

HIGH SYMMETRY CHIRAL MOLECULES

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Optically active compounds containing a few symmetry elements in their molecules were known very early in the history of stereochemistry. Tartaric acid, which was extensively studied by Pasteur, was one of the few examples of optically active compounds, the structure of which was known at the age of Van't Hoff and Le Bel. Some years earlier, Paternò had already considered the possibility that a bisubstituted ethane had a structure with C_2 symmetry.¹ Further series of chiral compounds containing two fold axes of symmetry were later discovered, i.e. allenes, spiranes, diphenyls and related compounds. Apart from few sporadic investigations, this topic did not receive much attention in the past. Spurred by the studies on natural products, which by far represent the major source of optically active compounds, organic chemists limited the phenomenon of optical activity to the presence of asymmetric molecules (without any symmetry) and in practice have reduced the concept of symmetry to that of mirror symmetry.

The situation has changed very much during these last 15 years. The application of the symmetry principles to the structure and properties of the molecules has been extensively discussed in books and scientific papers; the ever increasing use of analytical methods (in particular NMR spectroscopy and X-ray diffractometry) has divulged its knowledge even on a practical level. Thus a new sensitivity arose among chemists known as a symmetry consciousness.*

Our interest in high symmetry chiral molecules is derived from previous research on the stereochemistry of linear macromolecules and of cyclic compounds having sterically equivalent centres.³ In particular we synthesized^{4,5} and resolved^{6,7} one isomer of perhydrotriphenylene with D_3 symmetry, i.e. the highest symmetry synthetic organic compound obtained so far in optically active forms. On developing such research we realized the

importance involved in a systematic study on high symmetry chiral molecules, with a symmetry number σ higher than 2. Hence we dealt with the synthesis of some molecules exhibiting respectively C_3 , D_2 and D_3 symmetry and simultaneously we looked for the principles leading to the synthesis of chiral molecules with a higher symmetry. Some preliminary results have already been published.⁸⁻¹⁰

Projects in this field have been simultaneously and independently developed by different teams. The results obtained will be described in a subsequent section. At this stage we wish to stress the contribution given by Cahn, Ingold and Prelog with their well known specification of molecular chirality.¹¹ Their work gives a picture that is far more important than a simple rule of nomenclature and constitutes a deeper insight into molecular structures. During recent years Prelog has focused his attention on some aspects of chemical topology and published several theoretical^{12,13} and experimental^{14,15} contributions with clear references to the problem under examination.

On their turn, Caldwell and Eyring¹⁶ devoted several pages to high symmetry chiral molecules. They stressed the importance of a study in this sense for a better understanding of optical activity. They also proposed some hypothetical structures and invited experimental chemists to work for their realization.

The present paper points out the criteria allowing the design of high symmetry chiral molecules, the chief examples known so far and some suggestions for future research.

A few criteria for selection

In view of the purposes of this article, the term high-symmetry chiral compounds has been used to indicate the compounds that satisfy the following conditions:

(1) The instantaneous geometry of their molecular structure, considered as a rigid body and examined in the idealised form, by neglecting minor deformations, must belong to a chiral point group

*This term was coined by F. Woldbye² who also reports an interesting discussion.

of order equal to or higher than 3 (C_3 and D_2 as simpler groups).

(2) If different conformers of the compound under examination exist, the high symmetry chiral structure must be present in a large amount and possibly be predominant in the conformer mixture.

On the basis of the latter condition, it is possible to exclude unstable chiral structures that may be easily transformed into their antipodes or into non chiral forms or into forms with a different symmetry (e.g. the skewed conformations of ethane and of [2.2.2]bicyclooctane, both belonging to the D_3 group). The presence of a single conformer or at least of a mixture very rich in the high symmetry conformer is essential in order to study the quantitative aspects of the relations between some properties (CD, ORD, etc) and molecular structure.

From the former condition, it follows as a rule that a chiral substituent introduced in a basic framework cannot be simply indicated by letters (D, L, R, S) or by signs (+, -), but must show its internal symmetry. The criterion to observe instantaneous symmetries of convenient conformers has already been applied to other problems. We mention D-menthyl, L-menthyl - 2,6,2',6' - tetranitro - 4,4' - diphenate synthesized by Mislow and Bolstand¹⁷ which is more correctly interpreted in terms of C_1 rather than of S_6 symmetry.

The same criterion is not followed in other cases, especially as far as the arrangement of light atoms, in particular H atoms, is concerned. The $[\text{Co}(\text{NH}_3)_6]^{3+}$ ion is generally considered as octahedral (point group O_h) even if its complete instantaneous geometry at most reaches D_{3d} symmetry (the presence of three H atoms around nitrogen is not consistent with the presence of a fourfold axis passing through N and Co atoms). However, in such cases, and in general where very low rotational barriers or very rapid exchange phenomena may be expected, the most adequate symmetry group for the representation of flexible systems is of much higher order than foreseen for rigid molecules. According to Longuet-Higgins¹⁸ it is necessary to make into account the permutations among all equivalent atoms. However, in our opinion, in most cases, when static (structural) stereochemistry of complex molecules is involved, the assumption of the rigid body is adequate to the purpose. A problem arises when some structural features, which do not involve either chiral centres or chromophoric groups, are largely undetermined (e.g. methylenic bridges in vespirenes or in cyclophanes). In that case, we assume that the molecule attains the highest symmetry¹⁹ unless indications to the contrary are available (as in the $[\text{Co}(\text{en})_3]^{3+}$ ion).

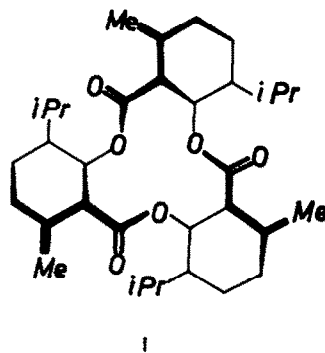
The present state of knowledge

The high symmetry chiral molecules known at

present are described in this section. The literature published prior to the beginning of 1973 has been considered; the authors apologise for any accidental omission due to the variety of items to be examined. In this work we have been helped by partial collections of dissymmetric molecules recently published.²⁰⁻²²

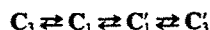
Examples will be divided on the basis of their symmetry group; examination will first concern the compounds known in optically active form and then those known only as racemic mixtures.

C_3 Group. The first C_3 organic compound obtained in optically active forms is triorthotimotide 1. Its synthesis dates back to 1909,²³ but its structure was determined only in the early fifties.²⁴ When crystallised by suitable solvents (among which hexane and benzene), 1 gives rise to inclusion compounds whose unit cell contains molecules with the same optical sign.^{25,26} Optically active solutions



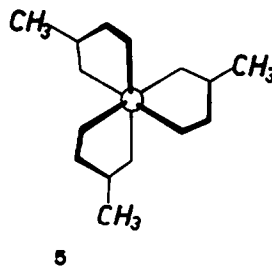
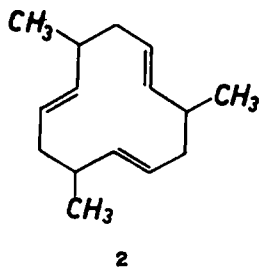
have been obtained by dissolving single crystals of large size. The highest rotatory power is about 80° (at the D line). The compound rapidly racemises, with a half-life of about 30 min at 0° . The activation energy for racemization calculated by Ollis and Sutherland²⁷ from the data reported²⁶ is 21.2 kcal/mole.

