulose acetate into samples exhibiting weak rotations: $[\alpha]_{405}$ +7.5° and −5° (unknown ee).[19]

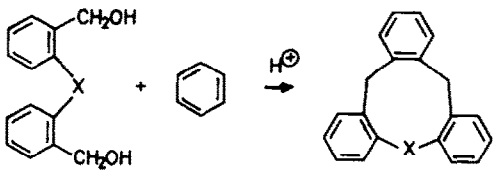


10

36 a $R_1 = OCH_3$ $R_2 = OC_2H_5$
b $R_1 = OCH_3$ $R_2 = CH_3$
c $R_1 = R_2 = OC_2H_5$

37 $R_1 = OCH_3$ $R_2 = OCH_2C_6H_5$

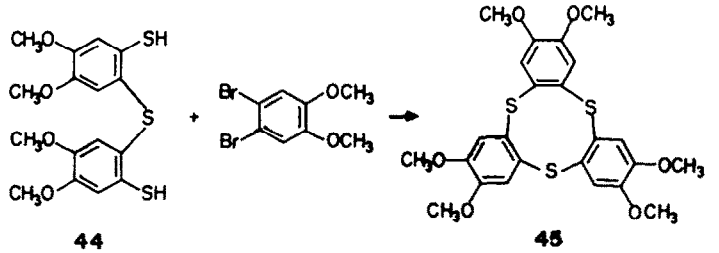
Sato *et al.*[36,54,55] have generalized this reaction to the synthesis of analogues devoid of methoxy substituents (**41–43**), by condensation of diols **38–40** with benzene in the presence of sulphuric acid, under high dilution conditions. This method was the first to give access to the parent hydrocarbon *cyclotribenzylene*, **41** (another synthesis of **41** is described in Section 2.1.2.5).



38 X = CH_2 **41**
39 X = O **42**
40 X = S **43**

Trithiacyclotriveratrylene **45** has been prepared by a similar route, by reacting the ditiol **44** with 4,5-dibromoveratrole in the presence of Cu_2O.[56,57] This trimer forms metal complexes, such as [**45**.CuBr.H_2O.acetone], in which the copper is tetrahedral,[58] [**45**.$Rh(NO_3)_3$.(dimethylacetamide)$_3$], in which the rhodium is octahedrally co-ordinated[59] and [**45**.$PtCl_2$.(dimethylacetamide)$_{3/2}$] in which the platinum atom has a distorted square pyramidal coordination.[60]

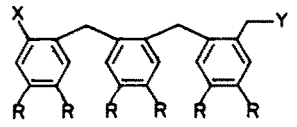
The corresponding tetrathiacyclotriveratrylene is also known. It forms a complex with copper(I), the crystal structure of which has been determined.[97]



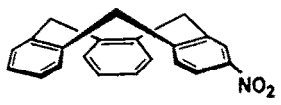
44 **45**

2.1.2.4. *Chemical transformation of the ring system.* Only few reactions allow the functionalization of the CTV structure itself, without destroying the 9-membered ring. Nitration, as well as

bromination and chlorination of **1**, exclusively afford cleavage products (**46**) which in turn are further cleaved to diphenylmethane and veratrole derivatives.[36,55,61,62] This behaviour, which easily explains Robinson's misassignments, should be ascribed to the high electron density induced in the vicinity of the 9-membered ring by the six methoxy substituents, rather than to ring strain; in effect the hydrocarbon cyclotribenzylene **41** gives on nitration the mononitro derivative **47**, with no indication of ring cleavage.[36]

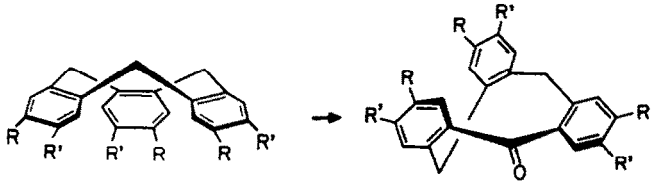


46 R = OCH_3 X = NO_2, Cl, Br Y = OH, Cl, Br

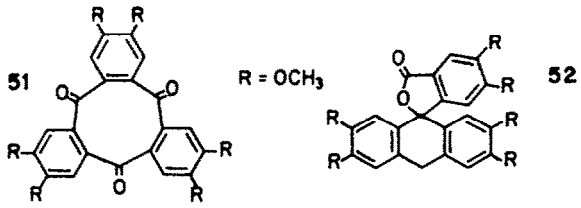


47

Cyclotriveratrylene **1** and cyclotribenzylene **41** can be oxidized in good yield to the monoketones **48**[12,13,63,64] and **49**,[54,55] and likewise oxidation of **30** presumably gives ketone **50**,[8] to which a hexameric diketone structure has been incorrectly assigned. Further oxidation of **48** leads to a compound which was first considered[64] to be the triketone **51**, and which in fact[65] is the rearranged lactone **52**.

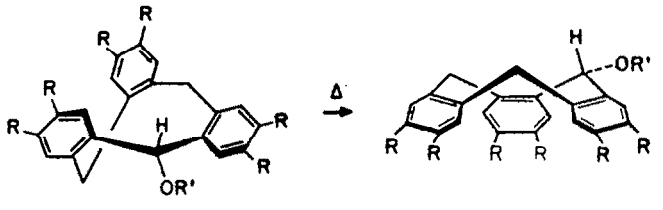


1 R = R' = OCH_3 **48**
41 R = R' = H **49**
30 R = OCH_3 R' = OC_2H_5 **50**



51 R = OCH_3 **52**

Ketones **48–50** no longer adopt the crown conformation of **1**, but instead exhibit flexible conformations (see 2.2). The carefully controlled reduction of **48** by sodium borohydride or lithium aluminium hydride affords the unstable, conformationally flexible alcohol **53a**, which in turn is readily converted into the stable isomer **54a**, having a locked crown conformation with the OH group equatorial.[63,64] The unstable alcohol **53a** can be virtually instantly etherified by alcohols such as ethanol,[64] chloroethanol or ethyl glycolate,[38] to give the conformationally flexible and unstable ethers **53b–d** which on heating transform to the stable ethers **54b–d**. The high reactivity of **54a** is probably due to a better stabilization of the cationic transition state (SN1 process) in the flexible conformer, than in the crown. The sequence of reactions **48** → **53a** → **53b–d** → **54b–d** therefore provides a convenient way, yet practically unexplored, to functionalize **1** and its analogues at the methylene bridge positions.[38]

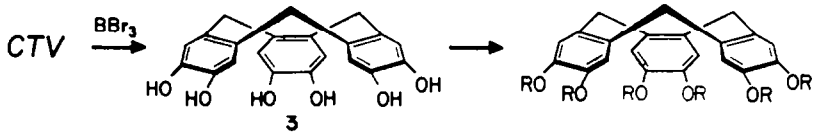


53a-d

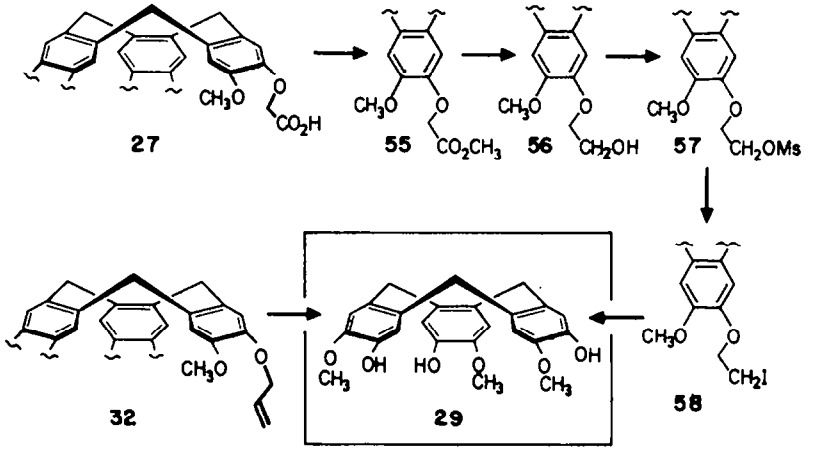
a R' = H
b R' = C_2H_5
c R' = CH_2CH_2Cl
d R' = $CH_2CO_2CH_3$

54a-d

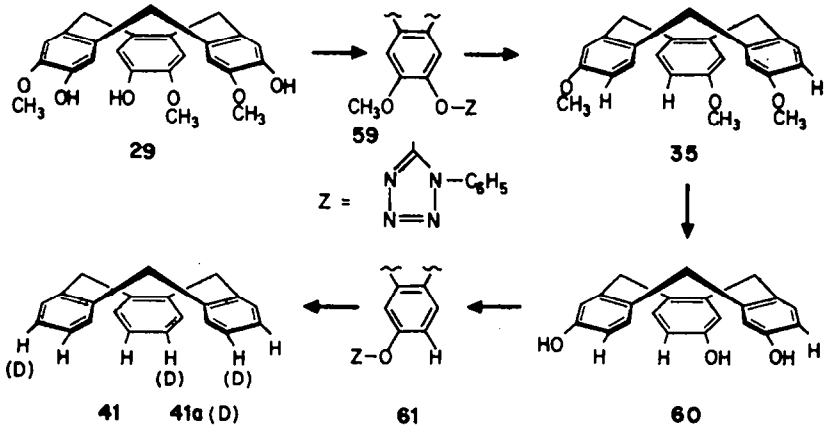
2.1.2.5. *Chemical transformation of the peripheral substituents.* A simple route for derivatization of CTV itself consists in its complete demethylation, which can be satisfactorily achieved with boron tribromide.[13] The resulting hexaphenol cyclotricatechylene **3** has been utilized for the synthesis of various hexa(*O*-alkylated) or hexa(*O*-acylated) derivatives, some of which possess interesting liquid crystal properties (Section 2.3) or complexing properties (Section 2.4).



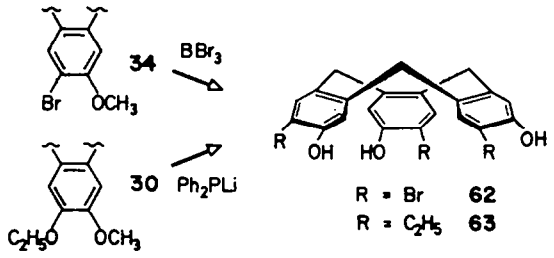
For the selective transformation of either the R or the R′ substituents of C3 cyclotriveratrylenes, several efficient solutions have been set up. C3-*Cyclotriguaicylene* **29**, which cannot be obtained directly by trimerization of vanillyl alcohol (see Table 2 above), can be prepared in five steps from the C3-triacid **27**,[51,66] or, better, in one step from the tris(*O*-allyl) ether **32**.[46,47]



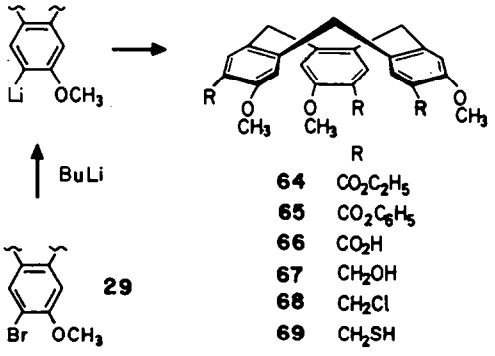
Stepwise deoxygenation of **29** to **41** can be effected[47,66] under mild conditions via the tris(*O*-phenyltetrazolyl) ether **59**, which on catalytic hydrogenolysis (r.t.) affords C3-*cyclotrianisylene* **35**. The latter on reaction with boron tribromide is converted to C3-*cyclotriphenolene* **60**, an interesting compound lending itself to various applications. Deoxygenation of **60** to **41** can eventually be achieved by hydrogenolysis of the tetrazolyl ether **61**. The same sequence starting from optically active **60** and using deuterium instead of hydrogen for the deoxygenation of **61** leads to optically active C3-cyclotribenzylene-d_3 **41a**, the chirality of which is solely due to isotopic substitution.[47]



Although the tribromide **34** is satisfactorily demethylated to **62** by reaction with boron tribromide,[48] this reagent does not allow a selective cleavage of the methoxy *vs* the ethoxy ethers of **30**, to give **63**. This reaction can be cleanly achieved by using lithium diphenylphosphide, a mild and selective demethylation reagent.[50]



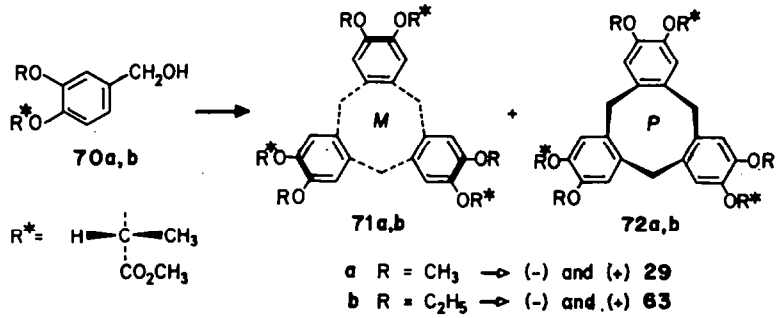
Keipert and Cram have described[49,53] several interesting reactions, starting from the tribromide **34**, and permitting the introduction on the benzene rings of functionalized sp_2 or sp_3 carbon atoms. Thus **34** is converted into the triesters **64** and **65** by lithium halogen exchange, followed by the reaction of the resulting aryl lithium with ethyl chloroformate and diphenyl carbonate, respectively. The triethyl ester **64** can subsequently be hydrolyzed to the triacid **66**, or reduced to the triol **67**, which in turn leads to the trichloride **68** and the trithiol **69**.



