Isomer Enumeration Methods

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1 Prologue

As the year 1974 marks the centenary of the first application of a mathematical technique for the enumeration of chemical isomers, it was felt to be an appropriate time to review the development of isomer enumeration methods. The field has never been adequately reviewed, the only sources presently available being some cursory accounts of aspects of the field in elementary texts, an incomplete survey of methods used up to 1931,[1] two unpublished surveys, by Carr in 1942,[2] and Wiswesser in 1958,[3] and two introductory accounts[4] of the principal methods now in use. We remedy this situation here by presenting a review of all the significant work carried out in this field up to the end of 1973.

Because much effort and ingenuity has been expended on the enumeration of the structural isomers of organic species, a considerable portion of the review relates to this area. The enumeration of stereoisomers in both organic and inorganic species is also covered, as are the techniques employed for enumerating the boron hydrides, cluster compounds, and topological and valence isomers.

One problem which must be settled before any isomer enumeration can be carried out is that of deciding exactly what is to be enumerated. This involves us in the formal definition of the term 'isomer', and the assignment of isomers to 'classes' or 'categories'. These deceptively simple questions have been investigated by several workers.[5] For our purposes isomers will be regarded as individual chemical species of identical molecular formulae which display at least some differing physico-chemical properties, and which are stable for periods of time long in comparison with those during which measurements of their properties are made. We thereby exclude relatively unstable species such as mesomers, and polymeric species of identical empirical formulae.

The assignment of isomers to classes is also often fraught with difficulties. If, for instance, an isomer is assigned to one of the many homologous series, we are then confronted with the problem of defining precisely what is meant by such

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[1] H. R. Henze and C. M. Blair, *J. Amer. Chem. Soc.*, 1931, **53**, 3077.

[2] R. E. Carr, 'The Number of Isomeric Alkenes', Thesis, Iowa State College, Ames, Iowa, 1942.

[3] W. J. Wiswesser, unpublished paper, 1958.

[4] (*a*) S. Rios, *Gaz. Mat.*, 1945, **6**, 1; (*b*) D. H. Rouvray, *Chemistry*, 1972, **45**, 6.

[5] (*a*) P. Gordan and W. Alexejeff, *Z. Phys. Chem.*, 1900, **35**, 610; (*b*) A. C. Lunn and J. K. Senior, *J. Phys. Chem.*, 1929, **33**, 1027; (*c*) S. W. Golomb, in 'Information Theory, Fourth London Symposium', ed. C. Cherry, Butterworths, London, 1961, p. 404; (*d*) G. Ege, *Naturwiss.*, 1971, **58**, 247; (*e*) I. Ugi, P. Gillespie, and C. Gillespie, *Trans. New York Acad. Sci.*, 1972, **34**, 416.

a series.[6] We shall avoid such problems here by assuming that classification is both a feasible operation and one that will be intuitively understood on the part of the reader.

2 The Mathematical Backdrop

We consider first the basic mathematical tools necessary for all isomer enumeration studies. These tools are the closely inter-related disciplines of graph theory and combinatorial theory and, to a lesser extent, group theory. Graph theory has been adapted mainly for the concise representation of chemical species, whereas combinatorial theory has been applied in the actual enumeration process. Group theory has been used wherever the symmetry of species plays an important role.

Graph theory[7] is the study of the nature and properties of topological graphs. A *topological graph*, which should not be confused with the more common Cartesian variety, consists of a pair $(X, \hat{\Gamma})$, where X represents a set of points, and $\hat{\Gamma}$ is an operator which maps points in X into other points of the set. This

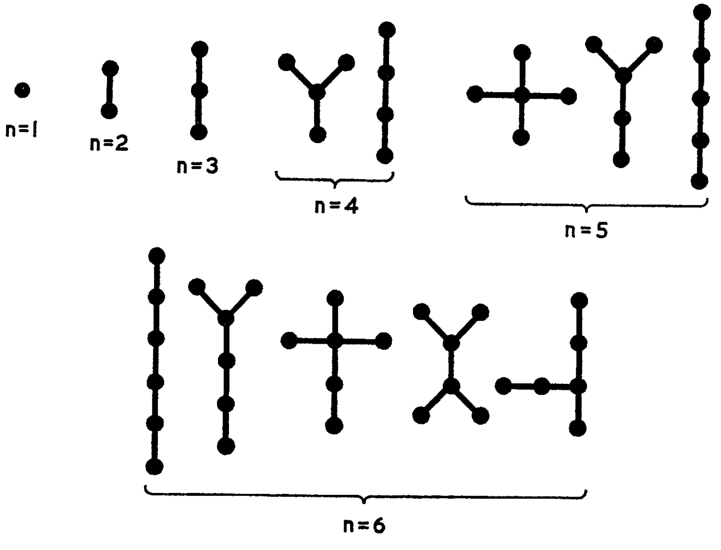

Figure 1 *Graph-theoretical trees representing the structural isomers of the first six members of the alkane series*

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[6] (*a*) J. K. Senior, *J. Org. Chem.*, 1938, **3**, 1; (*b*) F. L. Breusch, *Fortschr Chem. Forsch.*, 1966, **12**, 119; (*c*) I. Motoc, *Rev. Roumaine Chim.*, 1973, **18**, 1419.

[7] (*a*) C. Berge, 'The Theory of Graphs and its Applications', Methuen, London, 1963; (*b*) F. Harary, 'Graph Theory', Addison-Wesley, Reading, Massachusetts, 1969; (*c*) R. J. Wilson, 'Introduction to Graph Theory', Oliver and Boyd, Edinburgh, 1972; (*d*) F. Harary and D. Palmer, 'Graphical Enumeration', Academic, New York, 1973.

mapping process generates unordered pairs of points or lines in the set X. The points are usually referred to as *vertices*, whilst the lines are known as the *edges* of the graph. Graphs may be used for the representation of molecular species: the vertices depict the time-averaged positions of the atomic nuclei, the edges the valence bonds existing between the nuclei. In Figure 1 are depicted examples of *tree graphs*, representing the structural isomers for the first six members of the alkane series.

Combinatorial theory[8] is the study of the possible configurations of a finite set of objects, and normally involves an investigation of the number of *partitions* or *classes* into which the set may be partitioned by some well-defined mathematical operation. It has proved an indispensable aid in determining the numbers of molecules belonging to specified classes of isomer.

In the history of combinatorial theory are to be found many interesting interactions with chemistry, this resulting in a fair amount of cross-fertilization of both disciplines. As our narrative reveals, mathematicians have produced novel results whilst working under the challenge of chemical problems, and chemists working on isomer enumeration have developed several new combinatorial techniques.

The alliance of group theory with chemistry has proved even more rewarding than that of combinatorial theory. Since the main outlines of group theory are widely known among chemists today,[9] we shall not discuss them here.

3 The Curtain Raiser

The concept of isomerism is very old, being first adumbrated in the writings of Democritus around 420 B.C.[10] From the sixteenth century onwards numerous early pioneers, including Jungius,[11] von Humboldt,[12] Thomson,[13] Dalton,[14] and Gerhardt,[15] brought increasing clarification of the concept. The existence of chemical isomers was first demonstrated experimentally in 1811 by Gay-Lussac.[16]

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[8] (*a*) J. Riordan, 'An Introduction to Combinatorial Analysis', Wiley, New York 1958; (*b*) E. F. Beckenbach (ed.), 'Applied Combinatorial Mathematics', Wiley, New York, 1964; (*c*) C. L. Liu, 'Introduction to Combinatorial Mathematics', McGraw-Hill, New York, 1968; (*d*) M. Eisen, 'Elementary Combinatorial Analysis', Gordon and Breach, New York, 1969.