The conformational mobility of tri-*o*-timotide and analogous compounds has also been studied by NMR at different temperatures.^{28,29} Starting from a C_3 propeller-like conformation (for instance with three methyls up) the molecule converts into a C_1 conformation (with two methyls up and one down), then to conformation C'_1 , enantiomeric of C_1 (one methyl up and two down), and finally to conformation C''_1 with three methyls down, according to equation



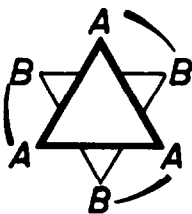
A discussion of the CD spectrum and the determination of the absolute chirality of the single enantiomers are also reported.²⁸

As a second example of optically active C_3 organic molecule, we quote *trans, trans, trans*. 3,7,11 - trimethylcyclododeca - 1,5,9 - triene 2



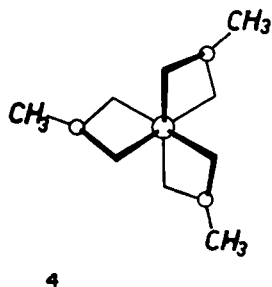
obtained by trimerization of 1,3-pentadiene.³⁰ Partial resolution (which led to a product with $[\alpha]_D = -8$) was carried out by asymmetric hydroboration.

In the field of inorganic chemistry several optically active complex ions with C_3 symmetry have been reported.²¹ They consist of a hexaco-ordinated transition metal ion, bound to three non symmetric (but not necessarily chiral) bidentate chelating groups (formula 3).

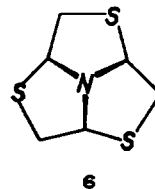


As interesting examples we quote the complexes of cobalt III with (*R*)(-)-propylendiamine.³¹⁻³⁴ They exist in two diastereoisomeric forms that may be separated by fractional crystallization or by chromatography; they rapidly interconvert in the presence of charcoal. In the two stereoisomers, the configuration of the Co atom and the conformations of the rings with respect to the threefold axis are different; however they both show the methyl group in equatorial position. The predominant form ($[\alpha]_D = -24^\circ$) is the $\Delta(\lambda\lambda\lambda)$ isomer (*lel* conformation) 4, while the second isomer ($[\alpha]_D = +214$) is $\Lambda(\lambda\lambda\lambda)$ (*ob* conformation) 5. Their UV and CD spectra have been reported and discussed by Mason.³⁵

Among the compounds that have been obtained



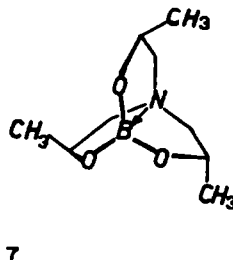
only in the racemic form we quote only few examples from organic chemistry. Hexahydro-1,3,5-triaza-6b-azacyclopenta[cd]pentalene 6 was synthesized by Thiel *et al.*^{36,37} and found to be identical with a supposed tritizaadamantane that had been previously obtained by Craig.³⁸ Fort Jr. and Semon have recently proved such an identity by NMR and evidenced the chirality of 6 due to its non planar form.³⁹



A three-blade propeller structure is shown by trisopropanolaminoborate 7,⁴⁰ which might be possibly obtained in optically active forms starting from a pure enantiomeric form (*RRR* or *SSS*) of tris*iso*propanolamine.

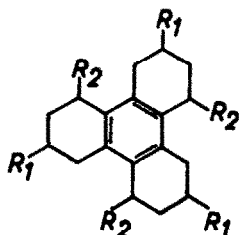
The case of trishomobullvalene 8 is certainly more sophisticated; this is a hexacyclic hydrocarbon that has been recently prepared by de Meijere and Weitemeyer;⁴¹ its resolution might be obtained at the stage of mono- or bishomobullvalene.

Some compounds with a predominantly planar and polycyclic structure have been prepared, but their stereochemistry was not investigated. Among them, the derivatives of dodecahydrotriphenylene i.e. 2,4,6,8,10,12-hexamethyldodecahydrotriphenylene 9a and 4,8,12-trimethyldodecahydrotriphenylene-2,6,10-tricarboxylic acid 9b, described by Canonne and Regnault are of interest due to the presence of a trigonally perturbed benzene ring.⁴²

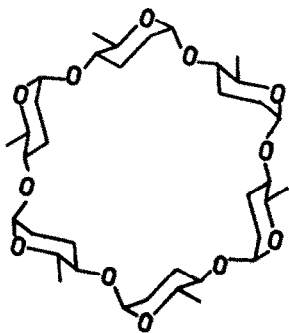




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9 a: $R_1=R_2=CH_3$ b: $R_1=COOH, R_2=CH_3$

Higher-order C groups. The only examples known are Schardinger's cyclodextrins, in particular α -cyclodextrin or cyclohexaamylose, a simplified representation of which is shown in 10, (group C_6).⁴³ This is a cyclic oligosaccharide consisting of six α -D-glucose residues with 1,4 glucosidic bond.



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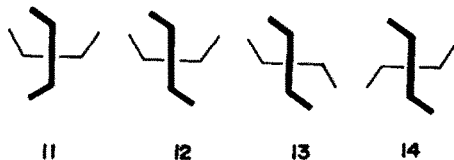
The geometry of cyclohexaamylose in the solid state was determined by Hybl *et al.*⁴⁴ by X-ray analysis of one of its complexes with K-acetate. The α -D-glucose residues are in the staggered-chair conformation (C1 conformation in the nomenclature of carbohydrates). On the whole the molecule is approximately hexagonal (idealized symmetry C_6), as its results from the tridimensional structural refinement. By "approximately" we mean that the molecular symmetry does not come directly down from that of the unit cell, but is determined *a posteriori* from the examination of the atomic coordinates. It is therefore affected by the deformations caused by the intermolecular packing and by inaccuracies in structural resolution. This remark is

valid for other molecules mentioned in this article. From the values of rotatory power Rees came to the conclusion that the conformation of cyclohexaamylose in DMSO solution should be similar to that determined in the solid state.⁴⁵ Some distortion should occur in aqueous solutions of pure cycloamylose, which is relieved by the addition of alkanic acids. This fact is attributed to the formation of an inclusion compound, stable in water solution, which stabilizes the hexagonal form.

Both 2,6-dimethyl and tetramethyl cyclohexaamylose have been studied by Casu.⁴⁶ They possess, as shown by NMR, the C1 conformation and show a greater affinity—over unsubstituted cycloamylose—for the formation of inclusion compounds with several substances.

D₂ Group. Some wonderful molecular structures belong to this group; they may be divided into four main types: spiranes, bridged biphenyls, twisted molecules and cyclophanes.

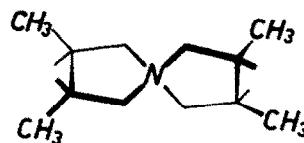
In 1955 Mc Casland and Proskow published a short communication in which two important stereochemical novelties were described.⁴⁷ They succeeded in synthesizing all four stereoisomers of 3,4,3',4' - tetramethylspiro - (1,1') - bipyrrrolidinium *p*-toluensulfonate, whose end views are schematically shown in 11-14. The interest of the authors



and of the many annotators of this article (which is a classic of modern stereochemistry) has been exclusively focused on the *trans-trans* inactive (meso) isomer 14, since it represents the first molecule in which non chirality must be uniquely attributed to the presence of a fourfold alternating axis (S_4).