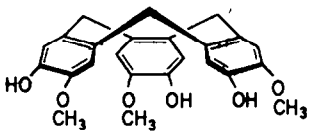
2.1.3. *Preparation of optically active* C3-*cyclotriveratrylenes*

C3-Cyclotriveratrylenes are resolvable because, as is discussed in Section 2.2, the conformational inversion of their 9-membered ring is very slow at room temperature. These compounds have been resolved by means of suitable diastereoisomers. To this end, appropriate chiral auxiliary groups have been introduced either during the synthesis of the CTV ring by trimerization, or by reaction of resolving agents with functionalized racemic C3-trimers.

2.1.3.1. *Synthesis of diastereoisomers by trimerization.* The treatment of an optically active vanillyl alcohol derivative such as **70** under acidic conditions affords a mixture of the diastereoisomeric C3-trimers **71** and **72**, which only differ in the configuration of the crown structure.[67,68] Chromatographic separation of **71** and **72** (which are not necessarily obtained in equal amount), followed by the cleavage of the chiral groups R* (five steps), lead to the enantiomers of C3-cyclotriguaiacylene **29**[67] or of the ethoxy analogue **63**.[68] The structure and absolute configuration of diastereoisomer **71b** have been established by X-rays,[68] which allowed the subsequent determination of the absolute configuration of **63** and of most of the optically active CTVs known to date, and which could be chemically correlated to **63**.

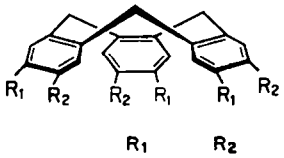


Since these compounds are conformational isomers, their handedness can be specified by means of the *P* and *M* descriptors.[68] The absolute configuration of cyclotriguaicylene **29** is thus *M*-(+) (as shown on the formula) or *P*-(−).

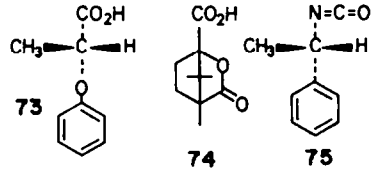


M-(+)-**29**

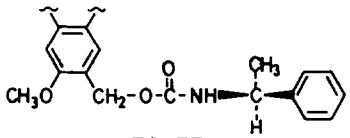
2.1.3.2. *Diastereoisomers from (±)-cyclotriveratrylenes.* Cyclotriguaicylene **29** has been resolved by esterification with ω-camphanic acid **74** and chromatographic separation of the diastereoisomeric triesters, followed by their reductive cleavage.[50] The related triphenols **60**,[47] **62**,[48] and **63**[50] have similarly been resolved with *R*-(+)-2-phenoxypropionic acid **73**. Finally, the triol **67** could be resolved by conversion to the diastereoisomeric carbamates **76** and **77**, obtained by reaction with the chiral isocyanate **75**.[49] The diastereoisomers can be separated chromatographically; alternatively, a 10-day heating of a mixture of **76** and **77** results in the epimerization of the CTV ring in solution, and to a complete conversion to a single diastereoisomer (80% yield) driven by its crystallization. Thus (±)-**67** can be converted into a single enantiomer by this elegant example of a crystallization induced asymmetric transformation.



	R_1	R_2
29	OCH_3	OH
63	OC_2H_5	OH
60	H	OH
62	Br	OH
67	OCH_3	CH_2OH



73 **74** **75**



76,77

2.2. *Geometry and Conformations*

One of the most interesting properties of CTV and its congeners is their stable crown conformation, evidenced, in the NMR spectra, by the characteristic AX quartet of the methylene bridges (Fig. 1). The geometry of the crown is accurately known from several X-ray structures,[17,22,68] and may be defined by the angle $\Phi = 47 \pm 2°$ between the plane of each benzene ring and the C3 axis, and by the distance $d = 4.79$ Å between their centres. The pseudo-axial hydrogens of the methylene bridges (H_a), separated by only 2 Å, resonate 1.2 ppm downfield with respect to their pseudo-equatorial counterparts (H_e), a consequence of the steric compression; there is therefore no hole at the top of the crown. The aromatic hydrogen atoms of two adjacent rings (e.g., H(1) and H(14)) are almost at contact distance (2.5±0.1 Å between their centres) and thus there is not much room in these positions for a substituent, except a small one (see below).

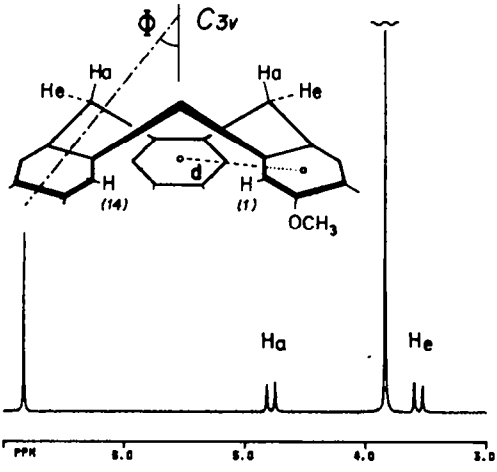
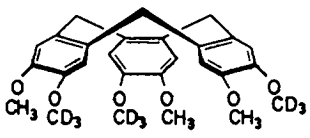


Fig. 1. Geometry and 200 MHz ^1H NMR spectrum of CTV **1** in $CDCl_3$.

The activation barrier for the crown-to-crown interconversion in **1**, which is too high to be measured by NMR techniques, has been found to be 26.5 kcal mol^{-1}, from the racemization rate of C3-cyclotriveratrylene-d_9 **78**, the chirality of which is due to isotopic substitution.[69]



M-(-)-**78**

Barriers of similar magnitude have been measured by the same method for various chiral CTVs, including hexasubstituted (**29**, **79**, **93**, **94**) and trisubstituted (**35**, **60**) derivatives, and the isotopically chiral hydrocarbon **41a**.[47,70] Although the activation barriers ($\Delta G^{\ddagger}$) show little variation from one compound to another, the differences in terms of rate constants may be more significant, and the time necessary to lose 1% of rotation at 20°C in solution ($t_{1/100}$) actually ranges from 12 h for **78** and **79** to 48 h for **60**. These compounds can therefore be handled in solution *at room temperature* without appreciable loss of optical activity, during a period of time generally sufficient for physical measurements of chemical transformations; they racemize, however, relatively rapidly on heating. Their racemization half-time ($t_{1/2}$) which is of the order of 3 years at 0°C, and 1 month at 20°C, is reduced to a few minutes at 100°C, and to less than 0.1 s at 200°C. This is not inconsistent with the invariance of the NMR spectra on heating,[16] which is simply due to the large frequency difference of the exchanging sites $H_a \Leftrightarrow H_e$ ($\Delta\nu \sim 75$ Hz at 60MHz, ~ 250 Hz at 200 MHz) with respect to the rate constant of the inversion at 200°C ($k \sim 4\ s^{-1}$ for **29**).

Table 3. Activation parameters for crown inversion

	X	Y	Solvent	$\Delta H^{\#}$ kcal/mol	$\Delta S^{\#}$ cal/mol/K	$\Delta G^{\#}$(298K) kcal/mol	$t_{1/100}$ at 20°C (h)
78	OCH_3	OCD_3	$CHCl_3$	25.9(0.3)	-1.9(1.4)	26.5	12.1
29	OCH_3	OH	$CHCl_3$	27.0(0.4)	-0.6(1.2)	27.2	40.3
41a	D	H	$CHCl_3$	26.5(0.7)	-1.4(2.2)	26.9	25.2
35	OCH_3	H	$CHCl_3$	28.1(0.1)	+3.1(0.5)	27.1	39.8
60	OH	H	dioxane	27.5(0.3)	+0.8(1.2)	27.2	48.0
79	$OCOCH_3$	OCH_3	$CHCl_3$	26.4(0.3)	-0.5(1.0)	26.5	12.0
93	OCH_3	(a)	$CHCl_3$	25.8(0.5)	-3.0(1.0)	26.6	16.8
94	OCH_3	$OCH(CH_3)_2$	$CHCl_3$	27.5(0.4)	0(1)	26.8	23.0

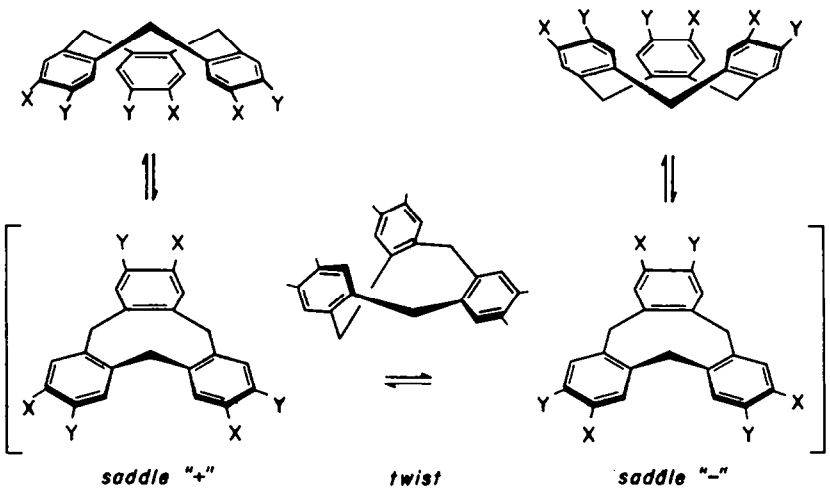
(a) Y = [(4-Hydroxymethyl-2-methoxyphenoxy)ethoxy]

The energy barrier for ring inversion in CTVs is about 12 kcal mol^{-1} higher than in the parent ring system *cis,cis,cis*-1,4,7-cyclononatriene **80**.

80

The mechanism of the conformational inversion in these compounds has been discussed by Sato and Uno,[55] and by Dale.[74] Energy calculations on the tribenzocyclononatriene system (**41**) have been reported by Ermer.[75] It is assumed that inversion does not take place via a planar transition state, but through a flexible conformer, readily pseudorotating, via *twist* forms, among six equivalent *saddle* forms, or among three equivalent pairs of enantiomeric saddles in the case of C3 compounds such as those of Scheme 4, or three non equivalent pairs for C1 compounds such as **37**.

The measured barrier, corresponding to the rate determining step, certainly represents the passage from a crown to a saddle form, a process which might involve either the flipping of one phenyl ring (of one double bond in **80**), or the flipping of one methylene bridge. The former mechanism has been preferred by Sato,[55] and by Dale,[74] whereas the latter has been favoured by Ermer,[75] on the basis of force-field calculations. The computational estimation of the energy barrier ($\Delta H^{\ddagger}$ 33.9 kcal mol^{-1}) is, however, $\sim 30\%$ larger than the measured value. One of the reasons for this overestimation is that the rate determining transition states involve very large bond angle

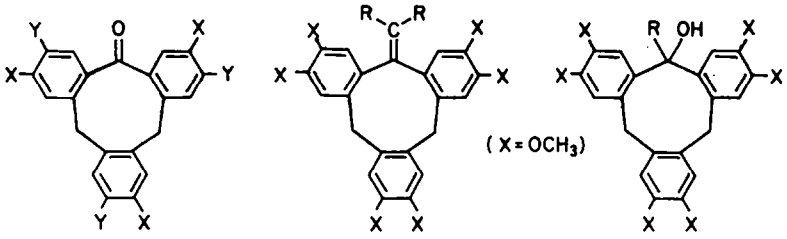


Scheme 4.

opening, the energetical description of which requires negative anharmonicity terms which as yet are improperly calibrated.[76]

The intermediate saddle/twist form, which is not observable in CTV itself, should therefore be disfavoured with respect to the crown by at least 3–4 kcal mol^{-1}, which might be due, in part, to a repulsive interaction between the inward hydrogen atom of the methylene bridge pointing into the ring, and the opposite phenyl ring. The flexible conformer may become populated only when structural changes in the molecule lead either to its stabilization, or to the destabilization of the crown form (or conceivably for both reasons).