[9] (*a*) F. A. Cotton, 'Chemical Applications of Group Theory', Interscience, New York, 1963; (*b*) D. S. Schonland, 'Molecular Symmetry', Van Nostrand, London, 1965; (*c*) L. H. Hall, 'Group Theory and Symmetry in Chemistry', McGraw-Hill, New York, 1969; (*d*) G. Davison, 'Introductory Group Theory for Chemists', Elsevier, London, 1971.

[10] H. A. M. Snelders, *Chem. Weekblad*, 1964, **60**, 217.

[11] R. Hooykaas, in 'Die Entfaltung der Wissenschaft', Jungius Memorial Volume, Augustin, Hamburg, 1957, p. 47.

[12] E. O. von Lippmann, *Chem.-Ztg.*, 1909, **33**, 1.

[13] T. Thomson, 'The History of Chemistry', Vol. 2, Colburn and Bentley, London, 1831, p. 304.

[14] W. V. Farrar, in 'John Dalton and the progress of science', ed. D. S. L. Cardwell, Manchester University Press, Manchester, 1968, p. 291.

[15] C. F. Gerhardt, 'Précis de Chimie Organique', Fortin, Masson, Paris 1844, Vol. 1, p. 22,

[16] (*a*) J. L. Gay-Lussac and L. J. Thenard, 'Recherches Physico-Chimiques', Deterville. Paris, 1811, Vol. II, p. 340; (*b*) J. L. Gay-Lussac, *Ann. Chim.*, 1814, **91**, 149.

Shortly thereafter Faraday made the prophetic observation[17] on isomers that 'now we are taught to look for them, they may probably multiply upon us'.

In 1830 the term *isomerism* was coined by Berzelius from the Greek roots 'ἴσος, equal and 'μερός', part; he also gave the first modern definition[18] of isomers as compounds 'possessing the same chemical constitution and molecular weight but differing properties'. Structural isomers were first fully recognized *ca.* 1862 by Butlerov.[19] He is usually also credited with the founding of modern structural theory in organic chemistry.[20] His investigations embraced several isomeric systems,[21] and he succeeded in obtaining the number of isomers for the chloro-substituted methanes.[19]

The earliest notion of stereoisomerism is probably due to Wollaston,[22] who in 1808 wrote of atoms that 'the arithmetical relation alone will not be sufficient to explain their mutual interaction, and that we shall be obliged to acquire a geometrical conception of their relative arrangement in all the three dimensions'. The concept of the asymmetric carbon atom stems from the work of Pasteur,[23] though its importance was first appreciated in the influential works of Le Bel[24] and van't Hoff.[25] It was shown by van't Hoff[25] that the number of stereoisomers which can be formed from a molecule containing n asymmetric carbon atoms is 2^n, though he indicated that in highly symmetric species this total may not be achieved.

The first attempts at isomer classification were made by Kekulé,[26] Butlerov,[27] Crum Brown,[28] and Berthelot.[29] Following Werner's classic studies on co-ordination compounds,[30] schemes including inorganic isomers were introduced.[31] In more recent years, when over thirty varieties of isomerism have been recog-

[17] M. Faraday, *Phil. Trans. Roy. Soc.*, 1825, **115**, 460.

[18] J. J. Berzelius, *Pogg. Ann.*, 1830, **19**, 326.

[19] A. M. Butlerov, *Z. Chem.*, 1862, **5**, 298.

[20] A. M. Butlerov, *Z. Chem.*, 1861, **4**, 549.

[21] (*a*) A. M. Butlerov, *Z. Chem.*, 1865, **8**, 614; (*b*) A. M. Butlerov, *Bull. Soc. Chim. Paris*, 1866, **5**, 17; (*c*) A. M. Butlerov, *Ann. Chem.*, 1867, **144**, 1.

[22] W. H. Wollaston, *Phil. Trans. Roy. Soc.*, 1808, **98**, 101.

[23] L. Pasteur, *Compt. Rend. Paris*, 1850, **31**, 480.

[24] J. A. Le Bel, *Bull. Soc. chim. France*, 1874, **22**, 337.

[25] (*a*) J. H. van't Hoff, *Arch. Néer. Sci. Exact. Nat.*, 1874, **9**, 445; (*b*) J. H. van't Hoff, 'Voorstel tot Uitbreiding der.... Structuur Formules in de Ruimte', Greven, Utrecht, 1874; (*c*) J. H. van't Hoff, (Translated by J. E. Marsh), 'Chemistry in Space', Clarendon, Oxford, 1891.

[26] F. A. Kekulé, *Ann. Chem.*, 1858, **106**, 129.

[27] A. M. Butlerov, *Z. Chem.*, 1863, **6**, 500.

[28] A. Crum Brown, *Trans. Roy. Soc. Edin.*, 1864, **23**, 707.

[29] M. Berthelot, 'Leçons de Chimie', Soc. Chim. Paris, Hachette, Paris, 1866, p. 1.

[30] (*a*) A. Werner, *Z. anorg. Chem.*, 1893, **3**, 267; (*b*) A. Werner and A. Vilmos, *ibid.*, 1899, **21**, 145; (*c*) G. B. Kauffman, 'Classics in Coordination Chemistry, Part I, The Selected Papers of Alfred Werner', Dover, New York, 1968.

[31] (*a*) A. W. Stewart, 'Stereochemistry', Longmans Green, London, 1907; (*b*) M. Delépine, *Bull. Sci. Pharmacol.*, 1907, **14**, 75; (*c*) C. Laar, *Ion*, 1909, **78**, 195; (*d*) C. Laar, *J. prakt. Chem.*, 1909, **78**, 165; (*e*) O. De Vries, *Chem. Weekblad*, 1909, **6**, 387; (*f*) H. R. Kruyt, *Chem. Ber.*, 1910, **43**, 540; (*f*) J. R. Mourelo, *Rev. Sci.*, 1919, **57**, 65.

nized, more complex classification schemes have had to be devised,[32] and resort is now being made to set-theoretical procedures.[33]

4 The Opening Scene

The first applications of combinatorial techniques to isomer enumeration were made in 1874. In that year investigations were carried out by the noted mathematician Cayley on alkyl radicals,[34] and by the chemist Körner on the substitutional isomers of benzene.[35] Both workers thereby initiated studies which were to remain of importance for at least the next seventy years. Cayley's limited success was later to inspire the valuable iterative procedures, whilst Körner's was a forerunner of the very powerful methods of enumeration which use group theory.

Cayley made the innovation of representing the carbon frameworks of alkane molecules by trees, as shown in Figure 1, and thus first introduced graph theory into the field. He attempted to find some general formula which would yield the number of isomeric alkanes of given carbon content n, but concluded that no such formula could be found.[36] Cayley then directed his efforts to determining the number of rooted trees on n vertices. A *rooted* tree is one in which a particular vertex is singled out and called the *root*.

He enumerated rooted trees[37] with a function of the type

$$(1 - x)^{-1}(1 - x^2)^{-A_1}(1 - x^3)^{-A_2}\ldots(1 - x^n)^{-A_{n-1}} = \\ = 1 - A_1x + A_2x^2 + \ldots \qquad (1)$$

where x is a variable, n the number of vertices, and A_n the number of rooted trees on n vertices. By considering the number of different *centric* and *bicentric* rooted trees Cayley obtained isomer counts for all the alkanes up to the thirteenth member. Examples of centric and bicentric trees are shown in Figure 2.