Vice-versa, we wish to draw the readers' attention (and we believe we are the first in doing so) to structure 13 or, in a more complete form, 15, i.e. the active *trans-trans* isomer with D_2 symmetry. In our opinion, this is the first example of optically active organic molecule with such a symmetry. Compound 15 melts at 150-152° and has $[\alpha]_D = +19.88$ in water.^{47,48}

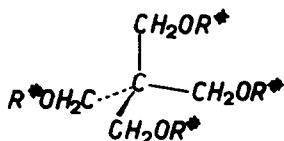
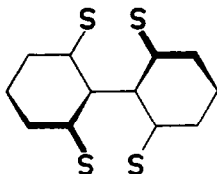
In a subsequent paper, Mc Casland examined a



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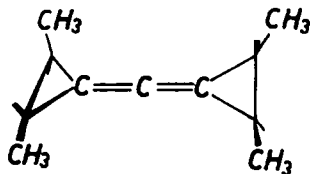
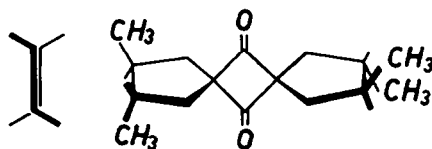
number of structures aiming at finding further examples with S_4 symmetry.⁴⁹ Some of them, with convenient changes, are also useful to our purpose. For example tetra(-)menthyloxyacetate of pentaerythrite **16** synthesized by the same author,⁴⁹ in spite of appearances, belongs to the D_2 group, as will be discussed in the last section of this paper.

A further example recently obtained by Helmchen *et al.* consists of (-)-*S*- α -phenylethylamide of biphenyl - 2,2',6,6' - tetracarboxylic acid **17** (m.p. 140°C, $[\alpha]_D = -16.8$).¹⁵

**16**

Among the other structures we quote multiple spiranes with an even number of cycles, and particular allenes, which exist in stereoisomeric forms, one of which with S_4 and another with D_2 symmetry. An approach toward the synthesis of these compounds was supplied by Skell⁵⁰ by causing to react carbon vapor (C_3) with 2-butene. The products consist of the four stereoisomers of 1,2,1',2' tetramethyl - bis - ethaneallene; their schematic views are equal to 11-14. The isomer with D_2 symmetry **18**, was obtained with 8-9% yields along with equal amounts of the S_4 isomer. The two isomers were separated and characterized (m.p. 45 and 93°) but the single structures have not been attributed.

A stereoisomer with D_2 symmetry may also exist within spiranes with an odd number of cycles. Its end view is shown in **19**. A possible route for its obtainment consists in the dimerization of conve-

**18****19****20**

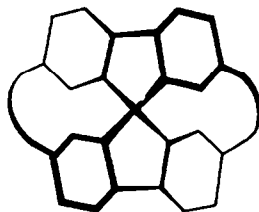
nient ketenes, e.g. that derived from *trans* - 3,4 - dimethylcyclopentancarboxylic acid.⁵¹ The structure of D_2 2,3,9,10 - tetramethyldispiro - (4,1,4,1) - cyclododecan - 6,12 - dione is indicated in **20**.

Incidentally, the symmetry properties of spiranes either with an even or odd number of cycles are similar to those of four co-ordinated chelate metal compounds, respectively with tetrahedral and planar structure.

The most interesting series of optically active D_2 spiranes was obtained by Haas and Prelog¹⁴ by the synthesis of *n,n*-vespirenes **21**. Such compounds derive from spirobifluorene and contain two methylenic bridges connecting the benzene rings of two different fluorene systems. They are characterized by the presence of a chirality center (the spirane atom) bound to four equal substituents, $C(A)$.

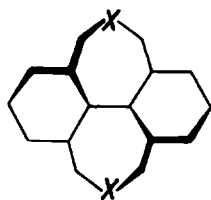
They show an exceptionally high optical activity ($[\alpha]_{586} = 600$ for 6,6-Vespirene) in comparison with the analogous spirobifluorenes that do not contain cyclic bridges. The rotatory power decreases by extending the methylenic bridges from 6 to 8 - CH_2 -. The chiroptic properties (CD and ORD) of vespirenes have been extensively studied by Haas *et al.*⁵² who have also determined their absolute configuration. Antipode *R* indicated in **21** shows a negative optical rotation at the sodium light.

Cahn *et al.* have discussed the configuration of [6.6.1]bicyclopentadecadiene **22** within the frame of axial chirality.¹¹ The stereochemical equivalence between allene and spirane structures indicates **22** as the simplest model of vespirenes. To date this compound does not seem to have been synthesized.

**21****22**

Bridged diphenyls **23** represent a second type of optically active D_2 molecules. They have been extensively studied by Mislow,^{53,54} who reports their synthesis, resolution, spectroscopic properties

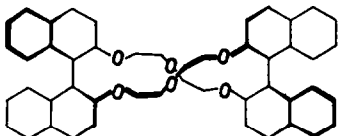
*See note 7 in Ref 49.



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(NMR, UV, ORD), absolute configuration and configurational stability. The energy of activation for the racemization was found to be lower than that of tetrasubstituted non cyclic diphenyls and primarily depends on the value of the torsion angle between the two benzene rings. The highest stability is obtained when $X=S$, then for $X=CO$ and $X=O$. The corresponding hydrocarbon ($X=CH_2$, hexahydro-dibenzoheptalene) as well as tetrahydropirene were not obtained in optically active forms owing to their high rate of racemization.

More recently Cram reported the synthesis of a crown ether with D_2 symmetry; its macrocycle contains two twisted binaphthyl residues 24.⁵⁵ The considerable interest aroused by such a compound depends on its property to include cations derived from chiral amines or other chiral compounds. This may lead to new methods of separation into optical antipodes based on partition processes.



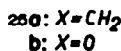
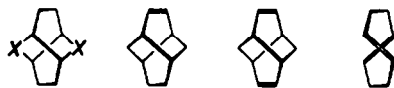
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Tricyclo[4.4.0.0^{3,5}]decane or twistane 25a, the most typical representative of the third type of D_2 molecules, was synthesized in the racemic form by Whitlock in 1962⁵⁶ and later in the pure enantiomeric form by Adachi *et al.*⁵⁷ This saturated hydrocarbon, which is an isomer of adamantane, exhibits a very high specific rotatory power ($[\alpha]_D^{25} = +414$ in ethanol). The absolute configuration of the positive antipode is *S*, on the basis of the examination of the ORD and CD curves of ketonic precursors. Such an attribution is in agreement with the Brewster's semi-empirical rules,⁵⁸ which, however, owing to the high degree of strain in the molecule cannot accurately determine the value of the rotatory power.

Tricyclo[4.4.0.0^{3,5}]dec-4-ene or twistene 26 is similar to and not less interesting than twistane; it was synthesised in optically active forms by Tichy and Sicher.⁵⁹ The molecule appears in this review,

though its symmetry is only C_2 , being an intermediate in the twistane 25-twistadiene 27 series; this last is an example—though not yet realized—of rigid structure containing a chiral *cis,cis*-1,5-cyclooctadiene ring.

trans,trans-Cycloocta-1,5-diene 28 was synthesized by Whitesides *et al.*,⁶⁰ however it is still uncertain whether the product has D_2 or C_{2h} conformation.