The former reason probably holds in the monoketones **48**[64] and **49**[55] (also, presumably, **50**),[8] which exist exclusively in a rapid interconverting twist form, allowing better conjugation of the carbonyl group with the adjacent phenyl rings. When the ketone **48** is reduced, the conjugation energy is lost, and the resulting, metastable, flexible alcohol **53a** rapidly returns to the crown form. In the exocyclic methylene (**81**) and isopropylidene (**82**) analogues, both flexible and crown forms are in equilibrium, and the barrier for the flexible to crown conversion has been estimated at ~22 kcal mol^{-1}.[64]



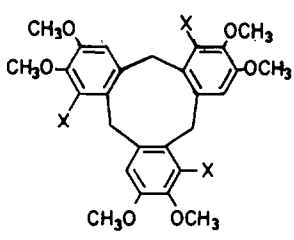
48 X = Y = OCH_3
49 X = Y = H
50 X = OCH_3 Y = OC_2H_5

81 R = H
82 R = CH_3

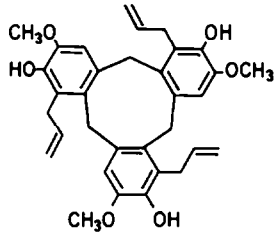
53a, 54a R = H
83 R = CH_3

Destabilization of the crown may arise from steric hindrance created either by geminal substitution of one methylene group, as in **83**,[64] or by the presence of bulky substituents at the aromatic positions *ortho* to the 9-membered ring. This is the case in the tribromo derivative **84**,[77] a substance isolated from red algae *Halopytis pinastroides* (probably as an artifact), in **85**,[46] and in **86–89**.[42] This is also the case in the indole, pyrrole, and thiophene CTV analogues **17**, **19** and **21** (Section 2.1.2) which all adopt a flexible conformation.[39–41] The nonamethoxy compound **90**,[43] however, displays a locked crown conformation, and CPK models actually show that a OCH_3 group can still be accommodated at this position, whereas a bromine atom (**84**) or an allyl group (**85**) cannot.

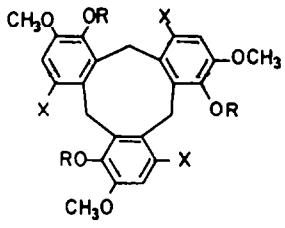
The replacement of one methylene bridge by heteroatoms such as oxygen or sulfur also has conformational consequences. The oxonin **42** is a flexible molecule, which probably undergoes interconversion between saddle and twist forms,[74] rather than a fast exchange between crown forms,



84 X = Br
90 X = OCH_3

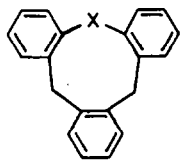


85

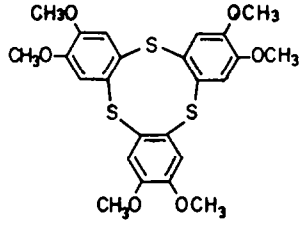


86 X = CH_3 R = H
87 X = CH_3 R = Ac
88 X = i-C_3H_7 R = H
89 X = i-C_3H_7 R = Ac

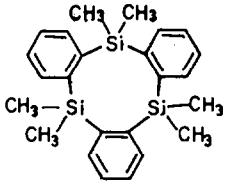
as was originally suggested.[55] The preferred conformation of **42**, which becomes observable by NMR at 183 K, might be a saddle with the ether oxygen pointing into the ring. In contrast, both the sulphide **43**, and the sulphone **91**, are conformationally locked. Although a rigid crown was proposed,[55] a rigid saddle form, with the sulphur atom pointing into the ring, as in the oxonin **42**, cannot be ruled out on the basis of the NMR data.



42 X = O
43 X = S
91 X = SO_2



45



92

Trithiacyclotriveratrylene **45** exists in a temperature and solvent dependent equilibrium of the crown and the saddle form.[56-59] Both conformers can be isolated in a pure state by a suitable choice of solvents, from which they form crystalline solvates. The crown form crystallizes from chloroform as a 1 : 2 adduct, and the saddle is obtained from benzene as a 1 : 0.5 adduct.

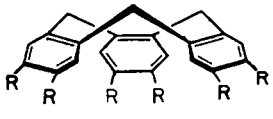
The recently synthesised silicium analogue **92** shows a flexible conformation on the NMR time scale.[78]

Finally, the conformational behaviour of cyclotetraveratrylene **8** has been studied by White and Gesner, [28,29] and has been later discussed by Dale.[74] This compound which is related to the (unknown) *cis,cis,cis,cis*-1,4,7,10-cyclododecatetraene,[75] is a flexible molecule. The preferred conformation, observable by NMR at 183 K, is a *sofa* (C2h), exchanging among 8 equivalent forms over a barrier of 12.9 kcal mol^{-1}. A similar behaviour has been found for the related tetraacid **28**.[38]

2.3. *Cyclotriveratrylene-Based Liquid Crystals*

Disc-shaped molecules that consist of a rigid, flat core (benzene, triphenylene, truxene, phthalocyanine, etc.), surrounded by a sufficient number of elongated, flexible chains, often form thermotropic *columnar* mesophases. Such columnar mesophases can also be obtained when the flat core is replaced by the cone-shaped cyclotriveratrylene unit.[79-84]

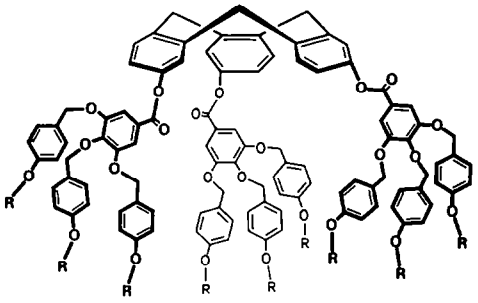
Three types of CTV-based mesogens have been synthesised so far; (i) hexa-*n*-alkylethers (**95**)[80] of cyclotricatechylene **3**; (ii) hexaesters of **3** with *n*-alkanoic acids (**96**),[79,80,82] *p*-*n*-alkylbenzoic acids (**97**),[81] and *p*-*n*-alkoxybenzoic acids (**98**);[79,82] (iii) a triester of cyclotriphenolene **60** with a 3,4,5-trisubstituted benzoic acid (**99**).[84] The latter was prepared in racemic and optically active forms.



3 R = OH

95 R = $CH_3(CH_2)_nO$ n = 3-11
96 R = $CH_3(CH_2)_n CO_2$ n = 6-14
97 R = $CH_3(CH_2)_n$-C6H4-CO_2 n = 6-9
98 R = $CH_3(CH_2)_nO$-C6H4-CO_2 n = 9, 11

In these mesophases, which often exist in a wide temperature domain (e.g., from r.t. to 150°C for **99**), the cone shaped CTV units stack in columns, at a distance of ~4.8 Å, identical to that observed in the crystals of **1**[79] (see Fig. 2 in Section 2.4.1.1 below). In a column, the cones are embedded in one another, making the column axis *polar*. The conical shape of the cores certainly contributes to the stability of these mesophases, in making the molecular displacements perpendicular to the column axes more difficult. The tight packing within the columns probably also accounts for the higher barrier for the CTV ring inversion in the mesophase ($\Delta G_{\ddagger}^{\ddagger}$ 30.3 kcal mol^{-1} at 100°C for **99**) than in isotropic solution (26.9 kcal mol^{-1}).[84] At ~145°C, the half-life of a given cone conformer in the mesophase is about 4 min., whereas in solution at the same temperature it is a few seconds. Such mesophases could be ferro-electric,[82,84] if all the columns could adopt the same orientation in a macroscopic domain, for instance under the influence of an electric field.



99 R = $C_{12}H_{25}$

Similar mesogens based on cyclotetraveratrylene **8** have been prepared, and also show columnar mesophases.[81]

2.4. *Cyclotriveratrylenes as Hosts*

Cyclotriveratrylene and several of its derivatives, like many compounds having trigonal symmetry,[85] form crystals which are not closely packed and which can thus accommodate guest molecules within voids of their lattice. This property is not necessarily associated with a crown conformation. On the inverse, the existence of a rigid, bowl-shaped geometry is of greater importance for the formation of host–guest molecular complexes.

2.4.1. *Crystalline inclusion compounds*

The compounds discussed here form crystalline inclusion complexes, but do not give any observable host–guest interaction in solution.

2.4.1.1. *Cyclotriveratrylene.* The ability of **1** to form crystalline solvates with water and benzene was first observed by Bhagwat.[20] Caglioti *et al.*[21] subsequently reported the formation of inclusion compounds with a variety of molecules ranging in size from ethanol to decaline (Table 4). From IR and X-ray measurements (determination of the cell dimensions) carried out on a number of these complexes, they identified two types of monoclinic phases (α and β), depending on whether bulky (benzene, chloroform) or thread-like molecules (carbon disulphide, butyric acid) were included. At that time, however, **1** was still considered to be a hexamer, and the host/guest ratios indicated by Caglioti should therefore be modified accordingly. The corrected values have been listed in Table 4, together with those of other complexes of **1** described by Hyatt,[22] and by Burlinson;[86] in the latter case, the inclusion compounds have been characterized by means of solid state ^{13}C NMR spectroscopy (the same technique has been applied for the study of the chloroform and dichloromethane solvates of cyclotetraveratrylene **8**).[88]

The crystal structure of the CTV–benzene–water complex was determined in 1979 by Cerrini *et al.*[17] and by Cesario *et al.*[87] (Fig. 2). The structure (C2/c) consists of columns of CTV molecules, juxtaposed parallel to a crystallographic axis (*b*). The guest molecules are accommodated in channels parallel to the columns. The channels have an approximately oval section, and are constricted every 9.63 Å by waists formed by methyl groups. A channel can thus be described as a succession of cages, communicating with each other. The same structure probably holds for the other compounds listed

Table 4. Cyclotriveratrylene inclusion compounds

Guest molecules	Type	b(Å)	CTV : guest ratio	Refs.
Benzene	α	9.61	1 : 0.6	21
"			1 : 0.59	86
Benzene-water	α	9.629	1 : 0.5 : 1	17
"			1 : 0.47 : 0.8	86
Chlorobenzene	α	9.64	1 : 0.55	21
Toluene	α	9.73	1 : 0.1	21
"			1 : 0.47	86
Chloroform	α	9.78	1 : 1.46	21
"			1 : 2.1	86
Acetone	β	8.39	1 : 0.27	21
"			1 : 0.42	86
Carbon disulphide	β	8.28	1 : 0.48	21
Butyric acid	β	8.07	1 : 1	21
Ethyl acetate			1 : 1.6	22
Methyl ethyl ketone			1 : 3.2	22
Ethanol			1 : 1.5	22
"			1 : 0.41	86
Acetic acid			unspecified	21
"			1 : 0	86
Tetrahydrofuran			1 : 0.45	86
Water			1 : 0.35-0.73	86
Thiophen			unspecified	21
Decalin			unspecified	21

in Table 4, since *b*, which represents the stacking of two CTV molecules in a column, is nearly constant.

