65. Structural Chemistry in *Helvetica Chimica Acta*, 1917–1992

by **Hans-Beat Bürgi**
Laboratory for Chemical and Mineralogical Crystallography, University of Bern, Freiestrasse 3, CH-3012 Bern
and **Jack D. Dunitz**
Organic Chemistry Laboratory, Swiss Federal Institute of Technology, ETH-Zentrum, CH-8092 Zurich

What is Structural Chemistry? – Around 1959 the elder author of this paper happened to meet the famous, recently retired Professor ***Leopold Ruzicka*** on the steps of the ETH Chemistry building in Zurich. To make conversation, he remarked that he had just determined the structure of cyclododecane – what he meant was that he had just determined the crystal structure of this compound and established the conformation of the molecule [1]. '*Ahah*' countered *Ruzicka*, '*Die kenne ich schon lange!*'. Clearly, *Ruzicka* understood the word 'structure' to mean something quite different from that understood by his younger colleague. Structure – molecular structure – has always been the stuff that chemistry is built on, even when the very existence of molecules was conjectural, and it has meant quite different things at different times to different kinds of chemist. Here we take 'structural chemistry' to be concerned not just with the determination and consequences of molecular constitution but rather more with the detailed study of the metrical aspects of atomic arrangements in molecules and its consequences for chemical properties. In this century, many different physico-chemical techniques have been directed to the investigation of molecular structure – various kinds of spectroscopy, as well as diffraction methods applied to all states of matter, in addition to theoretical calculations at all levels of sophistication and credibility. Since we assume that most of these physico-chemical approaches, as far as *Helvetica Chimica Acta* (*HCA*) are concerned, are at least mentioned in the article by *Günthard* and *Heilbronner* [2], we shall concentrate here on what is the most relevant for our purpose, the study of matter by X-ray crystallography; for this chapter, then, we define structural chemistry in a very limited sense as the study of structure, mainly in the solid state, and the implications of the results for chemistry as a whole.

Historical Development. – The development of structural chemistry as seen through the pages of *HCA* closely follows the development of the subject in the world at large. The journal is almost the same age as X-ray crystal-structure analysis, give and take a few years. *Laue*'s discovery that X-rays are diffracted by crystals was made in 1912 [3], and the atomic arrangements in several highly symmetrical crystals such as rock salt (NaCl), zincblende (ZnS), fluorspar (CaF_2), and diamond were determined by the *Braggs*, father and son, almost immediately afterwards in a series of fundamental studies [4] [5]. Nevertheless, in spite of important first steps made during the early years, the method was still in its infancy in 1917 and virtually unknown to chemists then and for many years to come.

Even forty years later, when X-ray analysis had developed into a powerful method of molecular structure determination, it was still far from being accepted – or even acceptable – by all chemists, especially in continental Europe, many of whom tended to regard the new method with suspicion, or puzzlement, or incredulity, in various proportions. It is interesting that even though X-ray diffraction was discovered in Germany, its application to chemical structural problems developed mainly in Britain, the United States, Holland, and Japan. In Germany (and in Switzerland), the development tended to be concentrated in mineralogical rather than in chemical laboratories, and it would be an interesting historical study to try to follow the reasons for this.

One factor, perhaps, was the very strength of organic chemical research in central Europe, with its concentration on the elucidation of the molecular constitution of natural products, involving a complicated interplay between degradative and synthetic chemistry. The masters of this approach were men of the highest intellectual ability, and their achievements in the realm of small-to-medium molecular-weight compounds were quite remarkable. However, the chain of logical inference, from chemical degradation experiments to structural deductions, was so indirect that any conclusions were necessarily in the nature of hypotheses, always liable to modification by further experiments or by new interpretations of the existing evidence. This speculative aspect is what made the whole business so fascinating to its practitioners. The final proof of such structural hypotheses was considered to be the synthesis of a key, target molecule by a sequence of well established steps.

Only gradually did it become apparent that structures of complex natural products, especially those containing new, unknown features, could be determined a good deal faster and more efficiently by X-ray analysis than by the classical degradative methods. Moreover, the structural formulas obtained by X-ray analysis were usually so clear-cut and unequivocal that there was no need to confirm them by chemical synthesis. Many chemists saw here a danger that organic chemistry, deprived of the intellectual stimulation and nourishment it had enjoyed from the combination of the degradative and synthetic approaches, might degenerate into a branch of applied technology, useful for providing some of the necessities and comforts of modern life, but devoid of the speculative character that had made it so fascinating. Of course, they were quite wrong.

There could really be no question that chemistry had to benefit enormously from the impact of X-ray crystallography and other physico-chemical techniques for molecular structure determination. Relieved from the burden of determining and confirming unknown molecular structures, chemists have been able to afford to turn their energy and inventiveness to other areas where prodigious advances have been made. Moreover, molecules, far from being merely intellectual constructions designed to explain the facts of chemical reactivity, have been shown to correspond to 'objects' of definite size and shape, which, studied systematically, can reveal features associated with their stability, their deformability, and their reactivity. The regular, repeating arrangements of molecules in crystals also tell us about details of the ways molecules can recognize and interact with one another – supramolecular chemistry. In fact, it is difficult to imagine what chemistry would be like today if X-ray crystallography had never been invented.

However, we should not forget that in the course of its eighty years of existence, crystal structure analysis has also gone through several stages. In the early days, it was more or less limited to highly symmetrical structures, mainly inorganic ones. The experimental data were, for powder samples, the positions and intensities of a few lines on a *Debye-Scherrer* diagram, or, for single crystals, the visually estimated intensities of a few hundred X-ray reflections recorded on a set of photographic films. When it came to organic molecules, a successful crystal structure analysis was usually only possible if fairly reliable information was available about the approximate arrangement of the atoms. Before direct methods were developed, these crystal structures were mostly solved by a trial-and-error procedure: this consisted of postulating a model, an atomic arrangement consistent with the available information, and checking whether the X-ray diffraction pattern calculated for the model was in qualitative agreement with the pattern obtained by experiment. If there was a reasonable level of agreement, the model could be refined by straightforward but time-consuming methods; if the agreement was poor, then it was time for a new model. Alternatively, by the 40's, once heavy-atom methods had been developed, a suitable heavy-atom derivative of the compound in question could be prepared, and, with any luck, a structural model could be derived. Before the computer age, this was about all one could do. Although direct methods were beginning to be applied to simple problems more than forty years ago, their development in practice has depended on the increasing power and availability of electronic computers to carry out the lengthy calculations that are required; and similarly for the development of least-squares refinement methods for determining the atomic positions, together with information about the averaged displacements of the atoms from these positions, associated with thermal vibrations or disorder or both. Together with the increased power and availability of computers has also come the development of automated diffractometers for measuring the intensities of the beams diffracted by the crystal. Whereas even forty years ago, a successful crystal structure analysis of a moderately complex organic molecule could involve two or three years of difficult and often frustrating effort, the situation changed dramatically as automation came more and more into the picture.