Cayley further investigated trees in which all vertices were of valence three or one (the so-called 'boron trees'), and trees having vertices of valence two and one (the so-called 'oxygen trees').[36b] In both cases he determined isomer counts for small values of n. He also gave isomer counts for the alkyl radicals C_nH_{2n+1}

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[32] (*a*) I. W. D. Hackh, *Chem. News (London)*, 1920, **121**, 85; (*b*) E. Hertel and J. Mischnat, *Ann. Chem.*, 1926, **451**, 179; (*c*) K. Weissenberg, *Chem. Ber.*, 1926, **59**, 1526; (*d*) P. Pfeiffer in 'Stereochemie: Eine Zusammenfassung der Ergebnisse, Grundlagen und Probleme', Deuticke, Leipzig, 1933; (*e*) F. P. A. Tellegen, *Chem. Weekblad*, 1935, **32**, 3; (*f*) P. Niggli, 'Grundlagen der Stereochemie', Birkhäuser, Basel, 1945; (*g*) M. Bargallo, *Ciencia (Mexico)*, 1950, **10**, 257; (*h*) R. L. Bent, *J. Chem. Educ.*, 1953, **30**, 220, 284, 328; (*i*) J. J. Jennen, *Ind. Chim. Belge*, 1954, **19**, 1051; (*j*) J. J. Jennen, *ibid.*, 1955, **20**, 1067; (*k*) R. T. M. Fraser, *Adv. Chem. Ser. No.* 62, 1967, 295.

[33] (*a*) J. J. Mulckhuyse, 'Molecules and Models: Investigations on the Axiomatization of Structure Theory in Chemistry', Thesis, University of Amsterdam, Amsterdam, 1960; (*b*) E. Ruch, *Theor. Chim. Acta*, 1968, **11**, 183; (*c*) E. Ruch, *et al.*, *ibid.*, 1970, **19**, 288; (*d*) I. Ugi, *et al.*, *Angew. Chem. Internat. Edn.*, 1970, **9**, 703; (*e*) Ref. 5*d*; (*f*) Ref. 5*e*; (*g*) W. Hässelbarth and E. Ruch, *Theor. Chim. Acta*, 1973, **29**, 259.

[34] A. Cayley, *Phil. Mag.*, 1874, **47**, 444.

[35] W. Körner, *Gazzetta*, 1874, **4**, 305.

[36] (*a*) A. Cayley, *Chem. Ber.*, 1875; **8**, 1056, (*b*) A. Cayley, *Rept. Brit. Assoc. Adv. Sci.*, 1875, 257.

[37] (*a*) A. Cayley, *Phil. Mag.*, 1857, **13**, 172; (*b*) A. Cayley, *ibid.*, 1859, **18**, 374.

up to the thirteenth member,[38] though in this, as for the alkanes, his results were correct only as far as the eleventh member.

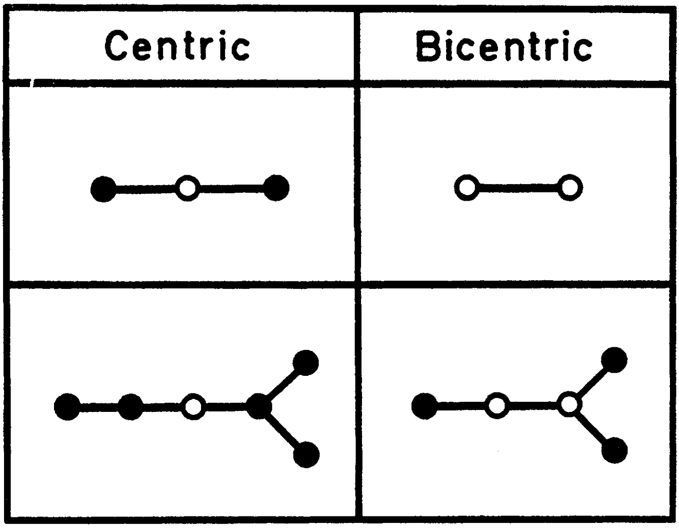

Figure 2 *Examples of centric and bicentric trees. A centric tree has one vertex for its centre whereas a bicentric tree has two*

5 The Early Developments

The limited success achieved by Cayley stimulated several other workers to try to improve upon his methods. In general, however, little progress was made as the procedures introduced were cumbersome and frequently led to erroneous results. None of these early methods succeeded in enumerating the alkanes beyond the fourteenth member.

In 1875, Schiff developed a method[39] in which trees were drawn in the form of symmetric main chains with shorter side chains attached, but got no further than the twelfth member. The errors in both Cayley's and Schiff's work were corrected five years later by Hermann,[40] who enumerated the alkanes by classifying the trees into types according to the number of branches attached to the main chain. At a congress held in 1893 Tiemann described an abbreviated numerical system for enumerating the alkanes.[41] However, in spite of earlier work, he gave incorrect answers for the eleventh and twelfth members.

Several more sophisticated approaches fared no better. These were made by Delannoy,[42] who developed a formula to which additional terms were attached

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[38] (*a*) Ref. 34; (*b*) A. Cayley, *Phil. Mag.*, 1877, **3**, 34.

[39] H. Schiff, *Chem. Ber.*, 1875, **8**, 1542.

[40] (*a*) F. Hermann, *Chem. Ber.*, 1880, **13**, 792: (*b*) F. Hermann, *ibid.*, 1897, **30**, 2423; (*c*) F. Hermann, *ibid.*, 1898, **31**, 91.

[41] F. Tiemann, *Chem. Ber.*, 1893, **26**, 1595.

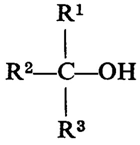
[42] M. Delannoy, *Bull. Soc. chim. France*, 1894, **11**, 239.

for succeeding members, Losanitsch,[43] and Goldberg[44] both of whom used a combinatorial approach. In the present century Trautz published a combinatorial analysis of the whole problem,[45] and David attempted to improve upon Delannoy's formula.[46] But the problem remained essentially unresolved until the development of iterative techniques.

6 Iteration's Début

The first significant advance in enumeration techniques came in 1931 when the chemists Henze and Blair started to develop recursion formulae.[47] This approach proved to be very successful and results were obtained for all the common homologous series. Several accounts of their work have been given in the chemical literature.[48] In essence their method rested upon three postulates: (i) Cayley's conclusion that no general formula could be found giving isomer counts for members of homologous series; (ii) free rotation about single C—C bonds did not yield new isomers; and (iii) if the isomer count for a given member of an homologous series having n carbon atoms could be ascertained, an appropriate recursion formula would yield the isomer count for the succeeding member containing $n + 1$ carbon atoms.

We examine the application of this method to enumeration of the alcohols, $C_nH_{2n+1}OH$.[47a] All alcohol molecules were represented by the general formula



$$\begin{array}{c} R^1 \\ | \\ R^2\text{—}C\text{—}OH \\ | \\ R^3 \end{array}$$

where the R groups represented either hydrogen atoms or alkyl radicals. The symbols p_n, s_n, and t_n were used to represent, respectively, the number of primary, secondary, and tertiary alcohols containing n carbon atoms. The total number of alcohols of all types T_n was thus given by

$$p_n + s_n + t_n = T_n \tag{2}$$

Since the replacement of an —OH group in any alcohol molecule by a

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[43] S. M. Losanitsch, *Chem. Ber.*, 1897, **30**, 1917, 3059.

[44] A. Goldberg, *Chem.-Ztg.*, 1898, **22**, 395.

[45] M. Trautz, 'Lehrbuch der Chimie', De Gruyter, Berlin, 1924, Vol. III, p. 23.

[46] L. David, *Rev. Gén. Sci.*, 1928, **39**, 142.

[47] (*a*) H. R. Henze and C. M. Blair, *J. Amer. Chem. Soc.*, 1931, **53**, 3042, 3077; (*b*) H. R. Henze and C. M. Blair, *ibid.*, 1932, **54**, 1098, 1538; (*c*) C. M. Blair, 'The hydrolysis of hydantoinoxindoles and the number of structurally isomeric aliphatic compounds', Thesis University of Texas, Austin, Texas, 1933; (*d*) D. D. Coffman, *et al.*, *J. Amer. Chem. Soc.*, 1933, **55**, 252; (*e*) H. R. Henze and C. M. Blair, *ibid.*, p. 680.