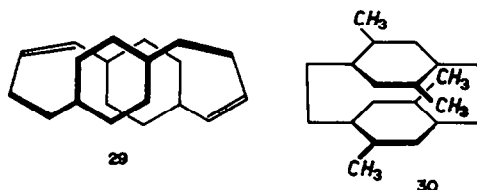
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A heterocyclic derivative of twistane with D_2 symmetry, i.e. 2,7 dioxatwistane, 25b, was obtained in the racemic form by Ganter and Wicker.⁶¹

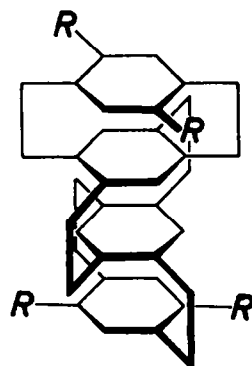
The first cyclophane with D_2 symmetry was prepared, but not resolved, by Cram and Dewhirst,⁶² i.e. 1,2,3,4,11,12,13,14-dehydro[4.4]paracyclophane 29, a highly strained molecule without substituents on the benzene rings.



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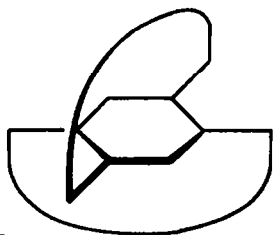
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Tetramethyl[2.2]paracyclophane 30 was prepared in the racemic form and later partially resolved by Longone.^{63,64} The same author later synthesised a racemic multi-layer [2.2]paracyclophane 31a, of which one form has D_2 symmetry.⁶⁵ In turn, Nakasaki, Yamamoto and Tanaka synthesised a

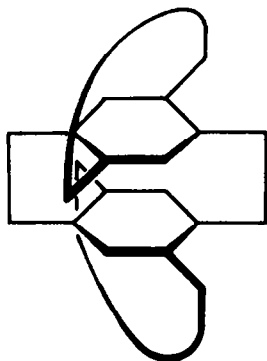


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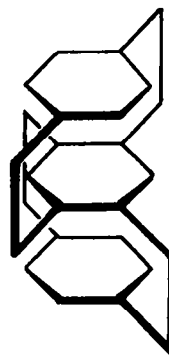
racemic[8][8]paracyclophane containing a benzene ring associated with two octamethylene bridges **32** and two [2.2]paracyclophanes, doubly bridged with 8- and 10-membered polymethylene chains **33**.⁶⁶ The NMR and UV spectra of all these compounds have been reported and discussed; furthermore, their CD spectrum should be interesting since they contain a bent benzene chromophore.



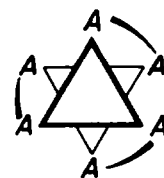
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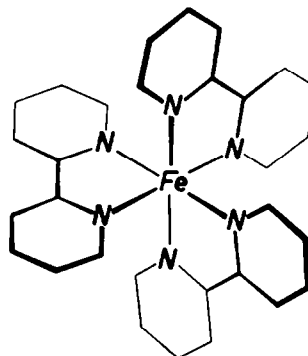
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The same Japanese authors have recently reported the synthesis in optically active form of **31b** (a 4-layered [2.2]paracyclophane, $[\alpha]_D^{25} = +250$), of **34** (a 3-layered [2.2]paracyclophane, $[\alpha]_D^{25} = -265$)⁶⁷ and of **33** ([2.2]paracyclophane with a decamethylene double bridge, $[\alpha]_D^{21} = +61$).⁶⁸ The absolute configuration of the first two compounds was discussed in terms of planar chirality and was determined as follows: (+)-(S,S)- **31b** and (-)(R) **34**. The CD spectra have not been reported.

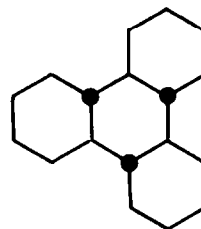
D₃ Group. In this group too, as in the C₃ one, several examples may be drawn from inorganic chemistry. Due to the relationships existing with octahedral figures, the molecules having D₃ symmetry may be easily obtained starting from metal ions with co-ordination number 6. Several examples have been reported by Woldbye²¹ and by Mason.⁶⁹ As examples we report the general formula **35** and quote trisbipyridyl iron **36**, whose chiroptic properties were discussed by Mc Caffery *et al.*⁷⁰ along with those of Fe trisphenantroline and of other related complexes.

The well known [Co(en)]³⁺ complex is less typical from our point of view. In the solid state it

shows D₃ symmetry⁷¹ but in solution a considerable exchange of conformation of ligands takes place between δ and λ ; the predominant conformer in solution is $\Lambda(\delta\delta\lambda)$ and its antipode $\Delta(\lambda\lambda\delta)$.⁷² The effect of both configurational (of Co^{III}) and conformational (of ligands) changes on the CD spectra of these complexes has been discussed.⁷²

The only D₃ organic compound isolated so far in optically active forms is the *trans-anti-trans-anti-trans* stereoisomer of perhydrotriphenylene **37**, whose stereochemical properties have been studied by Farina and Audisio.^{4,7}

The rotatory power $[\alpha]_D^{25}$ is -93 for the enantiomer with absolute configuration R. Optical purity was ascertained by isotopic dilution. Like in the case of twistane, the optical sign coincides with that foreseen by the Brewster method.⁵⁸ Due to the

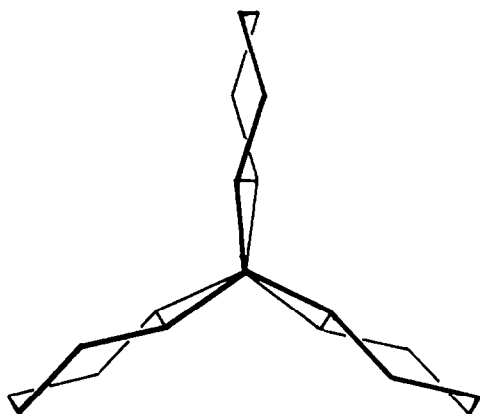


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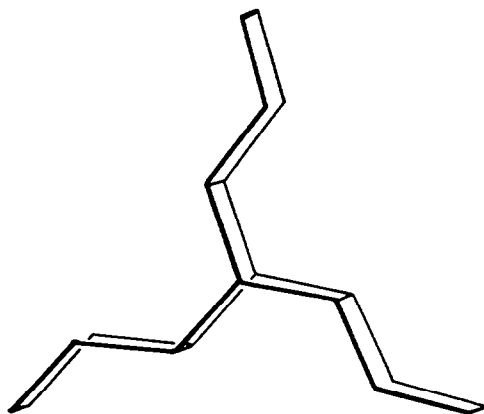
absence of strain, also the calculated value is fairly correct, being lower than the experimental value only by 20%.

Perhydrotriphenylene exhibits a very high configurational stability. It undergoes a slow epimerization, accompanied by a even slower racemization, only in the presence of Pd at 250–300°. Like other substances quoted such as triorthotimotide and cycloamylose, perhydrotriphenylene gives rise to inclusion compounds with several substances.^{74–75} Asymmetric transmission between the two components of the inclusion compound has been evidenced by the γ -ray induced asymmetric polymerization of a prochiral monomer (1,3 pentadiene) included in optically active perhydrotriphenylene.⁷⁶ This proves that the diastereoisomerism relationships, which are at the basis of asymmetric syntheses and of resolutions into antipodes, are operative not only in the case of ion-dipole interactions—as in Cram's chiral crown-ethers already quoted⁵⁵—or of other strong interactions, but also in the case of weak Van der Waals forces among hydrocarbons.