One sees this development in the papers published in *HCA* over the years. Until the mid-60's reports of crystal structure analyses were few and far between. Typically, the experimental data and the course of the structure analysis were described in considerable detail; there were tables of observed and calculated structure amplitudes, atomic coordinates (and later, sometimes vibrational parameters too), bond distances and angles, dihedral angles, *etc.*, and there was often an extended discussion of the results as well, all this amounting to 10–15 pages of the journal. As the number of crystal structure analyses began to increase, so the amount of description devoted to the results of any individual analysis began to shrink, a tendency that has continued over the years until today results of most crystal structure analyses described in *HCA* usually merit at most a computer-drawn picture of a molecular structure and a few words in the text. Yet the result of a modern routine crystal structure analysis (in favorable cases, a matter of a few days rather than of a few years) is usually far more accurate than in pre-diffractometer days. What one usually looks for in vain is a description of the molecular packing. Without the atomic coordinates the packing cannot be reconstructed. There is a danger here that valuable information may be lost. The interactions among neighboring molecules that determine the crystal packing are just the same as those that control molecular recognition and self-assembly at all levels of organization, so that careful study of the packing in molecular crystals should be a valuable source of information in supramolecular chemistry.

What is worth preserving? Crystallographic Databases. – However, one has to admit that not all the information that is discarded nowadays is worth preserving. The tables of observed and calculated structure amplitudes that used to be published in crystallographic papers in *HCA* were sometimes quite space-consuming. They were probably included only because this information was required at the time for papers appearing in *Acta Crystallographica*, the organ of the *International Union of Crystallography*, and it did not seem appropriate that *HCA* should adopt less stringent requirements than the International Union. To save space, these tables were often reduced in size by photographic shrinkage of a typed table to such an extent that the individual numbers were legible only with the help of a magnifying glass. Gradually they disappeared from *HCA* and from most other journals many years ago, and are generally no longer requested even by the most scrupulous referees. (The International Union still requires them, although they are no longer published but deposited as supplementary publications with the *British*

Fig. 1

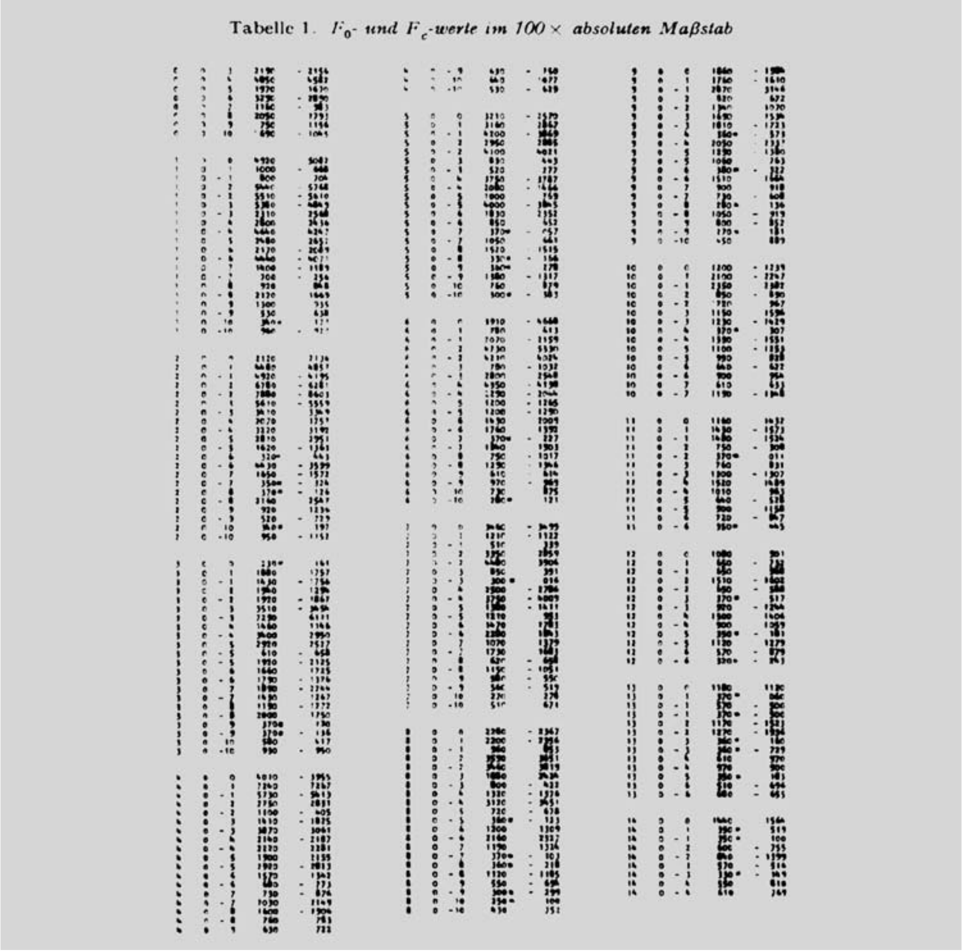


Tabelle 1. F_0- *und* F_c-*werte im 100 × absoluten Maßstab*

Library Document Supply Centre.) The idea was that these numbers constitute the basic experimental data and have to be available in case anyone wants to check up on the correctness of the structure proposed or to improve it. As we shall see later when we discuss early work on adamantane, this was sometimes done and led, occasionally, to sobering insights. For most of these numerical tables, however, it is doubtful if anybody ever even cast a glance on them. As an example, we can draw attention to two tables of observed and calculated structure amplitudes published in 1964 (*Fig. 1*), one for 1,6-dibromocyclodecane [6], the other for azacyclododecane hydrobromide [7]. The two sets of numbers are identical! The table actually belongs to the latter paper, and how it found its way into the former one cannot be explained so easily after nearly thirty years. In any