[48] (*a*) E. J. Leeming, *Sch. Sci. Rev.*, 1935, **16**, 412; (*b*) J. Zuidweg, *Faraday*, 1943, **13**, 94, 132; (*c*) J. Zuidweg, *Chem. Weekblad*, 1951, **47**, 686; (*d*) J. Zuidweg, *Faraday*, 1951, **6**, 81; (*e*) T. Benfey, 'The Names and Structures of Organic Compounds', Wiley, New York, 1966; (*f*) R. W. Payne, *Sch. Sci. Rev.*, 1969, **51**, 374.

—CH_2OH group must always result in the formation of a primary alcohol, p_n will be given by the simple expression

$$p_n = T_{n-1} \tag{3}$$

The evaluation of s_n is made by imagining the joining of two alkyl radicals R^1 and R^2 to the free bonds in the CHOH group, keeping the total carbon content in R^1 and R^2 fixed at $n - 1$. When the resulting alcohol molecule has an even number of carbon atoms s_n is given by the equation

$$s_n = T_1.T_{n-2} + T_2.T_{n-3} + \ldots + T_{(n-2)/2}.T_{n/2} \tag{4}$$

whereas, when n is odd,

$$s_n = T_1.T_{n-2} + T_2.T_{n-3} + \ldots . \\ + T_{(n-3)/2}.T_{(n+1)/2} + \tfrac{1}{2}T_{(n-1)/2}(1 + T_{(n-1)/2}) \tag{5}$$

In the case of tertiary alcohols formation of the molecule is regarded as arising from the attachment of the radicals R^1, R^2, and R^3 to the three bonds in the —COH group; again the carbon content of the radicals is fixed at $n - 1$. The equations for t_n are (i) when $R^1 \neq R^2 \neq R^3$

$$t_n{}^{(i)} = T_x.T_y.T_z \tag{6}$$

where x, y, and z are positive integers totalling $n - 1$; (ii) when $R^1 = R^2 \neq R^3$

$$t_n{}^{(ii)} = \tfrac{1}{2}\Sigma T_x(1 + T_x)\,T_y \tag{7}$$

where $2x + y$ now equals $n - 1$; and (iii) when $R^1 = R^2 = R^3$

$$t_n{}^{(iii)} = \tfrac{1}{6}T_x(1 + T_x)\,(2 + T_x) \tag{8}$$

where $3x$ equals $n - 1$.

The advantage of the iterative approach is that there is no need to consider centric and bicentric symmetry centres in molecules, or the addition of new terms to generating functions for succeeding members of series. A possible drawback that the method involves much tedious calculation has been overcome by the use of modern computers (see Section 11). It has been shown that the results for the hydrocarbon series may be used for enumerating many other series, including the organic acids, aldehydes, alkyl halides, amines, ethers, and nitriles.[49] Extensions of this approach have been made by Perry on the alkanes and alcohols,[50] Coffman on the alkynes,[51] Allen and Diehl on the stereoisomeric

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[49] H. R. Henze and C. M. Blair, *J. Amer. Chem. Soc.*, 1934, **56**, 157.

[50] D. Perry, *J. Amer. Chem. Soc.*, 1932, **54**, 2918.

[51] D. D. Coffman, *J. Amer. Chem. Soc.*, 1933, **55**, 695.

alcohols,[52] Rancke-Masden on the alkanes, alkenes, and alkynes,[53] and Kornilov on the tertiary alcohols.[54]

7 The Role of Symmetry

After the development of the iterative approach, increasing attention was focused on the role that symmetry might play in enumeration. The mathematical discipline involved was group theory and this now occupied a position of some prominence. Utilization of the symmetry of a species proved particularly effective in the enumeration of substitutional isomers. The earliest investigations usually included an actual preparation of the predicted isomers in an attempt to confirm their number.

Thus, many stereoisomers were prepared by Auwers and Meyer[55] to confirm the predictions of van't Hoff.[25] After Kekulé had postulated the existence of only one isomer for mono-, penta-,and hexa-substituted benzene and three isomers for the cases of di-, tri-, and tetra-substitution,[56] the predictions were confirmed by Körner.[57] Although this approach initially encountered some opposition,[58] it was not long before similar studies were undertaken on the naphthalene[59] and other substitutional isomers.[60] However, the lack of any well-defined mathematical technique for approaching this type of problem resulted in very little activity for the next few decades.

In an extensive treatise in 1929 the reasons for this limited progress were examined by Lunn and Senior.[5b] They pointed out that a prime reason was the considerable confusion existing in the definition of the basic concepts such as that of the term 'isomer'. After providing many new definitions, they went on to stress the importance of using permutation groups for the characterization of molecular configuration. A general mathematical formula for all classes of molecules was devised for the enumeration of substitutional isomers. This was of the form

$$N_G(p) = \frac{1}{g} \Sigma\, n_t K(p, t) \qquad (9)$$

where $N_G(p)$ is the isomer count for molecules of permutation group G within the class p, g is the order of the group, n_t is the number of symmetry operations of type t which may be performed on the molecule, and $K(p, t)$ is the number of invariant configurations left in p when operation t is carried out.

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[52] E. S. Allen and H. Diehl, *Iowa State Coll. J. Sci.*, 1942, **16**, 161.
[53] E. Rancke-Madsen, *Acta Chem. Scand.*, 1950, **4**, 1450.
[54] M. Y. Kornilov, *Zhur. strukt. Khim.*, 1967, **8**, 373.
[55] K. Auwers and V. Meyer, *Chem. Ber.*, 1888, **21**, 784.
[56] F. A. Kekulé, *Ann. Chem.*, 1866, **137**, 129.
[57] (*a*) Ref. 35; (*b*) W. Körner and V. Wender, *Gazetta*, 1887, **17**, 5486.
[58] A. Ladenburg, *Chem. Ber.*, 1874, **7**, 1684.
[59] (*a*) F. Reverdin and H. Fulda, Tabellarische Übersicht der Naphtalin-derivate, Georg, Basel, 1880; (*b*) M. E. Noelting, *Mon. Sci.*, 1894, **8**, 178; (*c*) H. Kauffmann, *Z. angew. Chem.*, 1900, 209; (*d*) H. Kauffmann, *Chem. Ber.*, 1900, **33**, 2131; (*e*) H. Rey, *ibid.*, p. 1910.
[60] (*a*)Ref. 59*c*; (*b*) Ref.59*d*; (*c*) H. Kauffmann, 'Die Valenzlehre', Enke, Stuttgart, 1911, p. 127.

Starting from equation (9) several other formulae were derived relating to specific classes of molecule. In one instance a formula was derived which was virtually identical with one originally used by Kaufmann in his enumeration of the substitutional isomers of naphthalene.[59] Lunn and Senior also gave extensive tables of $K(p, t)$ values for different molecular configurations. In fact, it was the considerable success achieved by these workers which was to inspire the next major step forward.

8 The Turning Point

The most notable advance in the history of isomer enumeration came in 1936, when the mathematician Pólya developed his Enumeration Theorem.[61] So important has this become in recent years that it is now referred to as the fundamental theorem in all enumeration work. Although the theorem had been foreshadowed in certain aspects, notably in the work of the mathematician Redfield[62] and the chemists Lunn and Senior,[5b] it exploited for the first time the full power of group theory by making an integrated use of symmetry classes of molecules, generating functions, and weighting factors. Several elementary accounts of the theorem are now available.[63]

As development of the underlying mathematics would be inappropriate here, we illustrate the use of the theorem by applying it to the enumeration of the substitutional isomers of benzene. Our exposition is based on the results contained in Table 1. There are listed all the symmetry operations which bring the benzene ring into coincidence with itself. For each of these twelve operations a listing of the vertex positions both before and after the operation is given. This listing is then rewritten to reveal the *permutation groupings* existing among the vertices, and from this the important *cycle index* is deduced for each operation.