Most of the (few) racemic D_3 molecules known are flexible and have low conformational stability. The only exception is the *iso-trans* isomer of perhydrotripticene **38** recently synthesised by Morandi *et al.*¹⁰ by catalytic hydrogenation of tripticene. Compound **38** represents the final product and is obtained after long reaction time (about one month). Among the kinetically favoured isomers, the *iso-cis*-perhydrotripticene **39** is noteworthy: it has C_{3h} symmetry, but may be potentially transformed into a chiral radical with C_3 symmetry. Compound **38** exists in chair conformation while **39** is eclipsed both in the crystal state and in solution. This notwithstanding, they show a very slight difference in free energy, of the order of few kcal/mole. This value proves the high degree of strain that exists in the bicyclo-octane ring of **38**. The stereochemistry of substituted bicyclooctanes



38



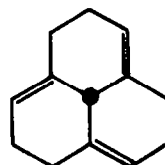
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was extensively investigated in view of the synthesis of high symmetry chiral compounds.⁷⁷

trans,trans,trans-Cyclododeca-1,5,9-triene **40** was obtained by Wilke and Kröner by butadiene trimerization⁷⁸ and its crystal structure was determined by Allegra and Bassi.⁷⁹ The molecule is not planar and assumes a D_3 conformation. In the molten state and in solution, such a conformation should not be stable. However, no studies have been published about its conformational equilibrium.



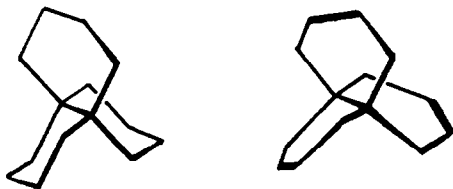
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Similar, to some extent, to dodecatriene **40** might be the hexahydrophenalene **41** discussed by Cahn *et al.*¹¹ The presence of the central atom stiffens the structure, but lowers the symmetry of the compound by destroying the binary axes (group C_3). As found in **2**, an analogous decrease in symmetry takes place by introducing substituents external to the ring.

As a further type of D_3 molecules we quote the propellanes described by Ginzburg and Altman,^{80–82} i.e. saturated [4.4.4]propellane **42**, m.p. 119–120° and [4.4.4]propella-3,8,12-triene **43**, m.p. 49–51°. Their molecular conformation in the crystal state has been determined by Ermer *et al.*⁸³ The end view of these compounds is analogous to that of the octahedral complexes $[\text{Co}(\text{en})_3]^{3+}$ and $[\text{Co}(\text{pn})_3]^{3+}$ previously discussed. Propellatriene consists of three cyclohexene rings joined on a single bond; a low interconversion energy of the antipodes should be expected. A higher stability, yet insufficient under

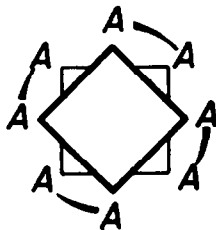


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43

ordinary conditions for its isolation in optically active forms, has been foreseen for the saturated propellane 42.

D. Group. As far as we know, only one molecule with **D**₂ symmetry has been obtained and only in the racemic form, Niobium IV tetrakis - (dipivaloyl-methanate) 44; its synthesis was recently reported by Pinnavaia *et al.*⁸⁴ Its structure, as revealed by X-ray analysis, is best interpreted as a square antiprism, in which chirality derives from the presence of chelating groups.



44

Compound 44 is monomeric both in the solid state and in solution. The above structure is preferred over a polymeric one—which had also been foreseen for compounds of this type—because of the presence of *t*-butyl end groups. As a matter of fact, acetylacetonates of different metals are reported as oligomeric compounds, while the corresponding dipivaloylmethanates are monomeric. No data are available on the configurational stability of 44.

Principles for the design of high symmetry chiral molecules

In view of a classification and as a guideline for synthesis, high symmetry chiral compounds may be divided into four classes:

I Rigid molecules with intrinsically chiral structure.

*The definition of submolecular asymmetric unit is taken from the crystallographers' usage and is not limited to the examination of chiral molecules. It may be quite profitably used in several instrumental techniques of analysis, especially in NMR spectroscopy. In particular we remind that the number of carbon atoms present in such a unit corresponds to the highest number of signals that may be observed by CMR spectroscopy.

II Molecules having a rigid non chiral basic framework, in which chirality derives from the presence of non chiral substituents in convenient positions.

III Flexible molecules containing equivalent chiral groups, provided that at least one conformer (possibly the stablest) exhibits high rotational symmetry.

IV Flexible molecules that do not contain chiral groups, in which at least one conformer that is stable and isolable under accessible experimental conditions is chiral and shows high rotational symmetry.

Whether a given molecule belongs to one or to the other class may sometimes be a matter of discussion. The most important parameter is the height of the energy barrier that hinders conversion among stereoisomers (including conformers). This is valid when considering whether a molecule is rigid or flexible (class I and III or I and IV), and also for the determination of what is meant (in class IV) by stable and isolable.

From among the examples considered in the previous section, the compounds 6, 8, 25, 26, 27, 31, 34, 36, 37, 38, 41, 44 belong to class I; the compounds: 7, 9, 15, 18, 20, 30 belong to class II; the compounds 2, 10, 16, 17, 22 to class III; the compounds: 1, 40, 42, 43 to class IV.

Compounds 23, 28, 29 may be considered as belonging to class I or IV; compounds 4, 5, 21, 32, 33 to class I or III, while compound 24 may belong to class III or IV.

The rather few cases of high symmetry chiral molecules known do not certainly represent all existing possibilities. With a bit of imagination and possibly with the help of the Ring Index, a large number of structures may be found that may fall within our definitions. The matter is to find a chiral molecular skeleton, which according to Prelog nomenclature¹² constitutes a chiral simplex, or else to find an achiral simplex that may be easily transformed into a chiral structure.

All that may be done on empirical grounds and by trials, but may also be dealt with by a logical process on the basis of some considerations on molecular symmetry.

On this regard we define a *submolecular asymmetric unit*, inside which no symmetry relation exists.*

Such a unit is bound to the whole molecular structure by symmetry operations. If the molecule is chiral, such operations exclusively consist in rotations and their number equals the symmetry number σ . If the molecule is not chiral, both rotations and roto-reflections will take place and the total number of operations, and hence of repetitions of the asymmetric unit, equals 2σ .

For example, the submolecular asymmetric unit contains a timotic acid residue in formula 1, an α -glucose unit in 10, half fluorene nucleus and half

polymethylene bridge in 21, half benzene ring and a double bond in 29, three carbon atoms in 37, four in 38 and only two in 40.

The recognition of the existence of asymmetric units allows one to determine whether some atoms in a molecule are equivalent or not, and to control to which symmetry group the molecule actually belongs (or at least which is the order of such group). The use of such criteria to construct high symmetry chiral molecules is illustrated in some significant examples.

A number n of asymmetric units may be linked up one to another to form a cycle (or macrocycle). Depending on the type of repetition, whether by simple rotation, or by rotation around the main axis and around other twofold axes perpendicular to the first, structures with C_n or D_m symmetry are obtained, where $m = \frac{1}{2}n$. Examples of this type are shown in formulas 1, 2, 10, 24, 40.