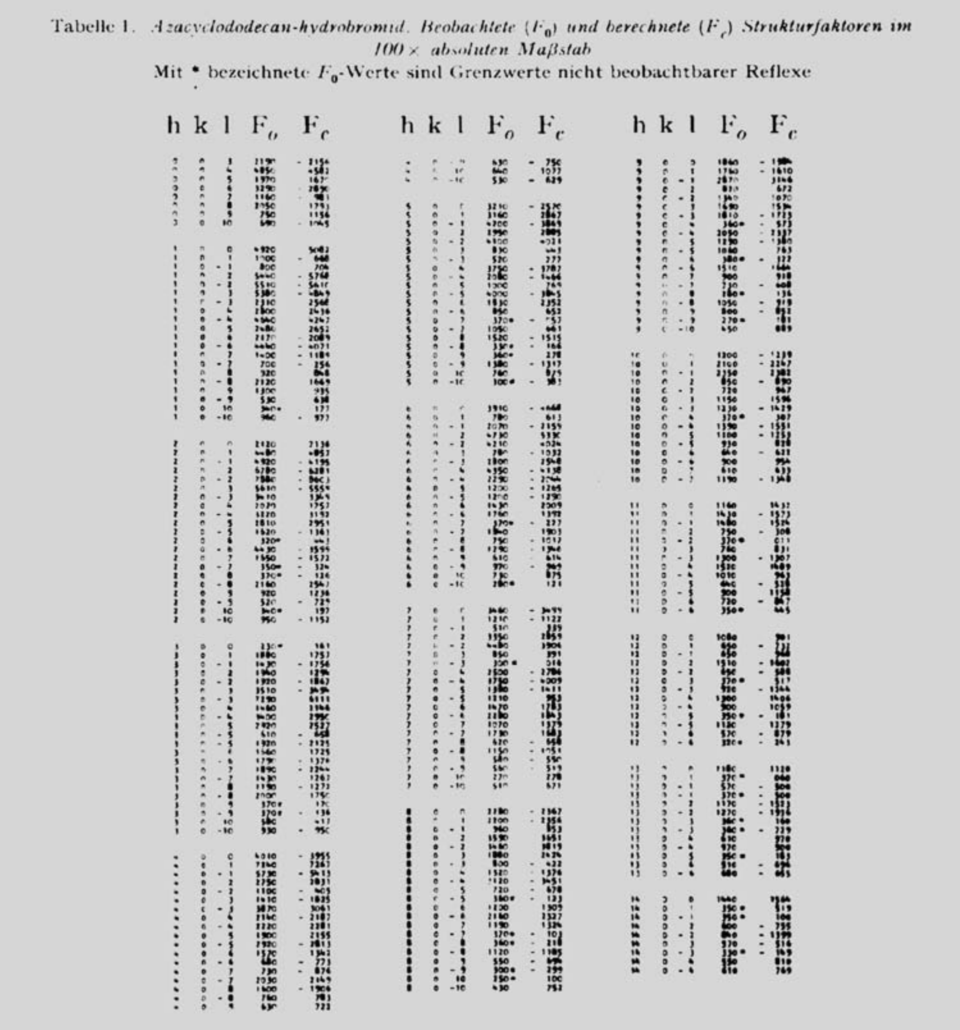


Tabelle 1. *Azacyclododecan-hydrobromid. Beobachtete* (F_0) *und berechnete* (F_c) *Strukturfaktoren im 100 × absoluten Maßstab*

Mit * bezeichnete F_0-Werte sind Grenzwerte nicht beobachtbarer Reflexe

h k l F_o F_c h k l F_o F_c h k l F_o F_c

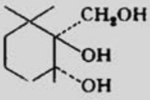
Fig. 1 (cont.)

case, nobody has drawn our attention to this slip. The elder author noticed it himself and would have kept silent about it, were it not for the invitation to help to celebrate this 75th anniversary.

Nowadays, it is probably quicker and more convenient to re-measure the diffraction data than to locate a printed table that would have to be converted into computer-readable form. To re-measure the data, of course, the compound itself would have to be available. Perhaps it is time to organize a depository not of physical data on new chemical compounds but of the compounds themselves – a few milligrams would be sufficient.

Fortunately, as far as crystallographic information is concerned, much of it can be recovered with the help of the *Cambridge Structural Database* (*CSD*), which contains, in computer-readable form, unit cell dimensions, atomic coordinates (although, unfortunately, not atomic displacement parameters), and bibliographic data for organic and organometallic crystals of known structure, excluding macromolecules [8]. In this context, an organic molecule is defined as one containing at least one C–C or C–H bond. The *CSD* is produced by the *Cambridge Crystallographic Data Centre* (*CCDC*), founded in 1965. It depends for its completeness and data retrieval possibilities on the hard work and skill of the staff of the *CCDC*, who are responsible for the compilation, upkeep, and distribution of the Database with the associated software. Published papers describing crystal structures have to be located and abstracted, and the chemical, bibliographic, and numerical data must be entered in computer-readable form into the Database. It is unavoidable that some papers containing structural results are overlooked, especially if these results are given too little prominence in the published text.

For example, although results of a crystal structure analysis of the trihydroxy molecule **1** are described in a 1971 paper in *HCA* [9], the corresponding entry is missing from the *CSD*. This is hardly surprising, as the crystal structure analysis is mentioned only very briefly in the paper, which deals with chromic-acid oxidation of polyenes. The only reference is '*Die Röntgenanalyse ... ergab die trans-axiale Lage der beiden tertiären Hydroxylgruppen und damit die für* **1** *angegebene Struktur und Konfiguration*'; space group and cell dimensions are given, but no atomic coordinates and no discussion of the crystal or molecular structure. This lack is a pity, because it makes it very difficult or even impossible for subsequent investigators to reconstruct the crystal structure and examine metrical details of the molecular structure and packing that may be important for some purpose or other but were of no interest to the original authors.



1

Indeed, it is now recognized that crystal structures may contain information that could well be of importance in quite different contexts and for quite different purposes from those that prompted the initial structure determination, especially when whole groups of related structures are considered together. For example, what are the directional preferences of nucleophiles in their approach to sulfonium ions? A 1980 analysis of the crystal environments of sulfonium ions [10] showed that short non-bonded contacts (secondary bonds) to sulfur tend to occur in directions opposite to the C–S primary bonds, *i.e.*, along the extensions of these bonds (*Fig. 2*). Such surveys of structural parameters or packing patterns in groups of related molecules can lead to rather general conclusions that could not have been drawn from the individual analyses. For this purpose and for others, results of crystal structure analyses that are not included in the *CSD* are to all intents and purposes lost to posterity; they are unlikely to be ever recovered by subsequent structural scientists. If the unit-cell dimensions and atomic coordinates are not listed in the publication, the structure will usually be irrecoverable, even if, by some chance, the original paper is encountered. Statements like 'These data may be obtained on application to the author' are not very helpful if the author is no longer active in science or has moved to a different address.

Fig. 2

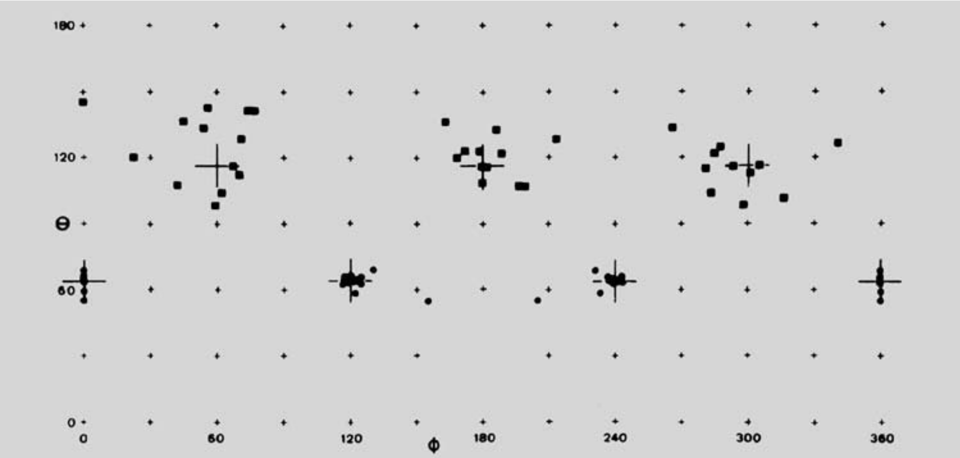
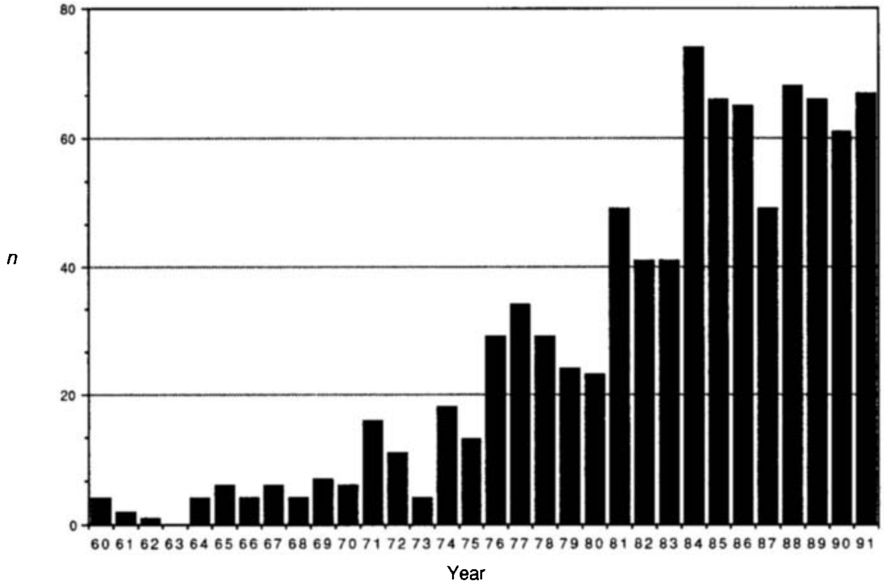