The cycle index is formally defined by the equation

$$Z(G) = \frac{1}{g} \Sigma' h_{j_1 j_2 \ldots\ldots j_p} f_1^{j_1} f_2^{j_2} \ldots\ldots f_p^{j_p} \tag{10}$$

where $Z(G)$ represents the cycle index for a group G of order g, p is the number of vertices permuted, the f_p are variables, and $h_{j_1 \ldots j_p}$ is the number of permutations of G consisting of j_1 cycles of order one, j_2 cycles of order two, *etc.* A cycle of order q is one involving the interchange of q vertices after performance of the symmetry operation. The prime over the summation signifies that the condition

$$\sum_{c=1}^{p} h_{jl} = P \tag{11}$$

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[61] (*a*) G. Pólya, *Compt. rend.*, 1935, **201**, 1167; (*b*) G. Pólya, *ibid.*, 1936, **202**, 1554; (*c*) G. Pólya, *Helv. Chim. Acta*, 1936, **19**, 22; (*d*) G. Pólya, *Vierteljahrsschr. Naturforsch. Ges. Zürich*, 1936, **81**, 243; (*e*) G. Pólya, *Z. Krist.*, 1936, **93**, 415; (*f*) G. Pólya, *Acta Math.*, 1937, **68**, 145.

[62] J. H. Redfield, *Amer. J. Math.*, 1927, **49**, 433.

[63] (*a*) N. G. De Bruijn, ref. 8*b*, p. 144; (*b*) N. G. De Bruijn, *Nieuw. Arch. Wisk.*, 1963, **11**, 142; (*c*) F. Harary, in 'Graph Theory and Theoretical Physics', ed. F. Harary, Academic, London, 1967, p. 5; (*d*) Ref. 8*c*, p. 126; (*e*) Ref. 7*b*, p. 180.

Table 1 *The derivation of the cycle index for each symmetry operation which may be performed on the benzene ring*

Symmetry operation	*Vertex interchange*	*Permutation groupings*	*Cycle index*
E	$\begin{pmatrix}1&2&3&4&5&6\\1&2&3&4&5&6\end{pmatrix}$	$\begin{pmatrix}1\\1\end{pmatrix}\begin{pmatrix}2\\2\end{pmatrix}\begin{pmatrix}3\\3\end{pmatrix}\begin{pmatrix}4\\4\end{pmatrix}\begin{pmatrix}5\\5\end{pmatrix}\begin{pmatrix}6\\6\end{pmatrix}$	f_1^6
C_6^+	$\begin{pmatrix}1&2&3&4&5&6\\6&1&2&3&4&5\end{pmatrix}$	$\begin{pmatrix}1&2&3&4&5&6\\6&1&2&3&4&5\end{pmatrix}$	f_6^1
C_6^-	$\begin{pmatrix}1&2&3&4&5&6\\2&3&4&5&6&1\end{pmatrix}$	$\begin{pmatrix}1&2&3&4&5&6\\2&3&4&5&6&1\end{pmatrix}$	f_6^1
C_3^+	$\begin{pmatrix}1&2&3&4&5&6\\5&6&1&2&3&4\end{pmatrix}$	$\begin{pmatrix}1&3&5\\5&3&1\end{pmatrix}\begin{pmatrix}2&4&6\\6&2&4\end{pmatrix}$	f_3^2
C_3^-	$\begin{pmatrix}1&2&3&4&5&6\\3&4&5&6&1&2\end{pmatrix}$	$\begin{pmatrix}1&3&5\\3&5&1\end{pmatrix}\begin{pmatrix}2&4&6\\4&6&2\end{pmatrix}$	f_3^2
C_2	$\begin{pmatrix}1&2&3&4&5&6\\4&5&6&1&2&3\end{pmatrix}$	$\begin{pmatrix}1&4\\4&1\end{pmatrix}\begin{pmatrix}2&5\\5&2\end{pmatrix}\begin{pmatrix}3&6\\6&3\end{pmatrix}$	f_2^3
$\sigma_v^{(1)}$	$\begin{pmatrix}1&2&3&4&5&6\\1&6&5&4&3&2\end{pmatrix}$	$\begin{pmatrix}1\\1\end{pmatrix}\begin{pmatrix}4\\4\end{pmatrix}\begin{pmatrix}2&6\\6&2\end{pmatrix}\begin{pmatrix}3&5\\5&3\end{pmatrix}$	$f_1^2 f_2^2$
$\sigma_v^{(2)}$	$\begin{pmatrix}1&2&3&4&5&6\\5&4&3&2&1&6\end{pmatrix}$	$\begin{pmatrix}3\\3\end{pmatrix}\begin{pmatrix}6\\6\end{pmatrix}\begin{pmatrix}1&5\\5&1\end{pmatrix}\begin{pmatrix}2&4\\4&2\end{pmatrix}$	$f_1^2 f_2^2$
$\sigma_v^{(3)}$	$\begin{pmatrix}1&2&3&4&5&6\\3&2&1&6&5&4\end{pmatrix}$	$\begin{pmatrix}2\\2\end{pmatrix}\begin{pmatrix}5\\5\end{pmatrix}\begin{pmatrix}1&3\\3&1\end{pmatrix}\begin{pmatrix}4&6\\6&4\end{pmatrix}$	$f_1^2 f_2^2$
$\sigma_v^{(4)}$	$\begin{pmatrix}1&2&3&4&5&6\\6&5&4&3&2&1\end{pmatrix}$	$\begin{pmatrix}1&5\\6&1\end{pmatrix}\begin{pmatrix}2&5\\5&2\end{pmatrix}\begin{pmatrix}3&4\\4&3\end{pmatrix}$	f_2^3
$\sigma_v^{(5)}$	$\begin{pmatrix}1&2&3&4&5&6\\2&1&6&5&4&3\end{pmatrix}$	$\begin{pmatrix}1&2\\2&1\end{pmatrix}\begin{pmatrix}3&6\\6&3\end{pmatrix}\begin{pmatrix}4&5\\5&4\end{pmatrix}$	f_2^3
$\sigma_v^{(6)}$	$\begin{pmatrix}1&2&3&4&5&6\\4&3&2&1&6&5\end{pmatrix}$	$\begin{pmatrix}1&4\\4&1\end{pmatrix}\begin{pmatrix}2&3\\3&2\end{pmatrix}\begin{pmatrix}5&6\\6&5\end{pmatrix}$	f_2^3

always holds, where P is the total number of permutations. The cycle indices for all the symmetry operations are added and the total divided by the number of operations for a given species.

For the benzene molecule the index has the form:

$$Z(C_6H_6) = \frac{1}{12}(f_1^6 + 4f_1^3 + 3f_1^2f_2^2 + 2f_3^2 + 2f_6^1) \qquad (12)$$

The number of isomers formed by successive substitution of a univalent radical X into benzene is obtained by making substitutions of the type

$$f_n^m = (1 + x^n)^m \qquad (13)$$

in equation (12). This in turn yields the polynomial

$$Z(C_6H_6) = 1 + x + 3x^2 + 3x^3 + 3x^4 + x^5 + x^6 \qquad (14)$$

The coefficients of x in equation (14) give the isomer counts directly. Thus, because the coefficient of x^4 is three, tetrasubstitution of benzene by the radical X will produce three isomers. The isomers for all the possible cases are illustrated in Figure 3.