Starting from 2,7 - dichloromethyl - 9,10 - dihydrophenantrene, Pajoni and Jenny have recently obtained hexahydro-[2¹]- (2,7)phenantrenophane and decahydro-[2¹]- (2,7)phenantrenophane respectively containing 3 and 5 units of dihydrophenantrene.⁶⁵ Such molecules are not chiral owing to the conformational instability of dihydrophenantrene. Were this reaction carried out on other diphenyl derivatives, which are sterically stabler but whose symmetry is always C_2 , the molecules obtained should have such a high symmetry as D_5 .

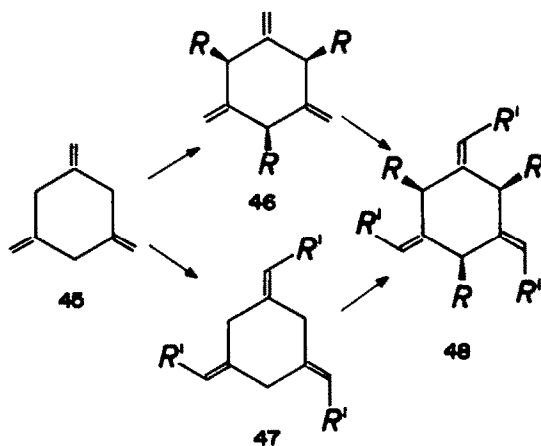
If the asymmetric unit is polyfunctional, i.e. it may be linked up with other units by more than two bonds, a chiral rigid skeleton may be built. Among the examples of this type we quote twistane 25a, perhydrotriphenyl 37 and perhydrotripticene 38.

In the case of an achiral simplex with $\sigma = n$, the simplest and most obvious route to make it chiral is the introduction of n asymmetric substituents, all with the same chirality. This is not always possible owing to the particular constitution of the asymmetric unit. The topic is well enlightened by the comparison between coronene and benzene, which both belong to the same D_{6h} group, with $\sigma = 12$.

Replacement of all H atoms of the two compounds by chiral groups, e.g. (*R*) sec-butyl, gives in the former case dodeca - sec - butylcoronene belonging to the D_6 or C_{12} group (depending on the conformations of the substituents, but always with $\sigma = 12$), in the latter case it gives hexa - sec - butylbenzene with D_3 or C_6 symmetry ($\sigma = 6$). Benzene derivatives with D_6 symmetry may be obtained only by applying the criteria that will be described when dealing with tetrahedral structures.

An achiral simplex may be transformed into a chiral structure even by the introduction of achiral substituents. In this case too, the symmetry number may either remain as such or may be reduced. An example of the first type might be the passage from coranulene⁶⁶ (group C_{5v}) to penta-aza- or to

pentamethylcoranulene (group C_5). An example of the second type is illustrated in formulas 45-48, where a logical (not necessarily synthetic) scheme of the obtainment of a C_3 molecule from a D_{3h} simplex is reported.



The decreased degree of symmetry described here is an expression of a general rule: symmetry is a subtractive property. This fundamental remark was made by Pierre Curie, who *verbatim* stated: "Quand plusieurs phénomènes de natures différentes se superposent dans un même système, les dissymétries s'ajoutent. Il ne reste plus alors comme éléments de symétrie dans le système que ceux qui sont communs à chaque phénomène pris séparément".⁶⁷

Compound 48 may be considered as resulting from the superposition along the ternary axis of the two partial structures 46 and 47, one with C_{3v} symmetry and the other with C_{3h} symmetry. The only element shared by the two figures is the threefold axis, which therefore constitutes the only symmetry element present in 48 (group C_3). On their turn, 46 and 47 derive from 45 by the introduction of substituents that destroy the twofold axes and one or more mirror planes.

The Curie principle is of fundamental importance for tackling one of the main topics of this paper, i.e. the design of molecules having instantaneous symmetry T, O and I. This topic is generally neglected in texts of stereochemistry, both organic and inorganic, although the corresponding achiral "simplex"—or at least the tetrahedral and octahedral ones—are well known. As far as we know, only two quotations exist concerning hypothetical molecules with T and O symmetry. Cahn *et al.* have pointed out the possibility of obtaining a T symmetry molecule by bridging in pairs with six like bridges (having internal C_2 symmetry, e.g. *trans* olefinic) four tetrahedral atoms situated at the vertices of a tetrahedron.¹¹ In their book, which even today contains the most exhaustive discussion

on these problems, Caldwell and Eyring propose an O symmetry Osmium complex more as an artistic object than as a chemical purpose.¹⁶

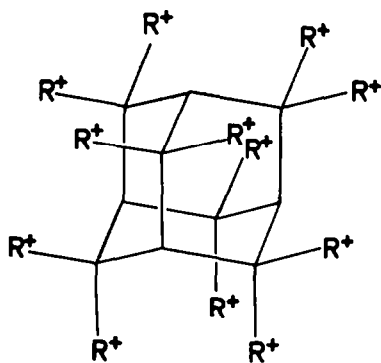
Previous papers, such as the classical ones by Ebel¹⁸ or by Shriner and Adams¹⁹—in spite of all appearances—do not deal with this topic. A tetrahedral atom bound to four like *asymmetric* substituents, e.g. C(A₄⁺) has *not* T symmetry. Its highest symmetry is D₂, as shown by considering the number of submolecular asymmetric units present in it (which is 4, like the symmetry number of the D₂ group). An example of this type, already obtained, has been shown in 16.⁴⁹

A high symmetry achiral simplex may give rise to a chiral structure with the same symmetry number if chiral substituents, with the same internal symmetry as the axis, are placed along all rotation axes of a given order present in the simplex, or else if a number of asymmetric substituents equalling the order of the axis are symmetrically placed around each axis.* By a chiral substituent we do not necessarily mean groups containing asymmetric atoms, but we mean whatever arrangement of atoms having the required symmetry. The asymmetric unit previously defined must occur in the molecule as many times as the symmetry number (12 for T, 24 for O and 60 for I).

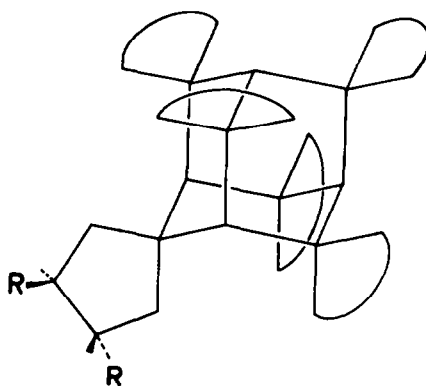
For example, let us consider an achiral tetrahedral simplex such as adamantane. It has 4 ternary axes passing along the C-H methynic bonds and 3 binary axes bisecting the H-C-H angle of the methylenic groups. A T molecule may be obtained by replacing tertiary hydrogen atoms by four chiral substituents with threefold internal symmetry or else by replacing all secondary H atoms by 12 asymmetric substituents or by 6 bifunctional chiral substituents with twofold symmetry. In any case mirror symmetry is lost while the rotational symmetry is entirely maintained ($\sigma = 12$).

As a bifunctional chiral substituent one might consider a disubstituted ring joined in a spiranic way, or more complex structures, such as twistane. Possible candidates for a threefold chiral substituent are trisubstituted bicyclooctanes. Among them, the already quoted derivatives of iso-*cis*-perhydrotripticene **39** may show some interest. Schematic formulas of these hypothetical compounds are shown in 49-51.