Fig. 3. *Mercator projection of the S–C (●) and S···X (■) directions.* The large crosses show the average S–C directions and the diametrially opposed directions.

Since about 1982 authors of papers submitted for publication to *HCA* are, therefore, required to provide, together with the manuscript, the basic crystallographic data for all new crystal structures determined in the course of the work. These data are sent directly to the *CCDC*.

Whereas thirty to forty years ago a good memory was perhaps the best guide to the world's structural literature, this is no longer the case. Since the number of crystal structures that have been determined is by now of the order of 10^5, it would be an almost impossible task to retrieve the structural information without the database and its associated software. A histogram showing the annual number of *CSD* entries for structures published in *HCA* is shown in *Fig. 3*. Starting with one or two entries per year in the early 60's, there is a somewhat erratic increase over the next three decades to a figure of *ca.* 70 entries per year. The total yield is almost a thousand.

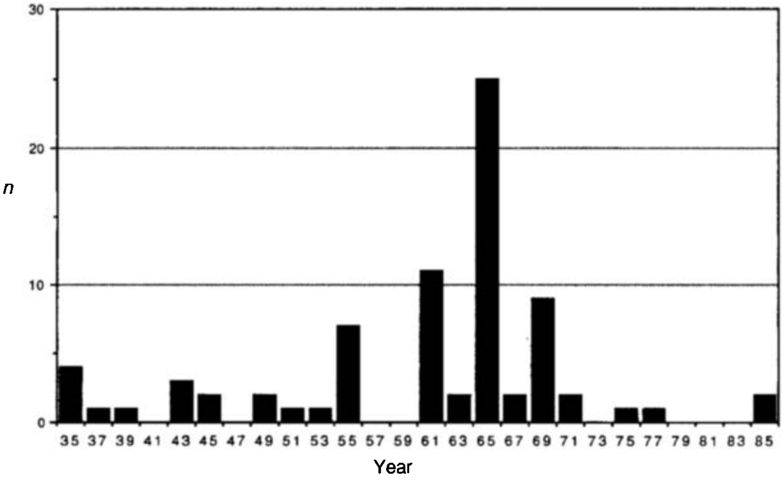
Fig. 3



Annual yield of X-ray structures from HCA *retrieved from the* Cambridge Structural Database *(*CSD*)*

More recently, a similar *Inorganic Crystal Structure Database* (*ICSD*) has become available for purely inorganic compounds, those that do not contain a C–C or a C–H bond [11]. Whereas the early literature on organic crystal structures is not well represented in the *CSD*, the *ICSD* does somewhat better in this respect, as can be seen from the histogram showing the bi-annual yield of inorganic structures published in *HCA* (*Fig. 4*).

Fig. 4



Bi-annual yield of X-ray structures from HCA *retrieved from the* Inorganic Structural Database *(*ICSD*)*

The total number of *HCA* structures retrieved from the *ICSD* is much less than the number of 'organic' structures (*ca.* 80 compared with *ca.* 900), and comparison of *Figs. 3* and *4* shows that the patterns are quite different. Whereas the *CSD* yield begins in the early 60's and shows an unmistakable although erratic increase over the years since then, the *ICSD* yield goes back to the 30's and peaks in the early 60's. Although one should not put too much significance into such comparisons, because of the different criteria for inclusion adopted by the two databases, the main trend is clear: the early years of *HCA* contain occasional papers on inorganic structural chemistry, the later years are dominated by reports on organic crystal structures, whereby the adjective 'organic' needs to be understood in a rather broad sense – an ethylenediamine ligand in an otherwise inorganic structure is enough to qualify it for inclusion in the *CSD*.

Names that occur most frequently in the *CSD* as authors of papers in *HCA* that describe crystal structures are, among the crystallographers: *R. Prewo* and *J.H. Bieri* (University of Zurich), *M. Dobler*, *W.B. Schweizer*, and *M. Egli* (ETH-Zurich), *M. Zehnder* (University of Basel), *P. Schönholzer*, and *J.J. Daly* (*F. Hoffmann-La Roche*, Basel), *G. Rihs* (Ciba Geigy, Basel), *H.P. Weber* (*Sandoz*, Basel), *G. Bernardinelli* (University of Geneva), *H. Stoeckli-Evans* (University of Neuchâtel), *J.W. Bats* (Frankfurt/Main); and among the chemists: *H. Heimgartner*, *C.H. Eugster* (University of Zurich), *D. Seebach* (ETH-Zurich), *G. Quinkert* (Frankfurt/Main).

We could spend much effort trying to understand and explain these statistics, but it is time to leave generalities and discuss a few selected themes in more detail. We begin by describing the development of structural work between 1917 and 1960. In particular, we draw attention to two concepts in structural chemistry which have their forgotten origins in *HCA*. Among the topics chosen for discussion, we follow the structural work on medium and large carbon rings over a period of fifty years. The presentation of a few selected papers after 1960 is intended to illustrate the transition of crystal structure analysis from a method aimed primarily at the determination of molecular constitution to one that can provide relationships between three-dimensional molecular architecture and chemical properties.

The Early Years 1917–1960. – During this period, detailed diffraction studies in *HCA* are few and far between, with occasional flurries of activity in certain areas. It was only in 1960 that single-crystal structure determinations became a regular feature of *HCA*. The only diffraction technique to have been used fairly continuously throughout the years is that due to *Debye* and *Scherrer* [12]. This technique serves mainly to characterize, identify, and differentiate between materials, as nicely exemplified in the very first report in *HCA* of a diffraction experiment. ***V. Kohlschütter*** (Bern) had studied the conditions leading to the red and yellow forms of lead oxide [13] and had interpreted his results with the hypothesis that the two forms are polymorphs. Two years earlier, *Glasstone* had interpreted the difference in color in terms of a difference in particle size [14]. The controversy was conclusively and elegantly resolved by *Kohlschütter* and *Scherrer* [15] with the help of two *Debye-Scherrer* diffractograms and one sentence of interpretation (*Fig. 5*). A text-book solution to a text-book problem, just eight years after *Debye* and *Scherrer* had published their method [12]. *Kohlschütter* must have been quite impressed by this method, as may be judged from a passage in his necrology [16]: '*V. Kohlschütter ... hat es*

Fig. 5

Die Entscheidung der Polymorphiefrage bei den Formen des Bleioxyds

von **V. Kohlschütter** und **P. Scherrer.**

(11. II. 24.)