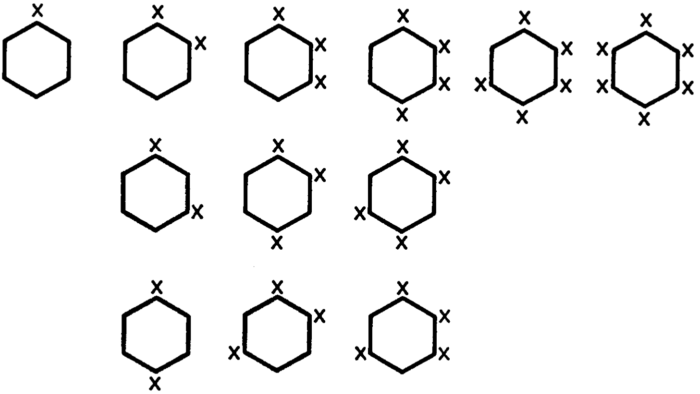

Figure 3 ***A representation of all the positional isomers formed when benzene is substituted by a univalent radical X***

To date there have been comparatively few direct applications of the theorem. It was employed by Hill[64] and Taylor[65] in a general discussion on isomerism, by Huebner[66] and Balaban[67] for enumerating isotopic isomers, by Riemschneider[68] and Balaban and Harary[69] on cyclic molecules, by Kornilov[54] on tertiary alcohols, and by Rouvray[70] on the arenes. Applications to inorganic systems are given in Section 10.

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[64] T. L. Hill, *J. Chem. Phys.*, 1943, **11**, 294.

[65] W. J. Taylor, *J. Chem. Phys.*, 1943, **11**, 532.

[66] H. Huebner, *Abh. Deutsch. Akad. Wiss. Berlin, Kl. Chem., Geol., Biol.*, 1964, **7**, 701.

[67] A. T. Balaban, *J. Labelled Compounds*, 1970, **6**, 211.

[68] R. Riemschneider, *Österr. Chem.-Ztg.*, 1956, **57**, 38.

[69] A. T. Balaban and F. Harary, *Rev. Roumaine Chim.*, 1967, **12**, 1511.

[70] (*a*) D. H. Rouvray, *J. S. African Chem. Inst.*, 1973, **26**, 141; (*b*) D. H. Rouvray, *ibid.*, 1974, **27**, 20.

9 The Unfolding Panorama

Significant generalizations and extensions have been made in recent years to all of the methods discussed thus far. The work of Cayley[37] and Henze and Blair[47] on the enumeration of trees has been extended by the mathematicians Otter,[71] Clarke,[72] and De Bruijn.[73] An improved generating function for the alkyl halides has been devised by Fisher.[74] The assumptions that no general formula could be found for enumerating the alkanes was shown to be invalid by Wiswesser,[75] who devised a new method of enumeration based on a partitioning of the  CH_2 groups around and between branched carbon atoms. The method was successful because each branched atom arrangement established a partition-counting series.

The well-known 2^n formula of van't Hoff, giving the number of stereoisomers in species containing n asymmetric carbon atoms, has been modified by several workers to allow for cases when this total is not attained for any reason. These include Fischer,[76] Weissenberg,[32c] Senior,[77] Hahn,[78] Branch and Hill,[79] and Feldman,[80] who studied systems ranging from the sugars to chain compounds. New formulae for determining the stereoisomers in a variety of systems have been proposed by Snell,[81] Dienske,[82] Carr,[2] Mai,[83] Eliel,[84] and Breusch.[85]

After Lunn and Senior had stressed the importance of symmetry in the enumeration of species, many formulae were developed which used this symmetry. These included the work of Ramirez,[86] Hill,[87] Riemschneider,[88] and De Loach *et al.*[89] on cyclic organic species, Evans and Le Quesne,[90] Yoshino,[91]

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[71] R. Otter, *Ann. Math.*, 1948, **49**, 583.

[72] L. E. Clarke, *Quart. J. Math.*, 1959, **10**, 43.

[73] N. G. De Bruijn, *Proc. Ned. Akad. Wetensch.*, 1959, **21**, 59.

[74] R. A. Fisher, *Ann. Eugenics*, 1942, **11**, 395.

[75] W. J. Wiswesser, 'Structure Counting Functions: A New Synthesis of Chemistry and Arithmetic', Wilson Research Center, Reading, Pennsylvania, 1958.

[76] E. Fischer, *Chem. Ber.*, 1891, **24**, 1836.

[77] J. K. Senior, *Chem. Ber.*, 1927, **60B**, 73.

[78] G. Hahn, *Chem. Ber.*, 1927, **60B**, 1362.

[79] G. E. K. Branch and T. L. Hill, *J. Org. Chem.*, 1940, **5**, 86.

[80] A. Feldman, *J. Org. Chem.*, 1959, **24**, 1556.

[81] J. F. Snell, *Chem. News (London)*, 1932, **144**, 321.

[82] J. W. Dienske, *Chem. Weekblad*, 1938, **35**, 243.

[83] L. A. Mai, *Zhur. obshchei Khim.*, 1958, **28**, 2860.

[84] E. L. Eliel, 'Stereochemistry of Carbon Compounds', McGraw-Hill, New York, 1962, p.180.

[85] F. L. Breusch, *Fette, Seifen, Anstrichm.*, 1970, **72**, 1.

[86] M. A. M. Ramirez, *Anal. Fis. Quim.*, 1941, **37**, 594.

[87] T. L. Hill, *J. Phys. Chem.*, 1943, **47**, 253, 413.

[88] R. Riemschneider, *Z. Naturforsch.*, 1956, **11B**, 228, 291, 675.

[89] (*a*) M. L. Shivar and W. S. De Loach, *J. Elisha Mitchell Sci. Soc.*, 1968, **84**, 367; (*b*) E. F. Wells and W. S. De Loach, *ibid.*, 1969, **85**, 45; (*c*) W. S. De Loach and J. B. Levy, *ibid.*, 1970, **86**, 38.

[90] R. F. Evans and W. J. Le Quesne, *J. Org. Chem.*, 1950, **15**, 19.

[91] T. Yoshino, *J. Chem. Soc. Japan*, 1951, **72**, 501.

and Papulov and Lesnyak[92] on aromatic molecules, Pishnamazzade[93] on a variety of systems including the substituted alcohols, the ethers, and the esters, Vladimirskaya[94] on the alkenes, and Breusch[85] on the fatty acids.

Since its inception Pólya's Enumeration Theorem has been generalized by several mathematicians.[95] They have succeeded in extending the power and range of applicability of the theorem. In the chemical context the theorem has been elaborated by Kennedy *et al.*[96] and Leonard[97] who used point groups rather than permutational groups for species, by Balaban[98] who studied monocyclic aromatic species formed from three different types of atom, by Sala-Pala and Guerchais[99] who devised rules for enumerating geometric and optical isomers, by McDaniel[100] who restated the theorem to be applicable to the enumeration of inorganic species, by Leonard[97] and Mason[101] who studied many different systems including stereoisomers, and by Lloyd[102] who investigated cyclic molecules. Furthermore, in addition to the original work of Pólya[61f] on asymptotic values of isomer counts approached in various series, Francis[103] has studied the alkylbenzenes and Goncharov[104] the alkanes. The latter worker concluded that for the C_{400} alkane there would be *ca.* 10^{40} isomers.

10 The Inorganic Scene

Following on from Werner's work,[30] co-ordination chemistry soon developed into an important branch of chemistry. Many investigations of the isomers involved have been made. Isomers for the five-co-ordinate complexes have been enumerated by Gielen *et al.*[105] and Muetterties,[106] those for six-co-ordinate

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[92] Y. G. Papulov and G. N. Lesnyak, *Uch. Zap. Kalinin, Gos. Pedagog. Inst.*, 1970, **76**, 86.

[93] (*a*) S. Mamedov and B. F. Pishnamazzade, *Izvest. Akad. Nauk Azerb. S.S.R.*, 1950, 27; (*b*) B. F. Pishnamazzade, *ibid.*, 1952, 43; (*c*) B. F. Pishnamazzade, *ibid.*, 1957, 35; (*d*) B. F. Pishnamazzade, *Azerb. Khim. Zhur.*, 1962, 27, 41, 77; (*e*) B. F. Pishnamazzade, *ibid.*, 1963, 61, 69; (*f*) B. F. Pishnamazzade, *ibid.*, 1964, 49, 63.