The stability of the CTV inclusion complexes is not very high, and these can be desolvated

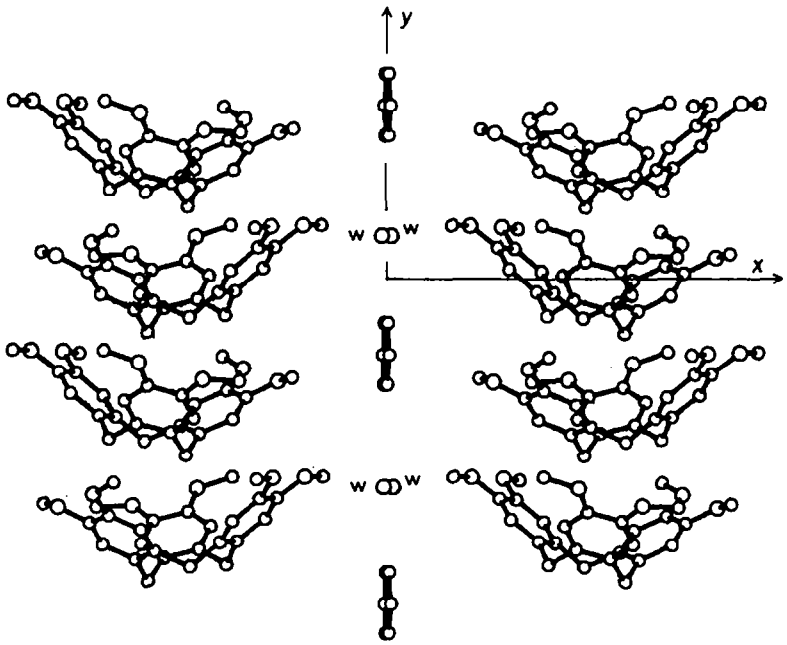


Fig. 2. Crystal structure of the CTV–benzene–water complex; projection on the *ab* plane showing the columns of CTV molecules and the channel containing the benzene and water (W) molecules (after Cesario *et al.*[87]).

relatively easily by heating under vacuum. Such complexes have been used for the storage of tritiated compounds, in order to protect them against self-radiolysis.[89]

2.4.1.2. *Cyclotricatechylene.* According to Hyatt *et al.*,[22] cyclotricatechylene 3 forms a wider range of well defined inclusion compounds than does CTV itself (Table 5). Several molecules, ranging in size from water to HMPA, give compounds having a 1:3 host/guest ratio, whereas others, of comparable size, give 1:2 compounds. The inclusion complexes listed in Table 5 are indefinitely stable in air, and release the guest molecules only upon heating under vacuum.

Table 5. Inclusion compounds of cyclotricatechylene

Guest molecules	Host:guest ratio
N,N-dimethylformamide	1 : 3.1
N-methylpyrrolidone	1 : 3.0
N,N-dimethylacetamide	1 : 3.1
Dimethylsulfoxide	1 : 3.0
Water	1 : 3.0
HPMA	1 : 3.0
Acetone	1 : 2.0
2-Propanol	1 : 2.0

(reproduced from J.A. Hyatt, E.N. Duesler, D.Y. Curtin and I.C. Paul, J. Org. Chem., 1980, 45, 5074, by permission of the publisher; © 1980, The American Chemical Society).

The crystal structure of the 3-2-propanol complex (Fig. 3) is very different from that of CTV discussed above. The crystals are triclinic ($P\bar{1}$), and the packing consists of rows of molecules parallel to the *b* axis, that provide channels running in the same direction. The channels are regularly constricted by OH groups, so as to give a series of cavities, each of which contains two crystallographically independent guest molecules. The structure is held by hydrogen bonding involving the six OH groups of each cyclotricatechylene molecule, which may explain the high stability of these complexes.

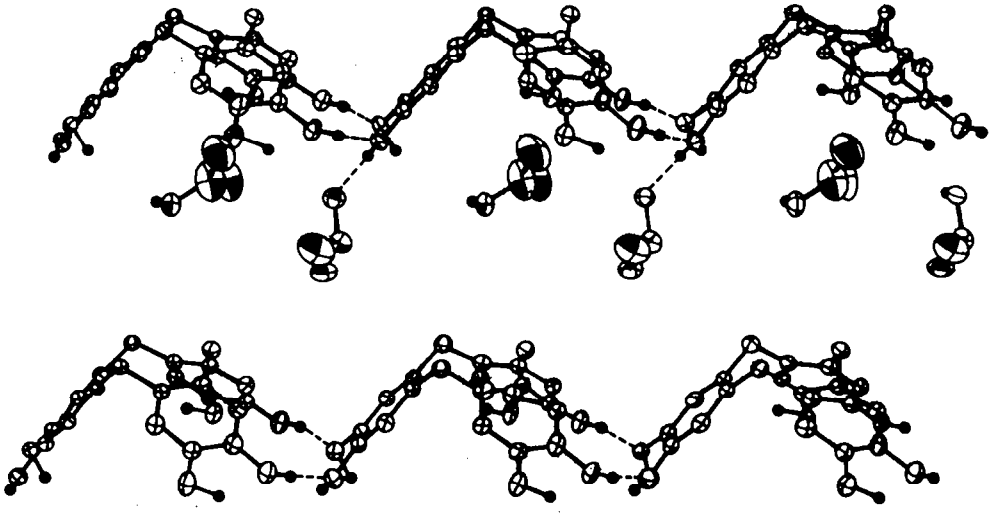
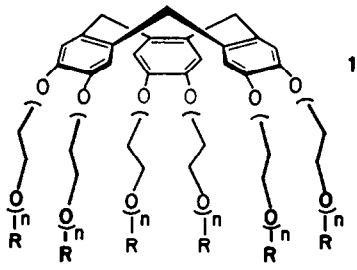


Fig. 3. Crystal structure of the cyclotricatechylene-2-propanol inclusion complex (reproduced from J. A. Hyatt, D. Y. Curtin and I. C. Paul, *J. Org. Chem.* 1980, 45, 5074, by permission of the publisher; © 1980, The American Chemical Society).

2.4.2. *Molecular complexes*

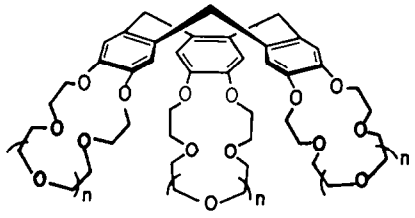
Certain CTV derivatives in which the six methyl groups have been replaced by long chains of various types are capable of complexation in solution. However, these 'octopus molecules' owe their complexing properties to the chains, rather than to the CTV structure.

The first CTV-octopus molecules have been described by Hyatt.[37] Compounds **100a–f**, bearing linear poly(oxyethylene) chains, solvate alkali metal salts in aprotic solvents. With the exception of the short-armed derivative **100a**, which is inactive, the solubilizing power of **100b–f** is relatively uniform and comparable to that of 18-crown-6. Namely, Na^+, K^+, NH_4^+, and Cs^+ are strongly, albeit non-selectively, complexed, while Ba^{2+} and Mg^{2+} interact only weakly.



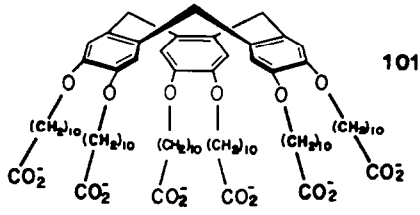
	n	R
100a	1	CH_3
b	2	CH_3
c	2	C_2H_5
d	2	n-C_4H_9
e	3	C_2H_5
f	4	CH_3

French and Vögtle[37] have described two compounds, **12c** and **12d** (Section 2.1.2), in which crown ethers are attached to the phenolic oxygens of CTV, so as to provide specific complexation sites for alkali metal ions. The complexing ability of these compounds in solution has not been described.



12
c n = 1
d n = 2

The hexa-10-carboxydecyl ether of cyclotricatechylene (**101**) synthesised by Menger *et al.*[91] is the only example of a CTV-octopus molecule that complex organic molecules in water. Its six carboxylate groups solubilize the compound in mildly basic water, in which it forms aggregates, even at concentrations as low as 1×10^{-5} M at pH 9.5 (compared to 1×10^{-2} M for a C_{12} surfactant). Each aggregate is formed from 9 ± 1 molecules of **101**, and thus contains about 54 chains, which corresponds to a typical aggregation number in micelles of single-chained surfactants. Host **101**, in 0.01 M aqueous solution at pH 9.5, is an effective, non-selective complexing agent for a variety of organic molecules. The water soluble dye phenol blue is strongly bound (1×10^{-4} M^{-1}); **101** solubilizes naphthalene, *p*-nitroaniline and slightly enhances the solubility of cholesterol in water. It also binds *p*-nitrophenyl butyrate, and inhibits its base-catalyzed hydrolysis. Whether the complexing properties of **101** are due to the molecule itself or to the micellar structure is not clearly established.



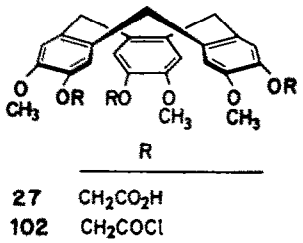
101

3. CRYPTOPHANES

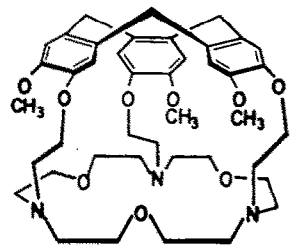
This section deals with *hollow molecules* in which one or two CTV units have been incorporated as building blocks: *speleands*,[52,92] combining a CTV subunit with a *specific binding site* for cations, and *cryptophanes*,[23] made of two CTV subunits linked in front of one another.

3.1. *Cyclotriveratrylene-Macrocycle Combinations: Speleands*

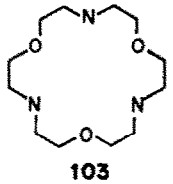
Two CTV-speleands have been described.[52] Condensation of the triacid chloride **102** (obtained from the triacid **27**, see Table 2) with the [18]-N_3O_3 crown ether **103** under high dilution conditions, followed by reduction of the resulting triamide, gives the speleand **104**. This compound associates a lipophilic cavity of ~5 Å depth with a binding site that is specific for small cations such as $-NH_3^+$. Similarly, the triacid chloride **105** (obtained from **31**) and **103** furnish the speleand **106**, in which the flexible bridges may allow the extension of the cavity depth up to ~8 Å.



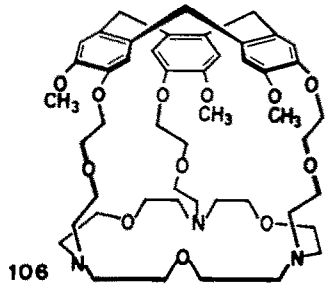
	R
27	CH_2CO_2H
102	CH_2COCl
31	$CH_2CH_2OCH_2CO_2H$
105	$CH_2CH_2OCH_2COCl$



104



103



106

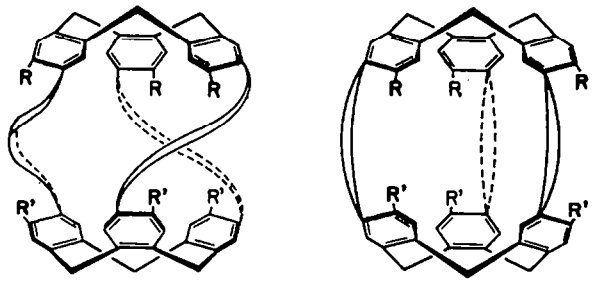
Complexation experiments (by NMR) show that host **104** dissolves about one equivalent of $CH_3NH_3^+$ in $CDCl_3/CD_3OH$ 9:1 or in CD_2Cl_2, yielding a 2:1 mixture of *exo* and *endo* complexes. In the latter, the methyl group is located in the cavity of the CTV cap. The slightly larger $C_2H_5NH_3^+$ cation does not bind inside, and only forms an *exo* complex. The complexing properties of the larger host **106** are not known.

3.2. *Cryptophane Design and Synthesis*

3.2.1. *Definitions and nomenclature*

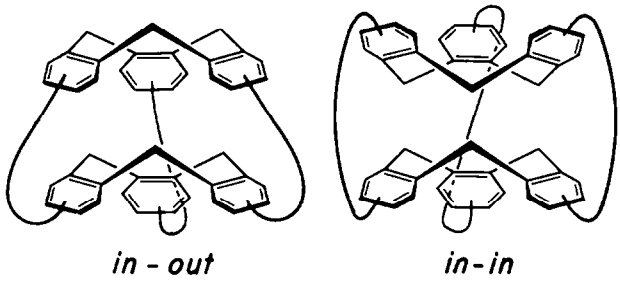
The name *cryptophane*,[23] which, originally, was given to molecules made of two CTV units assembled by three bridges in the way shown in Scheme 5, recalls the [1.1.1]orthocyclophane structure of CTV, and underlines the potential ability of these compounds to form molecular inclusion complexes. The cryptophanes in which the bridges are relatively short possess a roughly spherical and almost rigid lipophilic cavity, and three windows at 120° in the equatorial region, allowing suitable guests to go in. Stepwise changes in the size of the cavity and in the cross section of the windows can be achieved by varying the length and the structure of the bridges, and the way they are attached to the caps, or by modifying the R and R′ substituents. Only two types of cryptophanes have hitherto been synthesised, in which the three bridges are identical, and the R and R′ substituents display either an *anti* or a *syn* relationship as shown in Scheme 5.