Ein dunkelrotes Produkt (nach *Ostwald*'s Farbkörper: 29 p g) wurde nach der Methode von *Geuther* durch Erwärmen von überschüssigem Oxydhydrat mit 30-proz. Natronlauge erhalten, ein zitronengelbes (Farbkörper: 06 l b) daraus durch Erhitzen auf 600° gewonnen. *Beide gaben ganz verschiedene Roentgenbilder.* PbO_{rot} *und* PbO_{gelb} *sind also als wesensverschiedene polymorphe Formen anzusehen* (Fig. 1 u. 2).

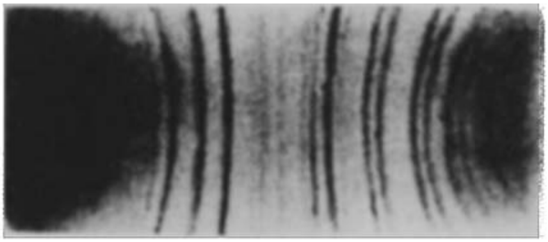


Fig. 1. PbO_{rot}

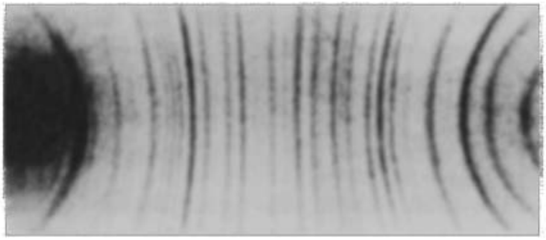


Fig. 2. PbO_{gelb}

verstanden mit dem bescheidenen ihm zur Verfügung stehenden Kredit die apparativen Einrichtungen des Institutes auszubauen und stets so weit wie möglich den modernen Anforderungen anzupassen. So gelangte beispielsweise Bern als eines der ersten chemischen Laboratorien in den Besitz einer Röntgeneinrichtung'. In any case, *Debye-Scherrer* diagrams are found in many subsequent papers of the inorganic group in Bern.

During these years much of the diffraction work in *HCA* deals with what can still be a difficult problem, namely the structure determination of synthetic and natural polymers from analysis of their fiber diffraction patterns: much effort but limited success. Studies

Fig. 6

121. Sur le soufre filiforme et sa structure

par **Kurt H. Meyer** et **Y. Go.**

(10. VIII. 34.)

Le roentgénogramme du soufre filiforme.

A cause de la grande sensibilité à la lumière du soufre filiforme, sensibilité qui se manifeste également sous l'effet des rayons X, il nous a fallu employer un artifice pour éviter la transformation décrite ci-dessus, pendant la longue exposition nécessaire à la suite du faible pouvoir de diffraction que possède le soufre de toutes modifications. Cet artifice consiste à passer, à une vitesse de 4 mm. par minute, un fil de soufre fraîchement préparé, qui se trouve dans une gaîne de plomb protecteur, devant le canaliseur (fig. 2).

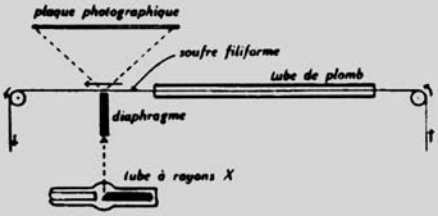
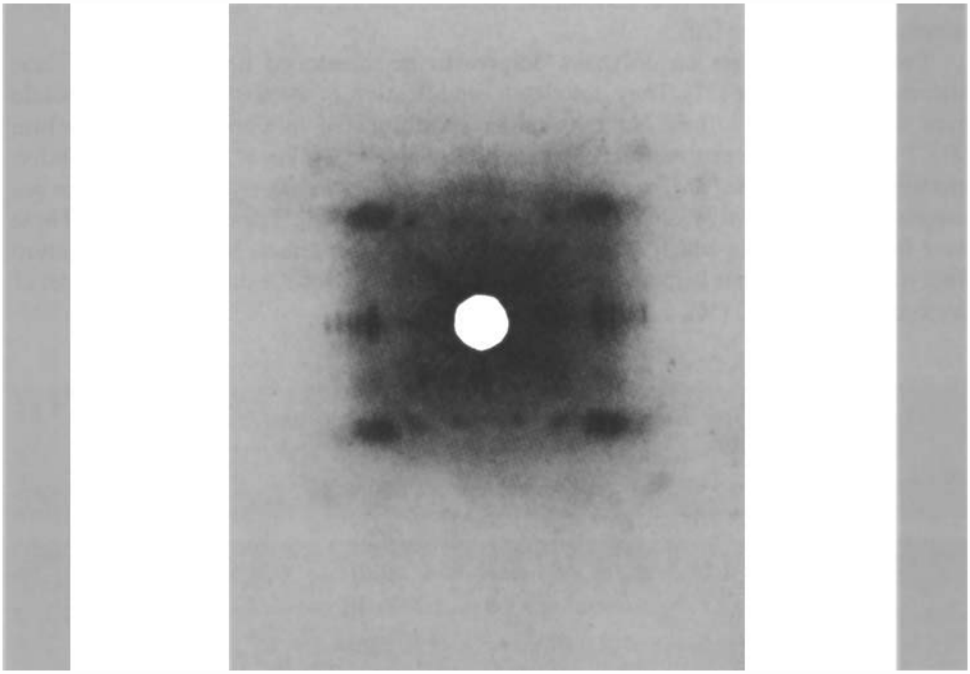


Fig. 2.



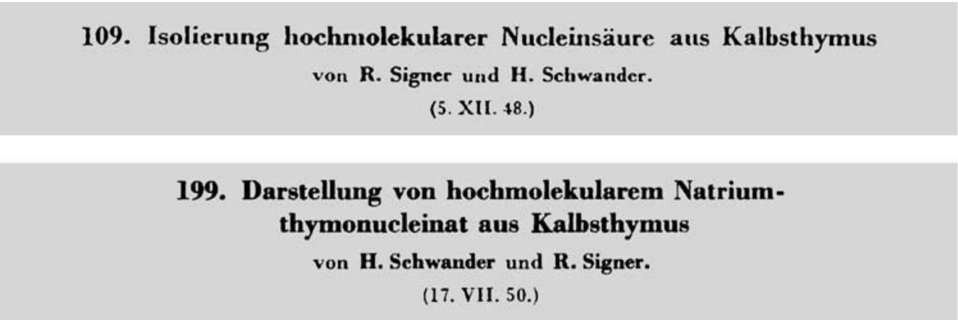
on celluloses and polyoxymethylenes provoked '*Bemerkungen*', '*Berichtigung*', and '*Erwiderung*', at the end of which the matter was closed by decree – and editorial footnote: '*Die Redaktion erklärt die Diskussion damit für geschlossen*' [17].