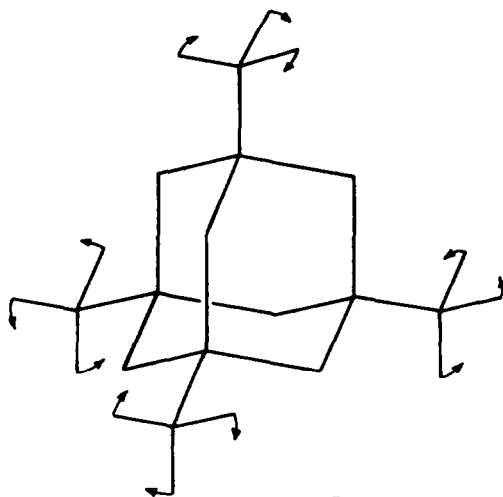
An analogous reasoning may be also applied to figures with O_h and I_h symmetry. The corresponding achiral "simplices" are, in the first case, the octahedron and the cube, in the second case, the dodecahedron and the icosahedron. The most interesting of them should certainly be the octahedron, although it involves many difficulties owing to the



49



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51

presence of fourfold axes passing across the vertices. The synthesis of a cubic compound might seem easier (e.g. of a substituted cubane with 8 ternary chiral groups or of the Osmium complex proposed by Caldwell and Eyring).¹⁶

It would be easy to describe other classes of

*If the rotation axis under consideration is perpendicular to a (2n)fold axis, its opposite directions are equivalent; as a consequence, the number of chiral substituents required is doubled.

molecules with fascinating symmetries, but we have preferred to tackle the problem on experimental grounds. We have devoted ourselves to the solution of a few of them. It is our hope to be able to give some new results on such topics in the future.

Note added in proof

A further example of an optically active D_2 molecule is given by Wittig and Rümpler.⁹⁰ *ortho*-Hexaphenylene exists in two stereoisomeric forms, one of which is chiral (see formula 52) and gives rise to enantiomeric crystals. The highest specific rotation observed was $[\alpha]_{D}^{20} = -16.3$; its molecular structure was determined by Irngartinger through X-ray analysis.⁹¹ The compound is noteworthy in particular for our discussion on the submolecular asymmetric units. In the conformation shown in 52 the six benzene rings are not equivalent, the symmetry number of the indicated structure being only four. As a consequence, the asymmetric unit contains nine carbon atoms.

Other D_2 molecules with analogous structures have been examined by Irngartinger.^{92,93} They possess two triple bonds or two *trans*-double bonds instead of the two tilted benzene rings of formula 52.

Wittig and Schoch described the synthesis of a racemic polycyclic propellane, hexabenzob[b,d,g,i,l,n] [4,4,4] propellamancen 53⁹⁴ with D_3 symmetry. According to what previously observed, compound 53 may be considered as a carbocyclic analogue of the hexaco-ordinated complex 36.

REFERENCES

- ¹E. Paternò, *Giornale di Scienze Naturali ed Economiche*, Vol 5 I, p 117 Palermo, (1869)
- ²F. Woldbye, *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry* (Edited by G. Sznatzke), p. 103. Heyden & Son, London (1967)
- ³M. Farina, M. Peraldo and G. Natta, *Angew. Chem. Int. Ed.* 4, 107 (1965)
- ⁴M. Farina, *Tetrahedron Letters* 2097 (1963)
- ⁵M. Farina and G. Audisio, *Tetrahedron* 26, 1827 (1970)
- ⁶M. Farina and G. Audisio, *Tetrahedron Letters* 1285 (1967)
- ⁷M. Farina and G. Audisio, *Tetrahedron* 26, 1839 (1970)
- ⁸C. Morandi, Graduation Thesis, University of Milan (1970-71)
- ⁹C. Morandi and M. Farina, *Preprints of the VII Meeting of Organic Chemistry*, p. 105. Taormina, Italy (1972)
- ¹⁰C. Morandi, E. Mantica, D. Botta, M. T. Gramegna and M. Farina, *Tetrahedron Letters* 1141 (1973)
- ¹¹R. S. Cahn, C. K. Ingold and V. Prelog, *Angew. Chem. Int. Ed.* 5, 385 (1966)
- ¹²V. Prelog, *Chem. in Britain* 4, 382 (1968)
- ¹³V. Prelog and G. Helmchen, *Helv. Chim. Acta* 55, 2581 (1972)
- ¹⁴G. Haas and V. Prelog, *Ibid.* 52, 1202 (1969)
- ¹⁵G. Helmchen, G. Haas and V. Prelog, *Ibid.* 56, 2255 (1973)
- ¹⁶D. J. Caldwell and H. Eyring *The Theory of Optical Activity*, p. 79-93 and 153-166. Wiley, New York (1971)
- ¹⁷K. Mislow and R. Bolstad, *J. Am. Chem. Soc.* 77, 6712 (1955)
- ¹⁸H. C. Longuet-Higgins, *Molec. Phys.* 6, 445 (1963)
- ¹⁹I. Ugi, D. Marquarding, H. Klusacek, G. Gokel and P. Gillespie, *Angew. Chem. Int. Ed.* 9, 703 (1970)
- ²⁰K. Mislow, *Introduction to Stereochemistry*. Benjamin, New York (1965)
- ²¹F. Woldbye, *Techniques of Inorganic Chemistry* (Edited by H. B. Jonassen and Arnold Weissberger), Vol. IV, p. 249. Interscience, New York (1965)
- ²²C. Reichardt, *Chemie in unserer Zeit* 4 (6) 188 (1970)
- ²³R. Spallino and G. Provenzal, *Gazz. Chim. Ital.* 39, II, 325 (1909)
- ²⁴W. Baker, B. Gilbert and W. D. Ollis, *J. Chem. Soc.* 1443 (1952)
- ²⁵H. M. Powell, *Nature* 170, 155 (1952)
- ²⁶A. C. D. Newman and H. M. Powell, *J. Chem. Soc.* 3747 (1952)
- ²⁷W. D. Ollis, and I. O. Sutherland, *Chem. Commun.* 402 (1966)
- ²⁸A. P. Downing, W. D. Ollis, I. O. Sutherland, J. Mason and S. F. Mason, *Ibid.* 329 (1968)
- ²⁹A. P. Downing, W. D. Ollis and I. O. Sutherland, *J. Chem. Soc. part B*, 24 (1970)
- ³⁰J. Furukawa, T. Kakuzen, H. Morikawa, R. Yamamoto and O. Okuno, *Bull. Chem. Soc. Japan* 41, 155 (1968)
- ³¹F. P. Dwyer, F. L. Garvan and A. Shulman, *J. Am. Chem. Soc.* 81, 290 (1959)
- ³²E. J. Corey and J. C. Bailar Jr., *Ibid.* 81, 2620 (1959)
- ³³F. P. Dwyer, T. E. Mac Dermott and A. M. Sargeson, *Ibid.* 85, 2913 (1963)
- ³⁴J. K. Beattie, *Acc. Chem. Res.* 4, 253 (1971)
- ³⁵S. F. Mason, *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry* (Edited by G. Sznatzke), p. 116. Heyden & Son, London (1967)
- ³⁶M. Thiel, F. Asinger and K. Schmiedel, *Liebigs Ann.* 611, 121 (1958)
- ³⁷F. Asinger and M. Thiel, *Angew. Chem.* 70, 667 (1958)
- ³⁸D. Craig, J. J. Shipman, A. Hawthorne and R. Fowler, *J. Am. Chem. Soc.* 77, 1283 (1955)
- ³⁹R. C. Fort Jr. and W. L. Semon, *J. Org. Chem.* 32, 3685 (1967)
- ⁴⁰H. Steinberg and D. L. Hunter, *J. Am. Chem. Soc.* 82, 853 (1960)
- ⁴¹A. de Meijere and C. Weitemeyer, *Angew. Chem., Int. Ed.* 9, 376 (1970)
- ⁴²P. Canonne and A. Regnault, *Tetrahedron Letters* 243 (1969)
- ⁴³D. French, *Advan. Carbohydrate Chem.* 12, 189 (1957)
- ⁴⁴A. Hybl, R. E. Rundle and D. E. Williams, *J. Am. Chem. Soc.* 87, 2779 (1965)
- ⁴⁵D. A. Rees, *J. Chem. Soc. part B*, 877 (1970)
- ⁴⁶B. Casu, *Chimica delle Macromolecole*, p. 309. Consiglio Nazionale delle Ricerche, Roma (1968)
- ⁴⁷G. E. Mc Casland and S. Proskow, *J. Am. Chem. Soc.* 77, 4688 (1955)
- ⁴⁸G. E. Mc Casland and S. Proskow, *Ibid.* 78, 5646 (1956)
- ⁴⁹G. E. Mc Casland, R. Horvat and M. R. Roth, *Ibid.* 81, 2399 (1959)
- ⁵⁰P. S. Skell, L. D. Wescott Jr., J. P. Golstein and R. R. Engel, *Ibid.* 87, 2829 (1965)
- ⁵¹M. Farina and G. Di Silvestro, work in progress
- ⁵²G. Haas, P. B. Hulbert, W. Klyne, V. Prelog and G. Sznatzke, *Helv. Chim. Acta* 54, 491 (1971)
- ⁵³K. Mislow and M. A. W. Glass, *J. Am. Chem. Soc.* 83, 2780 (1961)
- ⁵⁴K. Mislow M. A. W. Glass, H. B. Hopps, E. Simon and G. H. Wahl Jr., *Ibid.* 86, 1710 (1964)
- ⁵⁵E. B. Kyba, K. Koba, L. R. Sousa, M. G. Siegel and D. J. Cram, *Ibid.* 95, 2692 (1973)
- ⁵⁶H. W. Whitlock Jr., *Ibid.* 84, 3412 (1962)
- ⁵⁷K. Adachi, K. Naemura and M. Nakasaki, *Tetrahedron Letters* 5467 (1968)
- ⁵⁸J. H. Brewster, *J. Am. Chem. Soc.* 81, 5475, 5483 (1959)