When R = R′, the *anti* cryptophanes exhibit D3 symmetry, hence are chiral, whereas the *syn* ones, which belong to the C3h group, are achiral; both types are chiral, however, if R is different from R′ (C3 group). Another important difference between *anti* and *syn* cryptophanes is conformational in nature: as viewed along the C3 axis, the upper and lower caps are eclipsed in the *syn* type, whereas they are twisted away in the *anti* type, by an angle depending on the length of the bridges (e.g., 50–60° for $O(CH_2)_nO$ bridges with $n = 2$ or 3).[106]



Scheme 5.

The cryptophanes with longer bridges might also exist in the forms shown in Scheme 6. Models suggest that *in–out* structures might become possible with $O(CH_2)_nO$ bridges with $n \geq 7$, and that *in–in* structures, in which the convex side of the two CTV units are turned inward, would perhaps require $n > 12$. The *in–in* cryptophanes are topologically similar to the *out–out* ones depicted in Scheme 5 and, if their three bridges are identical, may exist in D3, C3h, and C3 forms. The corresponding *in–out* structures are always C3, whatever the *anti* or *syn* relationship of their R and R′ substituents. No examples of *in–out* nor *in–in* cryptophanes have been synthesised so far; investigations in this direction are currently under way.



Scheme 6.

To find a simple yet meaningful cryptophane nomenclature represents a problem that has not yet been solved satisfactorily.† In effect, a number of structural features of these molecules have to be considered: the number ($n \geq 3$) and the structure(s) of the bridges; the number, position, and nature of the peripheral substituents; the stereochemistry, including the *anti–syn* and *in–out* isomerisms, and the absolute configuration of the chiral isomers. All the cryptophanes that have been described to date are relatively simple, in the sense that they all contain three identical bridges of structure O—(Z)—O (where Z may be $(CH_2)_n$, CH_2—CH=CH—CH_2, or CH_2—C≡C—CH_2); in most of them, R = R′, and the *anti* and *syn* isomers have been identified; there also exists one pair of C3-*anti* and C3-*syn* isomers, with R ≠ R′. For the designation of these compounds, we have provisionally adopted a system based principally on the chronology of their description; the first member of the family was thus named cryptophane-A, and was followed by -B, -C, etc. Whenever possible, it may be useful to add to the generic name a stereochemical descriptor: D3-cryptophane-E, C3-*anti*-cryptophane-C, etc. A semi-logical extension of this nomenclature may also be coined to designate derivatives of a parent compound: for instance, cryptophane-A has been converted to cryptophanol-A (see below).

3.2.2. *Synthesis of* D3, C3h, *and* C3 *cryptophanes*

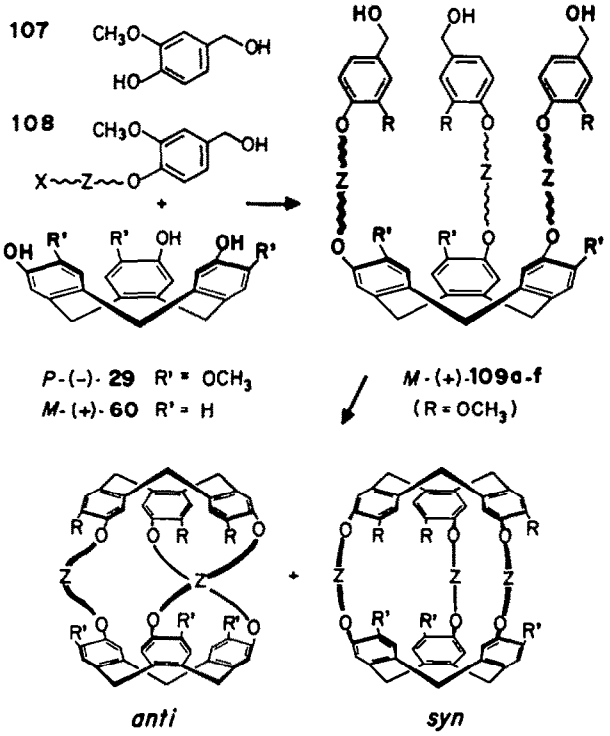
For the construction of the cryptophane structures depicted in Scheme 5, two synthetic routes have been employed. Both use vanillyl alcohol (**107**) as the starting material. In a first method ('the

† The Chemical Abstract name of the first cryptophane (A) is the following: 3,22 - (epoxyethanoxy) - 6,9 : 25,28 - dietheno-7,36 : 17,26 - dimethano - 14,18 : 33,37 - dimetheno - 18*H*,37*H* - dibenzo[j,a$_1$][1,4,18,21]tetraoxacyclotetratriacontin - 5,11, 12,19,21,30,31,38-octahydro-2,15,21,34,41,49-hexamethoxy.

template directed synthesis')[51] the latter is converted to a C3-cyclotriveratrylene, to which three new vanillyl alcohol units are attached and eventually cyclized *intramolecularly*, to afford D3, C3h, or C3 cryptophanes. In a second, very short route ('the two-step synthesis')[108] **107** is first transformed into a 'dimer' which under appropriate conditions trimerizes *intermolecularly* to give D3 and C3h cryptophanes (the C3 isomers are not accessible by this method).

Finally, it is also possible to modify the R and R′ cryptophane substituents, without destroying the rest of the molecule, to obtain new cryptophanes which cannot be prepared otherwise.[104]

3.2.2.1. *Template directed cryptophane synthesis.* The method is summarized in Scheme 7. The required cyclization precursors **109** are prepared by alkylation of the phenol groups of cyclotriguaicylene **29** or cyclotriphenolene **60** with the ω-halogenated vanillyl alcohol derivatives **108**, which already contain the cryptophane bridges. The intramolecular trimerization of the veratryl ends in **109** to give the *anti* and *syn* cryptophane isomer mixture is usually effected by warming (50–90°C) a highly diluted ($\sim 10^{-3}$–10^{-4} M) solution in formic acid. Relevant results are assembled in Table 6.

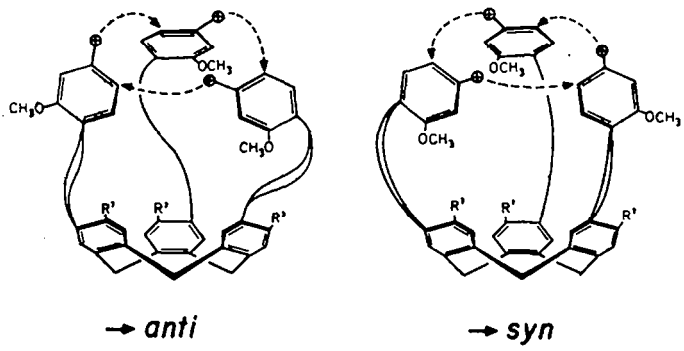


Scheme 7.

When R = R′, the identification of the *anti* and *syn* isomers is straightforward, since only the former (D3) can exhibit optical activity. For instance, the cyclization of *M*-(+)-**109c** (Table 6) affords a mixture of D3-cryptophane-E ($[\alpha]_D - 49°$) and C3h-cryptophane-F (inactive), while that of *M*-(+)-**109a** exclusively yields the D3 isomer cryptophane-A ($[\alpha]_D - 253°$). When R and R′ are different, the distinction between the stereoisomers is less obvious, since both are chiral; the *anti* and *syn* structures have been assigned by X-rays to the C3-cryptophanes C and D, respectively.[101,102]

Since the absolute configurations of the template triphenols **29** and **60** are known (Section 2.3.1), the sequence of reactions depicted in Scheme 7 also establishes the absolute configurations of the D3 or C3 cryptophanes obtained by this method.

The *anti*/*syn* ratio in the template directed synthesis markedly depends on the length and structure of the bridges. Precursors **109** with $O(CH_2)_2O$ bridges preferentially cyclize to the *anti* isomer (cryptophane-A, -C), whereas with $O(CH_2)_3O$ bridges the *syn* is preferred (cryptophane-F). Changing a double bond from *trans* to *cis* has a similar effect. The fact that the presence in the bridges of an *even* or *odd* number of atoms, or of a *trans* or *cis* double bond, affects the stereochemical outcome of the reaction is not surprising, since it determines the *orientation* of the reactive veratryl ends and,



Scheme 8.

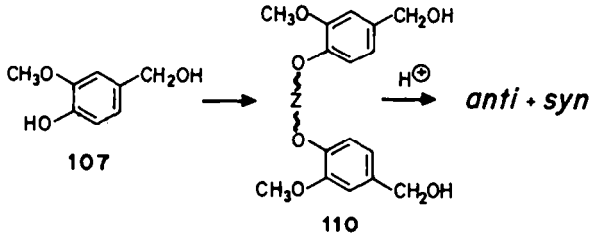
in turn, the clockwise or counterclockwise sense of the cyclization, as illustrated pictorially in Scheme 8.

Table 6. Template directed cryptophane synthesis

Precursors 109			Cryptophanes					Refs
	R	Z	Name	Type		Yield	$[\alpha]_D^{(a)}$	
a	OCH_3	$(CH_2)_2$	A	anti	(D3)	80	-254	51,106
			B	syn	(C3h)	0		
b	H	$(CH_2)_2$	C	anti	(C3)	25	-85	23,100-102
			D	syn	(C3)	5	+145	
c	OCH_3	$(CH_2)_3$	E	anti	(D3)	27	-49	103,106
			F	syn	(C3h)	50		
d	OCH_3	CH_2-C≡C-CH_2	G	anti	(D3)	43	-199	106
			H	syn	(C3h)	20		
e	OCH_3	E-CH_2-CH=CH-CH_2	I	anti	(D3)	34	-154	107
			J	syn	(C3h)	4.5		
f	OCH_3	Z-CH_2-CH=CH-CH_2	K	anti	(D3)	25	-71	107
			L	syn	(C3h)	50		

(a) Rotation in $CHCl_3$ of the enantiomer shown in Scheme 7.

3.2.2.2. *Two-step cryptophane synthesis.* New perspectives in cryptophane chemistry are certainly opened by the recent discovery of a surprisingly short and easy synthesis of these compounds in two steps from vanillyl alcohol **107**.[108] Bis(vanillyl alcohol) derivatives of type **110** are converted, under mildly acidic conditions (formic acid), into D3 and C3h cryptophanes in ~10–20% isolated yield (Scheme 9).

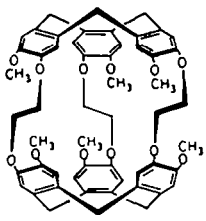


Scheme 9.

In addition to its simplicity and shortness, this new method has the advantage that *it does not require high dilution conditions*, and therefore lends itself well to the preparation of much larger quantities of cryptophanes than does the template procedure. It is also interesting that the *anti/syn*

cryptophane ratio is not the same in the two methods. For instance precursor **110** with a $O(CH_2)_3O$ bridge affords the *anti* isomer D3-cryptophane-E almost exclusively (17% yield), whereas the template directed synthesis yields the *syn* C3h-cryptophane-F preferentially. The scope and mechanism of this interesting reaction are currently under investigation, and a more detailed discussion in this report would be premature.

3.2.2.3. *Chemical transformation of the peripheral substituents.* So far there is only one example of the transformation of the peripheral substituents in a cryptophane. Hexademethylation of cryptophane-A **111** can be satisfactorily achieved by means of lithium diphenylphosphide to give the corresponding hexaphenol cryptophanol-A **112**. The latter, on reaction with Cs_2CO_3 and methyl bromoacetate is converted to the hexaester **113**, which eventually may be hydrolyzed to the hexa-acid **114** (a water-soluble cryptophane).[104] There is little doubt that such transformations could be effected in the other cryptophanes as well.



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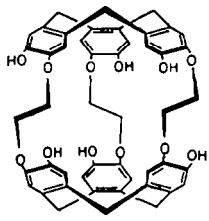

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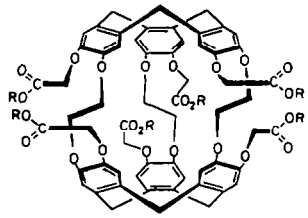


113 R = CH_3
114 R = H

3.3. *Cryptophane Complexes*

It is only rarely that the authors of a scientific paper present their results as the things have gone. The way in which the complexing properties of the cryptophanes have been discovered is worth telling, as the illustration of a research that was planned on naive concepts, often driven by wrong ideas and interpretations, and yet was successful not only in reaching its initial goal, but also in providing new ideas and information in the field of molecular recognition.