[94] G. N. Vladimirskaya, *Nauch. Doklady Vyss. Shkoly, Khim. i Khim. Tekhnol.*, 1958, **1**, 86.

[95] (*a*) J. Riordan, *J. Soc. Indus. Appl. Math.*, 1957, **5**, 225; (*b*) Ref. 73; (*c*) F. Harary and E. Palmer, *J. Comb. Theory*, 1966, **1**, 157; (*d*) J. Sheehan, *Canad. J. Math.*, 1967, **19**, 792; (*e*) S. G. Williamson, *J. Comb. Theory*, 1970, **8**, 162.

[96] B. A. Kennedy, C. H. McQuarrie, and C. H. Brubaker, *Inorg. Chem.*, 1964, **3**, 265.

[97] J. E. Leonard, 'Studies in Isomerism: Permutations, Point Group Symmetries, and Isomer Counting', Thesis, California Inst. Technol., California, 1971.

[98] A. T. Balaban, *Studii Cercetari Chim.*, 1959, **7**, 257.

[99] G. Sala-Pala and J. E. Guerchais, *Compt. rend.*, 1969, **268C**, 2192.

[100] D. H. McDaniel, *Inorg. Chem.*, 1972, **11**, 2678.

[101] K. H. Mason, 'Theoretical Aspects of Natural Optical Activity', Thesis, University of Kent, Canterbury, 1973, p. 159.

[102] E. K. Lloyd, 1974, in press.

[103] A. W. Francis, *J. Amer. Chem. Soc.*, 1947, **69**, 1536.

[104] M. A. Goncharov, *Vestnik Moskov Univ., Geol.*, 1973, **28**, 117.

[105] (*a*) M. Gielen and J. Nasielski, *Bull. Soc. chim. belges*, 1969, **78**, 339; (*b*) M. Gielen, C. Depasse-Delit, and J. Nasielski, *ibid.*, p. 357.

[106] E. L. Muetterties, *Inorg. Chem.*, 1967, **6**, 635.

complexes by Trimble,[107] Bailar,[108] Mayper,[109] Muetterties,[110] Gielen *et al.*,[111] Menez *et al.*,[112] and Musher,[113] and those for eight co-ordinate complexes by Marchi *et al.*,[114] and Porai-Koshits and Aslanov.[115] Other types of complex have been enumerated by Fernelius and Bryant,[116] Gazo,[117] Freeman and Liu,[118] Youinou *et al.*,[119] and King.[120] Co-ordination polyhedra and polynuclear structures have been studied by Niggli,[121] Krivoshei and Vvendenski,[122] Block and Maguire,[123] Muetterties and Wright,[124] Baker and Figgis,[125] King,[126] and Hawthorne.[127]

Most of this enumeration work was based upon a group-theoretical analysis of the various structures investigated. Certain workers merely adapted the approach of Pólya to their particular studies.[121,122] Reformulations of the Enumeration Theorem in an inorganic context were made by Kennedy *et al.*[96] and McDaniel.[100] Use of the symmetry properties of species has also been evidenced in the enumeration of the ferrocenes by Rinehart and Motz,[128] Rosenblum and Woodward,[129] Schlögl *et al.*[130] and Leonard;[97] and in enumeration of the clathrates[131] and cluster compounds[132] by King.

[107] R. F. Trimble, *J. Chem. Educ.*, 1954, **31**, 176.

[108] J. C. Bailar, *J. Chem. Educ.*, 1957, **34**, 334.

[109] S. A. Mayper, *J. Chem. Educ.*, 1957, **34**, 623.

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[111] (*a*) M. Gielen, *Bull. Soc. chim. belges*, 1969, **78**, 351; (*b*) M. Gielen, G. Mayence, and J. Topart, *J. Organometallic Chem.*, 1969, **18**, 1; (*c*) M. Gielen and J. Topart, *ibid.*, p. 7; (*d*) M. Gielen, *Med. Vlaam. Chem. Ver.*, 1969, **31**, 201; (*e*) M. Gielen and C. Depasse-Delit, *Theor. Chim. Acta*, 1969, **14**, 212.

[112] (*a*) A. J. Menez, J. Sala-Pala, and J. Guerchais, *Bull. Soc. chim. France*, 1969, 1115; (*b*) A. J. Menez, J. Sala-Pala, and J. Guerchais, *ibid.*, 1970, 46.

[113] (*a*) J. I. Musher, U.S. Nat. Tech. Inform. Serv. AD Rept. No. 733689, 1971; (*b*) J. I. Musher, *Inorg. Chem.*, 1972, **11**, 2335.

[114] (*a*) L. E. Marchi, W. C. Fernelius, and J. P. McReynolds, *J. Amer. Chem. Soc.*, 1943, **65**, 329; (*b*) L. E. Marchi and J. P. McReynolds, *ibid.*, 1943, **65**, 333; (*c*) L. E. Marchi, *ibid.*, 1943, **65**, 2257; (*d*) L. E. Marchi, *ibid.*, 1944, **66**, 1984.

[115] M. A. Porai-Koshits and L. A. Aslanov, *Zhur. strukt. Khim.*, 1972, **13**, 266.

[116] W. C. Fernelius and B. E. Bryant, *J. Amer. Chem. Soc.*, 1953, **75**, 1735.

[117] J. Gazo, *Chem. Zvesti*, 1966, **20**, 212.

[118] W. A. Freeman and C. F. Liu, *Inorg. Chem.*, 1968, **7**, 764.

[119] M. Youinou, F. Petillon and J. E. Guerchais, *Bull. Soc. chim. France*, 1968, 503.

[120] (*a*) R. B. King, *J. Amer. Chem. Soc.*, 1969, **91**, 7217; (*b*) R. B. King, U.S. Nat. Tech. Inform. Serv. A.D. Rept. No. 746829, 1972.

[121] P. Niggli, *Helv. Chim. Acta*, 1946, **29**, 991.

[122] (*a*) I. V. Krivoshei, *Zhur. strukt. Khim.*, 1963, **4**, 757; (*b*) I. V. Krivoshei, *ibid.*, 1965, **6**, 322; (*c*) I. V. Krivoshei, *ibid.*, 1966, **7**, 430, 638; (*d*) I. V. Krivoshei, *ibid.*, 1967, **8**, 321; (*e*) I. V. Krivoshei and V. Y. Vvendenski, *Theor. i eksp. Khim.*, 1967, **3**, 508.

[123] (*a*) B. P. Block and K. D. Maguire, *Inorg. Chem.*, 1967, **6**, 2107; (*b*) B. P. Block and K. D. Maguire, *U.S. Govt. Res. Dev. Reports*, 1967, **67**, 64.

[124] E. L. Muetterties and C. M. Wright, *Quart. Rev.*, 1967, **21**, 109.

[125] L. C. W. Baker and J. S. Figgis, *J. Amer. Chem. Soc.*, 1970, **92**, 3794.

[126] (*a*) R. B. King, *J. Amer. Chem. Soc.*, 1969, **91**, 7211; (*b*) R. B. King, *ibid.*, 1970, **92**, 6455, 6490.

[127] M. F. Hawthorne, *Pure Appl. Chem.*, 1972, **29**, 547.

[128] K. L. Rinehart and K. L. Motz, *Chem. and Ind.*, 1957, 1150.

[129] M. Rosenblum and R. B. Woodward, *J. Amer. Chem. Soc.*, 1958, **80**, 5443.

[130] (*a*) K. Schlögl, M. Peterlik, and H. Seiler, *Monatsh.*, 1962, **93**, 1309; (*b*) K. Schlögl, *Topics Stereochem.*, 1967, **1**, 39.

[131] R. B. King, *Theor. Chim. Acta*, 1972, **25**, 309.