- ⁵⁹M. Tichy and J. Sicher, *Tetrahedron Letters* 4609 (1969)
- ⁶⁰G. M. Whitesides, G. L. Goe and A. C. Cope, *J. Am. Chem. Soc.* **89**, 7136 (1967)
- ⁶¹C. Ganter and K. Wicker, *Helv. Chim. Acta* **53**, 1693 (1970)
- ⁶²D. J. Cram and K. C. Dewhirst, *J. Am. Chem. Soc.* **81**, 5963 (1959)
- ⁶³D. T. Longone and C. L. Warren, *J. Am. Chem. Soc.* **84**, 1507 (1962)
- ⁶⁴D. T. Longone and M. T. Reets, *Chem. Commun.* 46 (1967)
- ⁶⁵D. T. Longone and H. S. Chow, *Ibid.* **92**, 994 (1970)
- ⁶⁶M. Nakasaki, K. Yamamoto and S. Tanaka, *Tetrahedron Letters* 341 (1971)
- ⁶⁷M. Nakasaki, K. Yamamoto and S. Tanaka, *Chem. Commun.* 433 (1972)
- ⁶⁸M. Nakasaki, K. Yamamoto and M. Ito, *Ibid.* 433 (1972)
- ⁶⁹S. F. Mason, *Quart. Rev.* **17**, 20 (1963)
- ⁷⁰A. J. Mc Caffery, S. F. Mason and B. J. Norman, *J. Chem. Soc. part A*, 1428 (1969)
- ⁷¹K. Nakatsu, M. Shiro, Y. Saito and H. Kuroya, *Bull. Chem. Soc. Japan* **30**, 158 (1957)
- ⁷²A. J. Mc Caffery, S. F. Mason, B. J. Norman and A. M. Sargeson, *J. Chem. Soc. part A*, 1304 (1968)
- ⁷³M. Farina, unpublished data
- ⁷⁴M. Farina, G. Allegra and G. Natta, *J. Am. Chem. Soc.* **86**, 516 (1964)
- ⁷⁵G. Allegra, M. Farina, A. Immirzi, A. Colombo, U. Rossi, R. Broggi and G. Natta, *J. Chem. Soc. part B*, 1020 (1967)
- ⁷⁶M. Farina, G. Audisio and G. Natta, *J. Am. Chem. Soc.* **89**, 5071 (1967)
- ⁷⁷M. Farina, C. Morandi, E. Mantica and D. Botta, paper being prepared
- ⁷⁸G. Wilke and M. Kröner, *Angew. Chem.* **71**, 574 (1959)
- ⁷⁹G. Allegra and I. W. Bassi, *Atti Accad. Naz. Lincei* [8] **38**, 72 (1962)
- ⁸⁰D. Ginzburg, *Accounts Chem. Res.* **2**, 121 (1969)
- ⁸¹J. Altman, D. Becker, D. Ginsburg and H. J. E. Loewenthal, *Tetrahedron Letters* 757 (1968)
- ⁸²J. Altman, E. Babad, J. Pucknat, N. Reshef and D. Ginsburg, *Tetrahedron* **24**, 975 (1968)
- ⁸³O. Ermer, R. Gerdil and J. D. Dunitz, *Helv. Chim. Acta* **54**, 2476 (1971)
- ⁸⁴T. J. Pinnavaia, G. Podolsky and P. W. Coddling, *Chem. Commun.* 242 (1973)
- ⁸⁵R. Paioni and W. Jenny, *Helv. Chim. Acta* **53**, 141 (1970)
- ⁸⁶W. E. Barth and R. G. Lawton, *J. Am. Chem. Soc.* **93**, 1730 (1971)
- ⁸⁷P. Curie, *Journal de Physique* III, **3**, 393 (1894)
- ⁸⁸F. Ebel, *Stereochemie* (Edited by K. Freudenberg), p. 601. F. Deuticke, Leipzig (1933)
- ⁸⁹R. L. Shriner and R. Adams, *Organic Chemistry. An Advanced Treatise*, (Edited by H. Gilman), Vol. I, Cap. IV, p. 238. Wiley, New York (1943)
- ⁹⁰G. Wittig and K. D. Rümpler, *Liebigs Ann.* **751**, 1 (1971)
- ⁹¹H. Irngartinger, *Acta Cryst.* **B29**, 894 (1973)
- ⁹²H. Irngartinger, *Chem. Berichte* **106**, 761 (1973)
- ⁹³H. Irngartinger, *Ibid.* **106**, 2796 (1973)
- ⁹⁴G. Wittig and W. Schoch, *Liebigs Ann.* **749**, 38 (1971)