3.3.1. *How the cryptophane complexes were discovered*

Cryptophane-A (**111**) was actually *designed*,[51] in the earlier 1980s, so as to complex substrates of CHXYZ structure, and especially CHFClBr, the simplest chiral molecule. The aim of this work was to determine the enantiomeric purity of a weakly resolved sample of this haloform, which was then available from S. H. Wilen (New York),[109] and, more generally, to find any study host systems that would be capable of complexing *neutral* guest molecules selectively (and enantioselectively).

After cryptophane-A was synthesised, the first attempts to evidence its complexing properties were rather deceiving.[100] The NMR spectrum of the host in $CDCl_3$ did not clearly show that the solvent was complexed, the residual $CHCl_3$ peak being taken as a probe; under the same conditions, however, the *smaller* CH_2Cl_2 appeared to be *very weakly* complexed. These findings seemed to be satisfactorily explained by examination of CPK models, showing that the six OCH_3 groups of the host obstruct the windows, so that it is *almost* impossible to push a $CHCl_3$ model inside. The logical solution was therefore to enlarge the windows, which led to the synthesis of cryptophane-C (**115**), where only three of the OCH_3 groups remain. Then, *as was expected*, NMR showed that the new cryptophane complexed CH_2Cl_2 in $CDCl_3$ much better than did the former;[100] in Fig. 4, the broad peak at 5.20 ppm indicates a fast exchange, on the spectrometer time scale, between free (δ_o 5.31 ppm) and complexed CH_2Cl_2 (later observed at δ_c 0.74 ppm),[23] with only about 2% of the guest being bound in the host cavity. The stability constant K_a was estimated to be very small ($\sim 2\ M^{-1}$), but, at that time, nothing larger was known, nor even really expected, for complexes between neutral host and guest molecules in a lipophilic solvent.

Next, the same type of complexation experiments was done with Wilen's sample,[23] using optically active cryptophane-C as the host (Fig. 5). Not unexpectedly, the bulkier CHFClBr was found less easily complexed than the smallest CH_2Cl_2. Luckily, the diastereoisomeric inclusion complexes showed stability constants that differed enough (0.22 *vs* 0.30 M^{-1}) to allow the total separation of the fast exchange averaged resonances of the two enantiomers and thus the determination of the

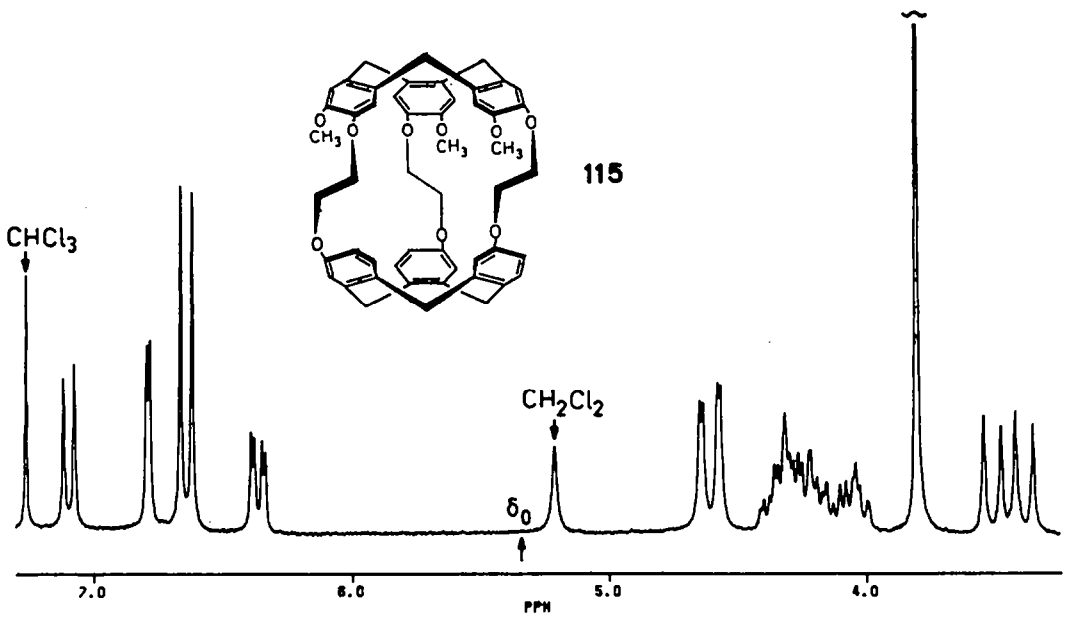


Fig. 4. NMR spectrum (250 MHz) of a 10^{-2} M solution of cryptophane-C in $CDCl_3$, in the presence of one equivalent of CH_2Cl_2 at 273 K (after J. Canceill, L. Lacombe and A. Collet, *C. r. Acad. Sci., Sér. 2* 1984, **298**, 39; by permission of the publisher).

composition of the sample (~4.5% ee), which in turn furnished the magnitude of the maximum rotation of the haloform, $[\alpha]_D$ 1.6±0.5° (data that had been sought for one century).

Even though the initial goal of this study has been reached, and its final conclusion remains entirely valid, it is a paradox that the reasons why the complexes could effectively be observed, in the experiments described above, have little to do with those that were originally raised.

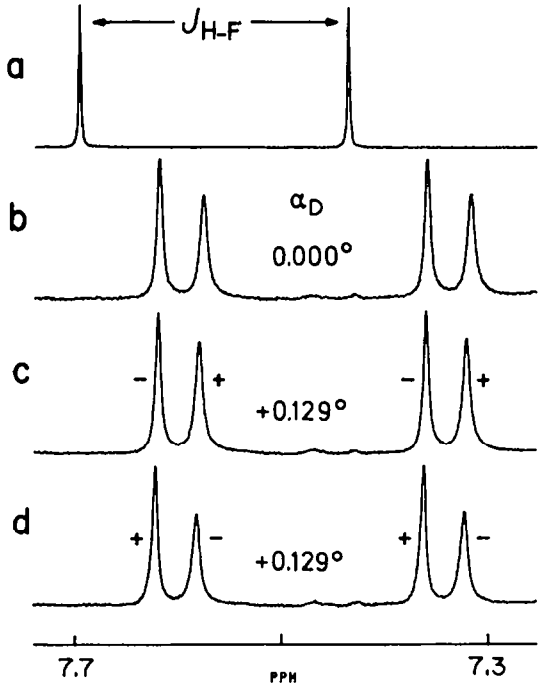


Fig. 5. 200 MHz NMR spectrum of CHFClBr in $CDCl_3$ at 332 K; (a) (±)-CHFClBr alone, and (b) with (+)-cryptophane-C added; (c) Wilen's sample with (+)-cryptophane-C, and (d) with (−)-cryptophane-C (after J. Canceill, L. Lacombe and A. Collet, *J. Am. Chem. Soc.* 1985, **107**, 6993, by permission of the editor, © The American Chemical Society, 1985).

Contrary to the earlier interpretations, $CHCl_3$ ($K_s \sim 230\ M^{-1}$ at 300 K) and CH_2Cl_2 ($K_s \sim 475\ M^{-1}$) are *both* strongly bound by cryptophane-A, as is revealed by experiments carried out in a bulky solvent ($(CDCl_2)_2$) which cannot easily enter the host cavity.[104] The use of $CDCl_3$, a too strong competitor, as the solvent, is not very appropriate to evidence complexation phenomena in this case.

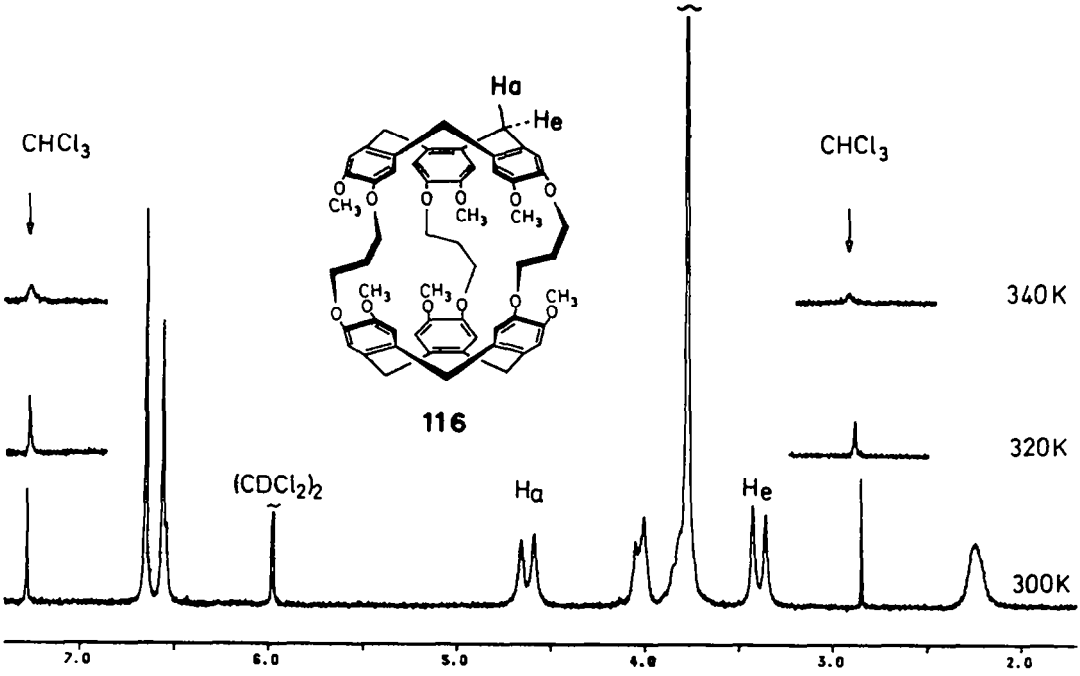
The behaviour of cryptophane-C is extremely interesting. Its CH_2Cl_2 complex is easily observed in $CDCl_3$ (Fig. 4), although its stability ($300\ M^{-1}$) is actually *less* than that of the cryptophane-A complex.[110] The reason is that $CDCl_3$ is only weakly complexed by cryptophane-C ($\sim 10\ M^{-1}$), hence is only a weak competitor for CH_2Cl_2. Thus, on passing from cryptophane-A to -C, the binding constants of the $CHCl_3$ and CH_2Cl_2 complexes do not increase as was initially supposed (the contrary is observed) but their ratio is modified to such an extent that the CH_2Cl_2 complex becomes highly favoured hence easily observable, even in $CDCl_3$ as the solvent.

Another interesting piece of information, which again contradicts some of the earlier ideas, is that the cross section of the windows only *indirectly* affects the binding constants, perhaps by its influence on the conformation of the host bridges, hence on the size and shape of the cavity. However, the windows certainly play a role in the *kinetics* of the inclusion and exclusion processes. One of the reasons why the enantiomeric purity determination worked with cryptophane-C, is that the complexation kinetics is fast enough with this host, so as to allow the observation of the averaged resonances of each enantiomer at a temperature not exceeding the boiling point of the solvent (like in ee determinations by means of chiral lanthanide shift reagents). Such a determination would not have been so easy to achieve with cryptophane-A, with which the exchange processes are slower.

3.3.2. *Investigation of cryptophane complexes*

As is already alluded to above, the complexes between cryptophanes and lipophilic substrates can easily be observed by NMR under appropriate conditions. Some of the complexes have also been crystallized, and their structures established by X-rays.

3.3.2.1. *NMR studies.* Thus far, there are only three short reports demonstrating the extraordinary ability of certain cryptophanes to bind neutral molecules of complementary size, in lipophilic as well as in aqueous solvents.[103–105] This behaviour is illustrated in Fig. 6, showing the NMR spectrum of cryptophane-E (**116**) in $(CDCl_2)_2$, in the presence of two equivalents of $CHCl_3$ at



116

Fig. 6. 200 MHz NMR spectrum of cryptophane-E in $(CDCl_2)_2$ in the presence of $CHCl_3$ at 300 K (after J. Canceill, L. Lacombe and A. Collet, *J. Am. Chem. Soc.* 1986, **108**, 4230, by permission of the editor; © The American Chemical Society, 1986).