Another problem in polymer chemistry may be known to many from a lecture demonstration in first-year general chemistry, that of plastic sulfur. ***Kurt H. Meyer*** and *Go* (Geneva) [18] developed an ingenious experimental procedure to produce fibers of plastic sulfur and to prevent (partial) transformation from the polymeric to a molecular modification during the 12-h exposure to X-rays (*Fig. 6*). From the fiber diagram, they proposed a structural model with 112 S-atoms per unit cell arranged in flat chains. The development that followed had many twists and turns and involved the great *Linus Pauling* [19] among others. Ironically, in 1957, *Prins*, *Schenk*, and *Wachters* [20] showed that the diffraction pattern observed by *Meyer* and *Go* is actually a superposition of two diffraction patterns, one due to plastic sulfur and the other to a molecular sulfur modification, monoclinic sulfur. This finding disposed of all foregoing interpretations. The entire story, including its completion in 1969 [21], is nicely summarized and documented by *Donohue* [22].

Subsequent papers by *Meyer* report on polypeptides [23], chitin [24], and an improved structural model of cellulose [25]. In the cellulose paper the authors attempted to define a detailed model, including atomic coordinates, that took into account all then known chemical and stereochemical facts: C–C and C–O distances of 1.54 and 1.45 Å, CCC angles of *ca.* 109.5°, and H-bond distances of 2.6 Å between OH groups. At the same time, the model was required to agree with the visually estimated diffraction intensities. Although this paper was not the last word on the subject, it illustrates what could be done in those days. *Meyer*'s later contributions to carbohydrate chemistry in *HCA* have been summarized elsewhere [26].

Two further papers on polymers deserve to be mentioned here because of their historical significance [27]. They describe a modification of a known method to isolate pure nucleic acids or their Na salts under conditions of minimal depolymerization (*Fig. 7*). These are the procedures described by ***R. Signer*** (Bern) in May 1950 at a London meeting of the *Faraday Society*. *Judson* writes that '*... at the meeting ... Signer gave out samples of his best, and Wilkins took some home to Kings*' [28]. The rest is history. These were the samples from which *Franklin*, *Gosling*, and *Wilkins* made the X-ray diffraction fiber diagrams [29] that helped *Watson* and *Crick* to discover the double-helix model of deoxyribonucleic acid [30].

Fig. 7



109. Isolierung hochmolekularer Nucleinsäure aus Kalbsthymus

von **R. Signer** und **H. Schwander**.

(5. XII. 48.)

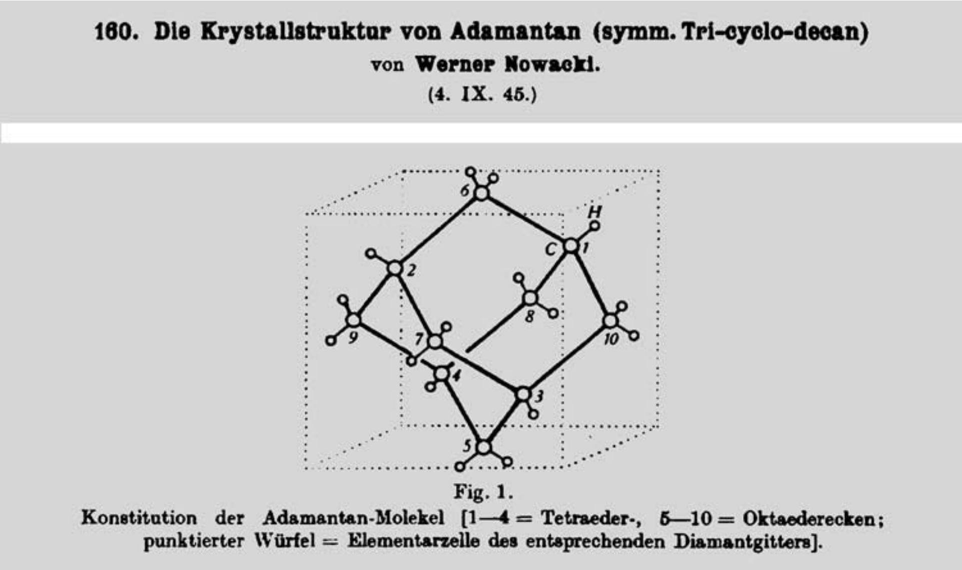
199. Darstellung von hochmolekularem Natrium-thymonucleinat aus Kalbsthymus

von **H. Schwander** und **R. Signer**.

(17. VII. 50.)

The first determination of a three-dimensional organic crystal structure to appear in *HCA* is that of adamantane, described by ***Werner Nowacki*** (Bern) in 1945 [31]1) (*Fig. 8*). In a sense, the structure is very simple, deceptively simple. From a *Debye-Scherrer* diagram, the crystal system was found to be cubic and the intensities of 16 reflections (including 4 overlapping pairs) were estimated from calibration photographs. It was assumed that the molecular symmetry $43m$ (T_d) is fully retained in the crystal, and (implicitly) that the crystal structure is fully ordered, leading to the assignment of the space group as $F\bar{4}3m$. If the bond angles at the C-atoms are tetrahedral ($\cos\theta = -1/3$), the coordinates of the eight methine C-atoms are $\pm x_1, \pm x_1, \pm x_1$ and those of the six methylene C-atoms are the permutations of $\pm 2x_1$, 0, 0. Thus, the problem could be reduced to the determination of a single positional parameter on which the C–C bond distance depends. This was given as 1.540(16) Å. The problem looked easy, otherwise it would probably not have been taken up in 1945, with no diffractometers to make large numbers of accurate measurements and no computers to interpret them. However, as is often the case with easy problems, they turn out to be more tricky than assumed initially. Twenty years later, *Nordmann* and *Schmitkons* measured 38 reflection intensities (still by visual estimation); they showed that the space group was not $F\bar{4}3m$ but the more highly symmetrical $Fm3m$, and that the structure was disordered [33]. The crystals contain a mixture of two orientations of adamantane related to one another by a 90° rotation about

Fig. 8



160. Die Krystallstruktur von Adamantan (symm. Tri-cyclo-decan)

von **Werner Nowacki.**

(4. IX. 45.)

Fig. 1.

Konstitution der Adamantan-Molekel [1—4 = Tetraeder-, 5—10 = Oktaederecken; punktierter Würfel = Elementarzelle des entsprechenden Diamantgitters].

---

1) In the same year, essentially the same results were published independently by *Giacomello* and *Illuminati* [32].

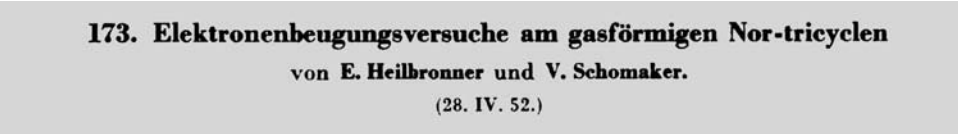
the molecular S_4 ($\bar{4}$) axes. This disorder affects the positions of the methine C-atoms but not those of the methylenes. Thus, *Nowacki*'s model accounted for only 80% of the total scattering. *Nordmann* and *Schmitkons* emphasized that the distinction between the ordered and disordered models was quite difficult, even with their improved data [33]. More details were filled in later; according to the *CSD*, the last publication by people foolish enough to get involved with this problem was in 1987 [34].