[132] R. B. King, *J. Amer. Chem. Soc.*, 1972, **94**, 95.

Enumeration of the boranes and carbaboranes has proved difficult mainly because of the three-centre bonds found in these species.[133] Simple enumeration of the graphs representing these molecules will not suffice. A decision must be taken for each species whether its bonding scheme is feasible or not by considering the conservation of electrons and orbitals, and the requirement that all pairs of neighbours have at least one common bond. At present results are available for boranes and carbaboranes containing up to about 12 boron atoms.[134] Because the sorting of feasible structures becomes exceedingly tedious for the higher boranes, resort is now being made to computer programmes.[135]

11 The Advent of the Computer

The appearance of high-speed computers in recent years has considerably facilitated several types of isomer enumeration. In addition to the work on the boranes mentioned above, the iterative procedures have proved readily adaptable to the computer. Enumeration programmes for the alkanes have been written by Davis *et al.*[136] and Lederberg,[137] and a general programme for enumerating co-ordination compounds has been devised by Bennett.[138] Programmes are now also available for the representation and storage of structural and other isomers,[139] and for the searching of given structures within a storage file.[140] Much progress has also been made in writing programmes which list all of the possible isomers for a given chemical formula.[141]

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[133] (*a*) W. N. Lipscomb, *Pure Appl. Chem.*, 1972, **29**, 493; (*b*) R. E. Williams, *ibid.*, p. 569; (*c*) W. N. Lipscomb, *Accounts Chem. Res.*, 1973, **6**, 257.

[134] (*a*) B. V. Nekrasov, *Zhur. obshchei Khim.*, 1940, **10**, 1021; (*b*) R. P. Bell and H. J. Emeléus, *Quart. Rev.*, 1948, **2**, 132; (*c*) J. R. Platt, *J. Chem. Phys.*, 1954, **22**, 1033; (*d*) R. E Dickerson and W. N. Lipscomb, *ibid.*, 1957, **27**, 212; (*e*) T. E. Haas, *Inorg. Chem.*, 1964, **3**, 1053; (*f*) W. N. Lipscomb, *ibid.*, 1964, **3**, 1683; (*g*) W. N. Lipscomb, *Science*, 1966, **153**, 373; (*h*) W. N. Lipscomb, U.S. Clearinghouse Fed. Sci. Tech. Inform. A.D. Rept. No. 662761, 1967; (*i*) H. D. Kaesz, R. Bau, H. A. Beall, and W. N. Lipscomb, *J. Amer. Chem. Soc.*, 1967, **89**, 4218; (*j*) N. V. Emelyanova and I. V. Krivoshei, *Zhur. strukt. Khim.*, 1968, **9**, 881; (*k*) S. F. A. Kettle and V.Tomlinson, *J. Chem. Soc.* (*A*), 1969, 2002, 2007, (*l*) A. T. Balaban, *Coll. Int. Cent. Nat. Rech. Sci.*, 1970, **191**, 233; (*m*) R. E. Williams, *Inorg. Chem.*, 1971, **10**, 210; (*n*) Ref. 132.

[135] (*a*) I. R. Epstein and W. N. Lipscomb, *Inorg. Chem.*, 1971, **10**, 1921; (*b*) I. R. Epstein, D. S. Marynick, and W. N. Lipscomb, *J. Amer. Chem. Soc.*, 1973, **95**, 1760.

[136] C. C. Davis, K. Cross, and M. Ebel, *J. Chem. Educ.*, 1971, **48**, 675.

[137] (*a*) J. Lederberg, N.A.S.A. Report CR-57029, 1964; (*b*) J. Lederberg, *ibid.*, CR-68899, 1966.

[138] W. E. Bennett, *Inorg. Chem* , 1969, **8**, 1325

[139] (*a*) Ref. 137; (*b*) J. Lederberg, N.A.S.A. Report CR-68898, 1965; (*c*) D. J. Gluck, *J. Chem. Docum.*, 1965, **5**, 43, (*d*) H. L. Morgan, *ibid.*, 1965, **5**, 107; (*e*) A. E. Petrarca, M. F. Lynch, and J. E. Rush, *ibid.*, 1967, **7**, 154; (*f*) A. E. Petrarca, M. F. Lynch, and M. F. Brown, Amer. Chem. Soc. 156th Meeting, INOR 147, Atlantic City, 1968; (*g*) A. E. Petrarca and J. E. Rush, *J. Chem. Docum.*, 1969, **9**, 32; (*h*) W. S. Hoffman, *ibid.*, 1968, **8**, 3.

[140] (*a*) W. E. Cossum, M. L. Krakiwsky, and M. F. Lynch, *J. Chem. Docum.*, 1965, **5**, 33; (*b*) Ref. 139*d*; (*c*) D. Gould, E. B. Gasser, and J. F. Rian, *ibid.*, 1965, **5**, 24; (*d*) Ref. 139*h*; (*e*) E. H. Sussenguth, *ibid.*, 1965, **5**, 36.

[141] (*a*) G. L. Sutherland, *U.S. Govt. Res. Dev. Reports*, 1968, **68**, 82; (*b*) Ref. 137*a*; (*c*) Ref. 139*b*; (*d*) J. Lederberg *et al.*, *J. Amer. Chem. Soc.*, 1969, **91**, 2973; (*e*) Y. M. Sheikh *et al.*, *Org. Mass Spectrometry*, 1970, **4**, 493; (*f*) V. V. Raznikov and V. L. Talroze, *Zhur. strukt. Khim.*, 1970, **11**, 357; (*g*) D. Mitchie, *Nature*, 1973, **241**, 507.

12 The Last Word

Over the past two decades several challenging new problems have been tackled in the field of isomer enumeration, and some new methods have also been developed. For instance, a number of the less frequently studied isomers have been investigated. For hydrocarbon species this includes the work of Balaban[142] and others[143] on the enumeration of valence isomers, of Pinkus and McLachlan[144] and others[145] on isotopic isomers, of Rouvray[146] and others[147] on topological isomers, and of Andreenko[148] and others[149] on rotational isomers. All of these workers employed an essentially combinatorial approach to the enumeration.

Other species which have been enumerated include the isomers in polymeric materials and those arising in biochemical systems. Polymers have been classified by Conix,[150] Elias,[151] Huggins *et al.*,[152] and Lewis.[153] Enumeration in chain polymers has been carried out by Schultz,[154] in vinylic polymers by Schildknecht *et al.*, [155] and in phenolic resins by Hollingdale and Megson.[156] Stereopolymers were studied by Costescu,[157] Hatz,[158] and Breusch.[85] Isomerism in its biochemical manifestations has been investigated by Blackman[159] on the porphyrins, Hirschmann and Hanson[160] on stereoisomerism, Plouvier[161] on enantiomorphism, and Urmantsev[162] on living systems.

The arenes have proved surprisingly difficult to enumerate. Graph-theoretical

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listings of all arenes containing up to eight benzene rings have been given by the chemists Wiswesser[163] and Balaban and Harary.[164] An attempt has been made by the mathematicians Harary and Read[165] to find general formulae for this purpose, but to date success has been achieved only with *cata*-condensed species which contain no rings of hexagons.

The isomers formed in intramolecular reaction processes have been studied in detail over the last decade. In this category mention may be made of the work of Dunitz and Prelog[166] and Lauterbur and Ramirez[167] on trigonal-bipyramidal systems, of Gielen *et al.*[168] on five- and six-co-ordinate complexes, of Balaban *et al.*[169] on 1,2-shifts in carbonium ions, of Muetterties[170] on polytopal rearrangements, of Gillespie *et al.*[171] on Berry-type pseudo-rotation reactions, of Klemperer[172] on permutational isomerization reactions, and of Musher[173] on the phosphoranes. As the literature in this area is too extensive to review fully here, the reader is referred to review articles on the subject.[174]

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