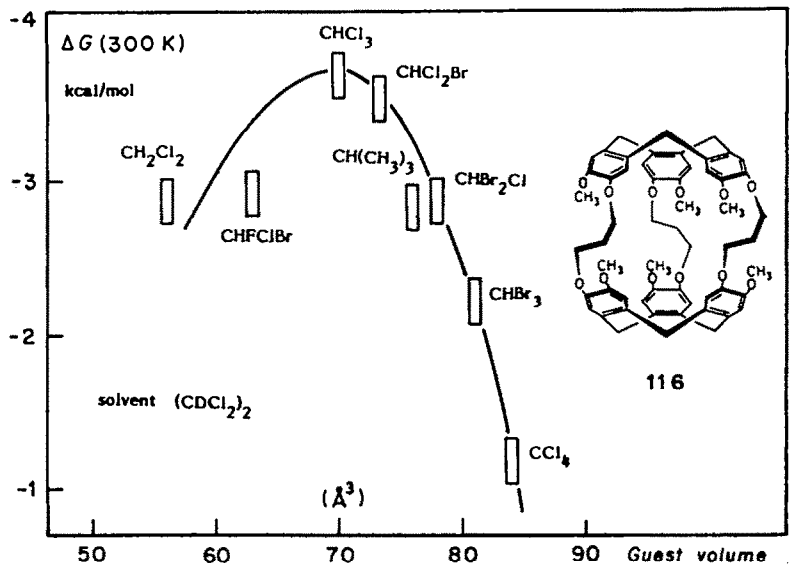


Fig. 7. Complexation free energy (ΔG_c) at 300 K as a function of the van der Waals volume of the guests (host 116) (after J. Canceill, L. Lacombe and A. Collet, *C. r. Acad. Sci., Sér. 2* 1987, **304**, 815, by permission of the editor).

300 K.[103] The peaks at δ_o 7.28 and δ_c 2.84 ppm correspond to the free and complexed $CHCl_3$ molecules, respectively, which slowly exchange ($\sim 2.5\ s^{-1}$) at this temperature. The same type of spectra has been observed with other halogenomethanes ranging in size from CH_3I to CCl_4, and even a hydrocarbon such as isobutane is strongly bound by **116** in the same lipophilic solvent.[105] Relevant data on the properties of these complexes are assembled in Table 7.

The strong enthalpic stabilization (ΔH_c) of the $CHCl_3$ and isobutane complexes has been ascribed to the almost ideal complementarity between host and guest, which enhances the dispersion forces operating in the interior of the cavity, like in a close-packed crystal.[105]

The sharp dependence of the complex stabilities *vs* the size of the guest molecules (Fig. 7) illustrates the host selectivity. At 300 K, cryptophane-E preferentially binds $CHCl_3$ (~ 70 Å^3) over bulkier or smaller guests, whereas cryptophane-A and -C, which have a smaller cavity, prefer CH_2Cl_2 (~ 56 Å^3).

Table 7. Properties of some cryptophane complexes at 300 K[103-105,110]

Host (Solvent)	Guest	$\delta_o - \delta_c$ ppm	K_s l/mol	ΔG_c kcal/mol	ΔH_c kcal/mol	ΔS_c cal/mol/K	$\Delta G^{\#}$(incl.)[a] kcal/mol
116	CH_2Cl_2	4.15	120	-2.87			
$(CDCl_2)_2$	CHFClBr	4.50	130	-2.92			
	$CHCl_3$	4.44	470	-3.69	-6.9	-11	13.5
	$CHClBr_2$	4.41	120	-2.87			
	$CHBr_3$	4.36	40	-2.21			
	CCl_4	-	7	-1.17			
	$CH(CH_3)_3$	4.25 (H) 2.95 (CH_3)	115	-2.85	-3.8	-3	13.9
111	CH_2Cl_2	4.33	475	-3.7			9.4
$(CDCl_2)_2$	$CHCl_3$	4.33	230	-3.3	-8.2	-16	9.6
114	CH_2Cl_2	4.35	ca. 5000	-5.1			9.8
(D_2O)	$CHCl_3$	4.54	ca. 7500	-5.3			10.5

(a) Energy barrier for guest inclusion.

In aqueous solvents, where the complexes are further stabilized by hydrophobic forces, the binding constants may become as high as 10^3–10^4 M^{-1}, for guests such as CH_2Cl_2 and $CHCl_3$ and the water-soluble host **114**, a 'halogenomethane scavenger'.[104]

3.3.2.2. *Structural studies.* The crystal structures of the dichloromethane complexes of cryptophane-C (**115**) and -D (**117**) have been determined.[102,103] In both cases (Fig. 8) the guest molecule is embedded in the host cavity, where it is tightly bound and shows no disorder. This feature is consistent with the negative ΔH_c measured for the formation of such complexes.

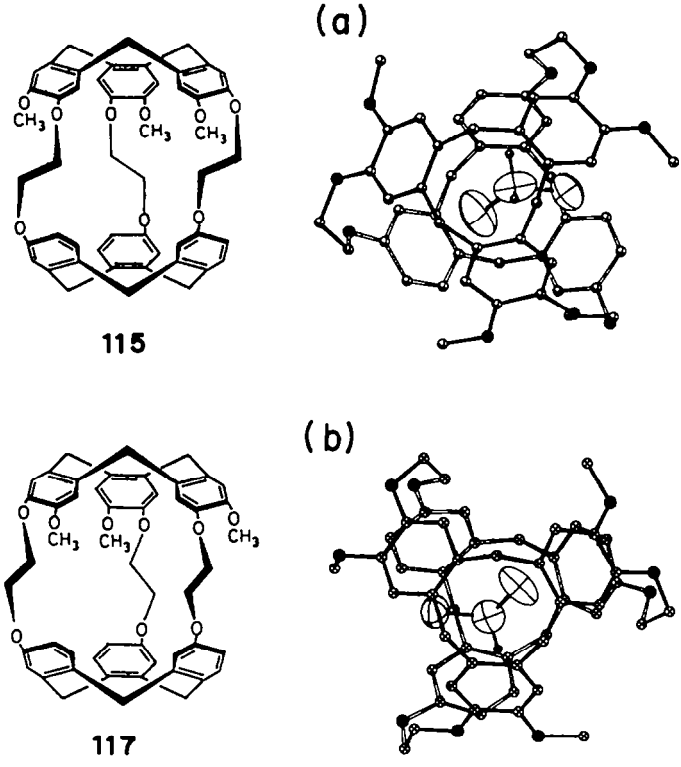


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Fig. 8. The CH_2Cl_2 complexes of cryptophane-C (a) and -D (b) (after J. Canceill *et al.*, *J. Chem. Soc., Chem. Commun.* 1985, 361; *ibid.*, 1986, 339, by permission of the editor; © The Royal Society of Chemistry, 1985, 1986).

3.3.2.3. *Future works.* The cryptophanes certainly represent valuable models for studying the interactions between a substrate and a receptor under well defined conditions, and most of the investigations in this field have yet to be done. Such studies may be useful in leading to a better understanding of the nature of the driving forces that are involved in the complexation of neutral or charged molecules. So far, nothing is known about the complexing properties of the larger cryptophanes, nor on the ability of the smallest ones to bind ionic lipophilic guests (ternary or quaternary ammonium salts, etc.). Also, several of the newly synthesised cryptophanes lend themselves to the introduction of reactive groups within reach of the complexed guest;[107] such functionalized hosts might therefore be capable of effecting chemical transformations on the guest molecules. There is little doubt that such studies will be undertaken, and will reveal new aspects and new applications of the cryptophane properties.

4. OPTICAL ACTIVITY OF CYCLOTRIVERATRYLENES AND CRYPTOPHANES

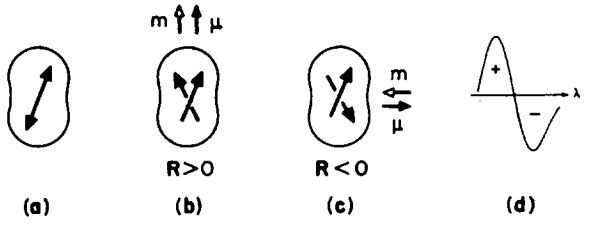
As in the well known case of the C2 biaryls,[111] the optical activity of cyclotriveratrylenes and cryptophanes merely originates from through-space interactions of the electric transition dipoles of equivalent aromatic units, and can thus be analyzed in the light of the Kuhn–Kirkwood coupled oscillator model (exciton optical activity).[24,25]

4.1. *The Physical Bases*

The coupled oscillator model is based on physical concepts that are simple and can easily be applied in many cases; it rests on the knowledge of the *polarization directions* of the electronic transitions in the considered molecule, which must contain *several* identical chromophoric groups.

4.1.1. *The exciton model*

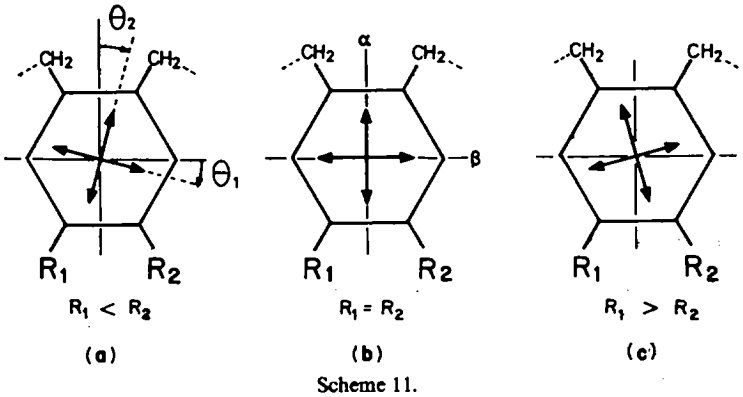
In this theory,[112,113] a single electric transition moment is represented by a double-headed arrow, which suggests its oscillatory nature [Scheme 10(a)]. In a molecule containing *two* such oscillators, their relative phase has to be considered, and the system is best represented by using pairs of single-headed arrows. For two transition moments, there are thus only two relative phases of motion, (b) and (c) in Scheme 10. In (b), which here is equivalent to a right-handed helix, the coupling of the transition dipoles generates overall *parallel* electric (μ) and magnetic (m) moments along the C2 axis, hence a positive rotational strength R. Conversely, the coupling (c) defines a left-handed helix in which *antiparallel* electric and magnetic moments create a negative rotational strength. The exciton mechanism therefore generates, for each electronic transition, a pair of oppositely signed circular dichroism (CD) bands. In order to establish whichever band will appear at higher or lower energy in the actual CD spectrum, the sign of the interaction energy (V) in each of the coupling modes (b) and (c) must be determined. In Scheme 10, the dipoles are arranged in such a way that the result is obvious: the head-to-head situation (b) is clearly repulsive (V > O), and should therefore be found at higher energy than the attractive head-to-tail coupling (c) (V < O). The CD spectrum will show a positive–negative sequence, from high to low energy, as shown in (d). Such a clear-cut situation is often encountered in real molecules, for instance in vicinal diol dibenzoates.[112] Ambiguous cases also exist, where the determination of the energy sequence of the two CD bands requires the calculation of the interaction potential V, as a function of the geometry of the system. Such calculations are usually effected by the point-dipole approximation.



Scheme 10.

4.1.2. *The benzene chromophore*

In order to use the exciton model, it is necessary to know which transitions are involved and how they are polarized. The chromophoric unit in cyclotriveratrylenes[50,70,99] and cryptophanes[106,107] is a 1,2,4,5-tetrasubstituted benzene (Scheme 11). The two lowest energy transitions that are accessible in the UV and CD spectra occur at ~280–290 nm and ~240–250 nm. These transitions will be thereafter designated as B_{2u} and B_{1u}, respectively, as in the parent benzene molecule. The higher energy (E_{1u}) transitions below *ca.* 220 nm are generally not considered in the coupled oscillator model, because their energy and polarization are not experimentally known nor easily predictable.



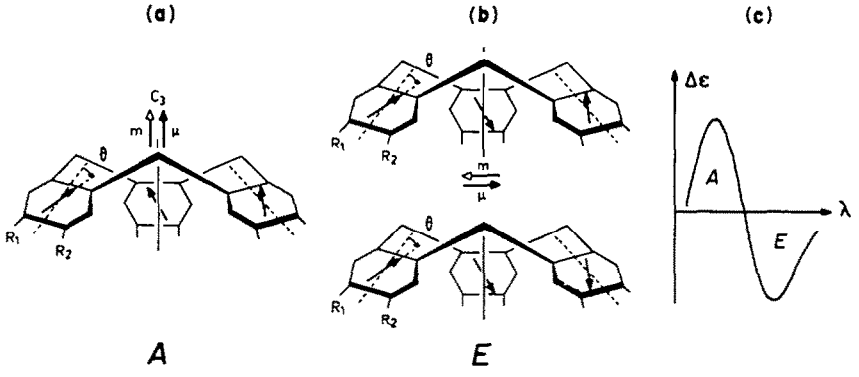
Scheme 11.