This story has a sequel which, although it did not lead to any publication in *HCA*, had its beginning in Switzerland. In 1965, *Jerry Donohue* spent one of several sabbatical leaves in the group of *Dunitz* at the ETH-Zurich. As was his habit, he carefully scrutinized the papers in each new issue of *Acta Crystallographica* as it arrived. One morning he noticed that the structure of the tetragonal low-temperature modification of adamantane given in the same paper as the description of the disordered high-temperature modification [33], showed a chemically unreasonable spread of C–C distances. He re-refined the experimental data (which were then routinely tabulated in *Acta Crystallographica*) by least-squares analysis to derive a model that gave a better fit and showed no deviant C–C distances. *Donohue* found that, starting from *Nordmann*'s structure, least-squares analysis failed to converge to his structure, and *vice versa*. A paper [35] on the subject concludes: '*Meanwhile, we find the occurrence of a false minimum (in least-squares refinement) which is quite close to the true minimum rather disturbing*'. To *Bürgi*, who was then a first-year graduate student of *Dunitz*, this was an impressive demonstration of the pitfalls of a technique that he, like many others, believed to be practically infallible.

Between the adamantane paper (1945) and the first reports on medium-ring crystal structures by *Dunitz* and coworkers (1960) there are three more *bona fide* three-dimensional structure determinations: two by *Aebi*, $V_{12}O_{26}$ [36], nowadays known as a *Magnéli* phase [37], and $Cu_4(OH)_6Br_2$ [38], and one by *Nowacki* and *Scheidegger*, $Cu_4(OH)_6(NO_3)_2$ [39]. This 1952 paper reflects the dawn of a new era in X-ray crystallography, as may be seen from the following passage: '*Diese (*Patterson-*) Synthesen ... wurden ausschliesslich mittels Lochkarten und der* International Business Machines *ausgeführt, nach einem System, das* W. Nowacki *im Institut von Professor* L. Pauling *in Pasadena (Calif.) kennengelernt hatte.*'

Also in 1952, *Heilbronner* and *Schomaker*, in their report on the structure of nortricyclene [40] (*Fig. 9*) state: '*Die theoretischen Intensitätskurven wurden mit Hilfe von Lochkarten berechnet.*' This work was actually done in Pasadena where punched cards had been in regular use for a number of years [41]. The paper by *Heilbronner* and *Schomaker* is a singleton: it is the only one we could find in *HCA* that deals with an electron-diffraction study of a molecule in the gas phase. When the structure of nortricyclene was reinvestigated many years later by *Kuchitsu* and coworkers [42] with very much better instrumentation, the authors comment that '*the ... structure reported by Heilbronner and Schomaker has been confirmed to be accurate to within their reported limits of error*'.

Fig. 9



173. Elektronenbeugungsversuche am gasförmigen Nor-tricyclen

von **E. Heilbronner** und **V. Schomaker.**

(28. IV. 52.)

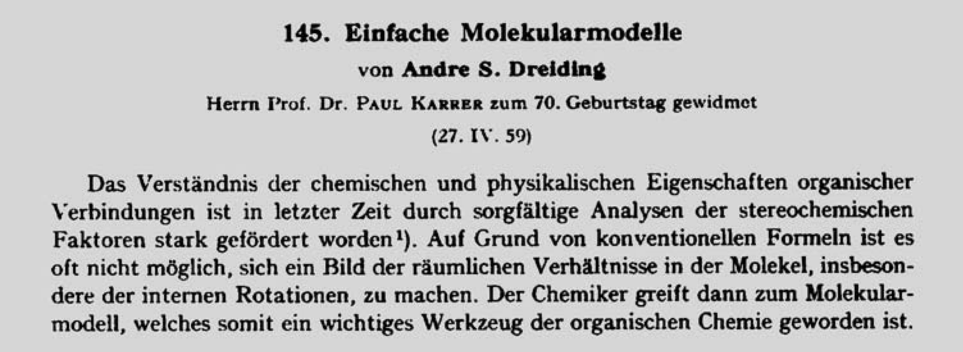


Fig. 10

145. Einfache Molekularmodelle

von **Andre S. Dreiding**

Herrn Prof. Dr. PAUL KARRER zum 70. Geburtstag gewidmet

(27. IV. 59)

Das Verständnis der chemischen und physikalischen Eigenschaften organischer Verbindungen ist in letzter Zeit durch sorgfältige Analysen der stereochemischen Faktoren stark gefördert worden1). Auf Grund von konventionellen Formeln ist es oft nicht möglich, sich ein Bild der räumlichen Verhältnisse in der Molekel, insbesondere der internen Rotationen, zu machen. Der Chemiker greift dann zum Molekularmodell, welches somit ein wichtiges Werkzeug der organischen Chemie geworden ist.

With the development in the 50's of computers, densitometers, and diffractometers, crystal structures were gradually becoming more and more easily accessible, and conformational aspects of molecular structure were beginning to be introduced in discussions of chemical reactivity. The stage was set for molecular modeling. *Dreiding*'s introduction [43] to his well known models (*Fig. 10*) needs no comment. Starting in 1960, reports on crystal structures are part of the regular diet in *HCA*.

Molecular Packing, Space Groups, and Topochemistry. – Two important concepts in modern structural chemistry have their forgotten origins in papers published in *HCA*. One has to do with the systematics of the ways molecules choose to arrange themselves in crystals – a branch of what is now called supramolecular chemistry. The other is concerned with chemical reactions in the solid state, which depend, among other factors, on the precise spatial relationships between neighboring molecules in the crystal – on what are now called topochemical factors.

We begin with the early history of the systematics of molecular packing in crystals, with a seminal pair of papers by *Nowacki* (Bern) [44] (*Fig. 11*). As a student of *P. Niggli*, *Nowacki* starts by explaining the concept of space groups, *i.e.*, the symmetry principles governing regular, periodic arrangements of structural motifs in three-dimensional space. He then gives a statistical survey of the *ca.* 3000 space-group determinations available in

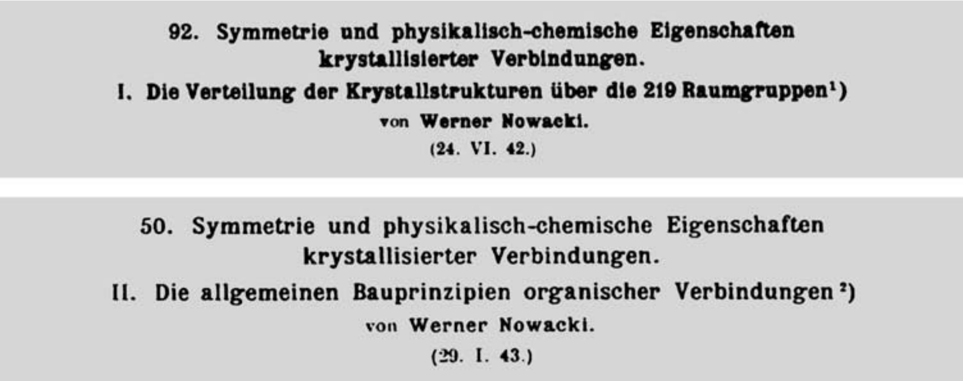


Fig. 11

92. Symmetrie und physikalisch-chemische Eigenschaften krystallisierter Verbindungen.

I. Die Verteilung der Krystallstrukturen über die 219 Raumgruppen1)

von **Werner Nowacki.**

(24. VI. 42.)