In achiral cyclotriveratrylenes (where $R_1 = R_2$), the B_{2u} and B_{1u} transitions are polarized along the short (α) and long (β) axes of the benzene ring, as shown in Scheme 11(b). The presence of two *different* substituents causes a rotation of these transition moments, from the α and β axes; the sign and magnitude of the rotation depend on the relative magnitude of the *spectroscopic moments* (SM) of the R_1 and R_2 substituents. The SMs are empirical parameters which have been introduced as a way to quantify the influence of the substituents on the absorption intensities in aromatic compounds. It is classically assumed that θ_2, the rotation angle of the B_{2u} transition dipole, can be evaluated by vector addition of the substituent spectroscopic moments, and that $\theta_1 = \theta_2$ (which is equivalent to saying that the transitions are polarized at 90°).[48] In Scheme 11, when the SM of R_2 is greater than that of R_1 ($R_2 > R_1$), one obtains a clockwise rotation (θ_2 and $\theta_1 > 0$), which is inverted when $R_2 < R_1$.

In the exciton model, the chiroptical properties of cyclotriveratrylenes and cryptophanes in the near UV entirely depend on the signs and magnitudes of the polarization angles θ_2 and θ_1.[50,106]

4.2. *C3-Cyclotriveratrylenes*

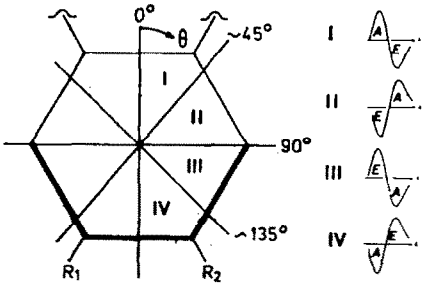
In these compounds, there are *three* identical chromophores, and three coupling modes for each of the B_{2u} and B_{1u} transitions. The symmetrical *A*-coupling (Scheme 12) gives rise to overall electric and magnetic moments along the C3 axis of the molecule, while the two degenerate *E*-coupling modes are polarized perpendicularly to this axis.[50]



Scheme 12.

As in the classical case of two oscillators, the exciton CD of cyclotriveratrylenes consists of two oppositely signed bands for each transition. As a pictorial example [Scheme 12(a)], it can be easily seen that the *A*-coupling of the B_{2u} transition dipoles generates, for a small positive value of θ_2, a *positive* rotational strength($m \cdot \mu > 0$) at *high energy* ($V > 0$), whereas the *E*-couplings (b) conversely give a negative component at low energy. For a small positive value of θ_1, the *A*-coupling of the B_{1u} transition is also positive, but the interaction of the transition dipoles being now attractive ($V < 0$), this component is at low energy. Accordingly, the overall CD spectrum for the B_{1u}–B_{2u} region has the shape shown in Scheme 12(c).

The dependence of the CD spectrum on variations of θ is shown in Scheme 13 ($\theta_2 = \theta$, or



Scheme 13.

$\theta_1 = \theta - 90°$). There are *four critical values* of θ, 0, ~45, 90 and ~135°, which correspond to a total inversion of the exciton pattern, by changing the sign of *either* m, V, μ, and V (respectively). These angles thus define the four sectors I–IV, each being characterized by a particular sequence of the *A* and *E* components, as sketched in the Scheme.

The validity of the exciton model in C3-cyclotriveratrylenes can be illustrated by the CD spectrum of *P*-(−)-cyclotrianisylene **35** (Fig. 9). In this case, the SM of the OCH_3 group (R_1) being much larger than that of the hydrogen atom (R_2), angles θ_2 and θ_1 are unambiguously negative (~ −38°), and the entire sequence of CD bands is exactly that predicted by the theory.[50]

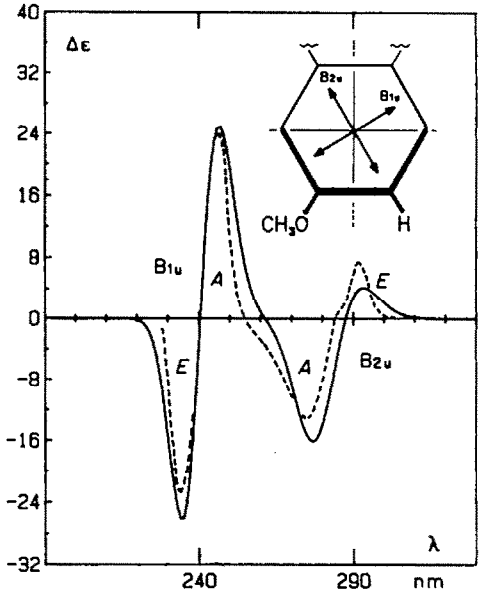


Fig. 9. Theoretical (——) and experimental (- - -) CD spectra of *P*-(−)-**35** in the B_{1u}-B_{2u} region, with the polarization direction of the transitions shown in the insert.

Conversely, since the absolute configurations of the C3-cyclotriveratrylenes are generally known, analysis of their CD spectra in the light of the exciton model provides information on the polarization directions of the transitions, when the substituents' spectroscopic moments are not known. More precisely, the CD spectra of these compounds can be employed for the determination of the *relative magnitude* of the SMs of R_1 and R_2 substituents attached to the CTV structure. For instance, the CD spectrum of cyclotriguaiacylene (**29**) clearly shows that the OH group must be given a SM larger than the OCH_3 group,[70] and, in general, it has been found by this method that the SM of alkoxy substituents decreases as their size increases. Actually, direct SM measurements (based on UV absorption intensities), are not accurate enough to reveal such weak differences between alkoxy substituents in most cases. Even very small rotations θ generate observable exciton CD patterns, and the system easily evidences SM differences due to isotopic substitution. In *M*-(−)-cyclotriveratrylene-d_9 (**78**), the sequence of signs of the exciton couplet (Fig. 10) indicates that the SM of OCD_3 is larger than that of OCH_3, which may be explained by conformational effects.[98] In C3-cyclotribenzylene-d_3 (**41a**),[47] which exhibits an exciton pattern in the 270 nm region, the rotation of the B_{2u} transition dipole is consistently explained by vibronic effects. The effect of the ionization of a phenol group on the polarization direction of the transitions has also been studied[50,99] by this CD method.

Finally, the CD spectra of several cyclotriveratrylenes in which R_1 = Br and R_2 = OCH_3, OH, or $OCOCH_3$ (see **34** in Table 2) provide evidence that the B_{2u} and B_{1u} transitions in these compounds are not polarized at 90°, a result which may have a general bearing, and which emphasizes the risk of using B_{1u} transitions for configurational assignments based on chiroptical methods.[48]

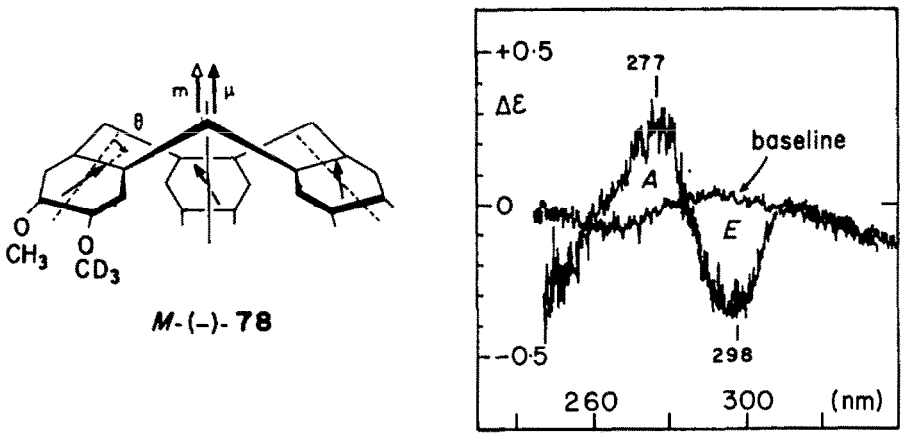


Fig. 10. CD spectrum of *M*-(−)-**78** (after A. Collet and G. Gottarelli, *J. Am. Chem. Soc.* 1981, **103**, 5912).

4.3. *D3-Cryptophanes*

In these molecules, the optical activity originates from the coupling of *six* identical chromophores in a D3 arrangement. Since a pictorial description of all the coupling modes would be very tedious in this case, the treatment has been accomplished mathematically, by using the formalism of the group theory, in order to extend the exciton model to a D3 array of six oscillators.[106]

The main conclusions of this analysis are as follows: (i) the coupling of the six transition dipoles generates, for each transition, *three* optically active components, one (A_2 symmetry) being polarized along the C3 axis of the molecule, and two (E symmetry) in the equatorial plane; (ii) the two E levels which, contrary to the case of the C3-CTVs' are not degenerate, have opposite signs and different intensities, the stronger having a sign opposite to the A_2 component (see Fig. 11);

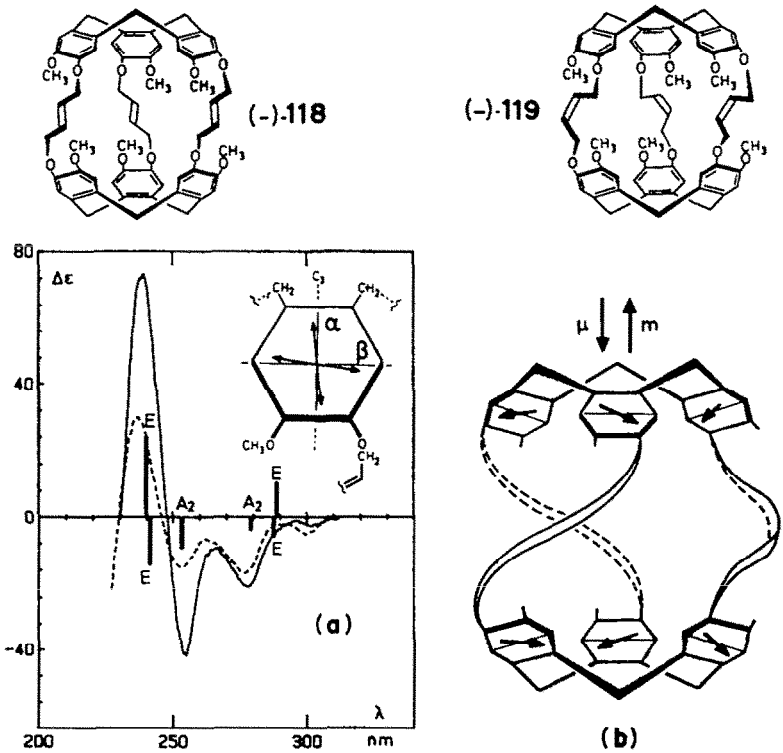


Fig. 11. (a) CD spectra of (−)-cryptophane-I (——) **118** and (−)-cryptophane-K (– – –) **119**. The bars represent the calculated CD components, and the insert shows the polarization direction of the B_{2u} (α) and B_{1u} (β) transitions; (b) sketch of the A_2 coupling of the individual transition dipoles which generates a negative rotational strength at lower energy for the B_{1u} system.

(iii) variations of the twist angle of the two CTV caps only slightly modulate the CD intensities and the interaction energies, without affecting the signs nor the sequence of the components; (iv) as in the C3-cyclotriveratrylenes, the chirality of the oscillator array in D3-cryptophanes is entirely governed by the *signs* and magnitudes of the polarization angles θ_1 and θ_2 of the benzene subunit.

The CD spectra of all the chiral D3-cryptophanes known to date (i.e. cryptophane-A and derivatives, -E, -G, -I, -K) have been satisfactorily analyzed in the light of this model.[106,107] The presence of the *three* predicted CD components has been experimentally observed in the B_{2u} region for several of these compounds, although very often extensive band overlap and cancellation occur, as illustrated in Fig. 11 (which also provides a pictorial representation of the A_2 symmetry coupling). These results demonstrate the general validity and usefulness of the Kuhn–Kirkwood model for explaining the optical activity of complex molecules.

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