50. Symmetrie und physikalisch-chemische Eigenschaften krystallisierter Verbindungen.

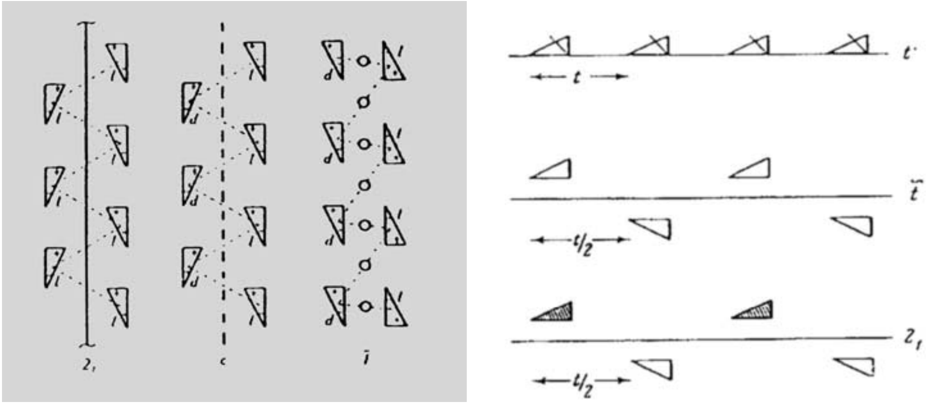
II. Die allgemeinen Bauprinzipien organischer Verbindungen2)

von **Werner Nowacki.**

(29. I. 43.)

1942. *Nowacki* finds that of the 219 space groups[2]) some occur much more often than others. He notes that simple (binary, ternary, *etc.*) inorganic compounds occur preferably in highly symmetric hexagonal and cubic space groups, whereas natural minerals tend to prefer the less symmetric orthorhombic and monoclinic space groups. For organic compounds, *Nowacki* remarks '*Die Selektion* (der Raumgruppen) *ist bei dieser Verbindungsklasse geradezu frappant*'. What he meant is that almost half (43.9%) of all organic compounds were found in only three space groups ($P2_1/c$, $P2_1$, $P2_12_12_1$). This point was taken up in more detail in the second paper, a year later [44b], where it is pointed out that the three groups in question contain as symmetry elements only twofold screw axes, glide planes, and inversion centers (in addition to translation operations), but no pure rotation axes or mirror planes. The screw and glide operations produce one-dimensional zigzag chains of molecules, which *Nowacki* considered to be favorable from an electrostatic point of view (*Fig. 12*). The packing of such chains into three-dimensional arrays, if governed by the same electrostatic principle, is shown to lead to the space groups $P2_1$, $P2_1/c$, $Pca2_1$, $Pna2_1$, $P2_12_12_1$, and $Pbca$ (and to $P\bar{1}$, which is not mentioned, however). Remarkably, the list includes the three most frequently observed space groups.

Fig. 12



Left: *Fig. 1 from* Nowacki [44b] ('*Zickzackkette erzeugt durch zweizählige Schraubenachse* (2_1), *Gleitspiegelebene* (c) *oder Symmetriezentren* ($\bar{1}$)'). Right: *Fig. 39 from* Kitaigorodski [47] ('*Symmetry elements which construct a chain; ...*').

Similar ideas were taken up in a series of papers by *Kitaigorodski*, published between 1944 and 1949[3]). His assumption was that bumps of one molecule insert into hollows of another copy of the same molecule to achieve an optimal packing of the typically unsymmetrical organic molecules. This generalization of the principle of close packing led *Kitaigorodski* to the same list of preferred space groups (including $P\bar{1}$), described in his influential book '*Organic Chemical Crystalllography*', published both in Russian and English [45]. *Kitaigorodski* mentions *Nowacki*'s statistical results in a footnote on p. 109

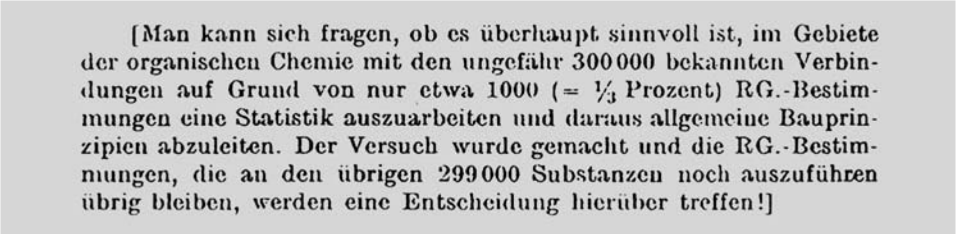
---

[2]) The number is 230, if enantiomorphic space groups are counted seperately.

[3]) *Kitaigorodski* explicitly mentions these years on p. 66 of [45]. The corresponding literature references are given in a footnote on the same page.

of [45], but does not refer to his rationalization of the preferred space groups. Conversely, *Nowacki*, when he updated his original table in 1951 [46], does not cite *Kitaigorodski*. In *Kitaigorodski*'s later books [47] [48], the reference to *Nowacki* [44b] is dropped. In the Russian original [47], the space-group frequencies are said (in a footnote) to be based on a table by *Belski* from 1969. In the German translation, a different table is quoted [49]. Finally, in the (earlier) English version [50], there is merely a three-line paragraph mentioning that the space groups expected on packing grounds are the ones that are most frequently observed; no table and no reference is given. Especially after the appearance of his book, *Kitaigorodski*'s work became very widely known, whereas *Nowacki*'s contributions seem to have fallen into oblivion and are no longer cited, at least not in two important recent papers on molecular packing [50] [51].

In his first paper, *Nowacki* makes a parenthetical remark on the significance of the size of his statistical sample (*ca.* 1000 structures; *Fig. 13*).



[Man kann sich fragen, ob es überhaupt sinnvoll ist, im Gebiete der organischen Chemie mit den ungefähr 300000 bekannten Verbindungen auf Grund von nur etwa 1000 (= ⅓ Prozent) RG.-Bestimmungen eine Statistik auszuarbeiten und daraus allgemeine Bauprinzipien abzuleiten. Der Versuch wurde gemacht und die RG.-Bestimmungen, die an den übrigen 299000 Substanzen noch auszuführen übrig bleiben, werden eine Entscheidung hierüber treffen!]

Fig. 13

The *Table* shows the relative frequencies of the most common space groups in which crystals of organic molecules are found. Results are given for statistics published in 1942 [44a], 1970 [49], 1987 [51] and 1992[4]). It is remarkable that overall the original conclusions have not changed, although the sample size has increased by a factor of *ca.* 70, almost two

Table

Relative Frequencies of Occurrence [%] of Common Space Groups of Organic Molecular Crystals

Year	1942	1970	1987	1992
$P\bar{1}$	2.4	9.5	16.0	18.8
$P2_1$	11.8	4.4	6.6	6.0
$P2_1/c$	21.7	38.8	38.9	38.3
$P2_12_12_1$	10.4	10.0	11.9	10.4
$Pca2_1$	< 2.7	–	0.8	1.7
$Pna2_1$	< 2.7	2.4	1.8	0.8
$Pbca$	3.0	3.7	4.6	4.4
Total sample size	~ 1000	?	34730	71086
Ref.	[44a]	[49]	[51]	*Footnote 4*

---

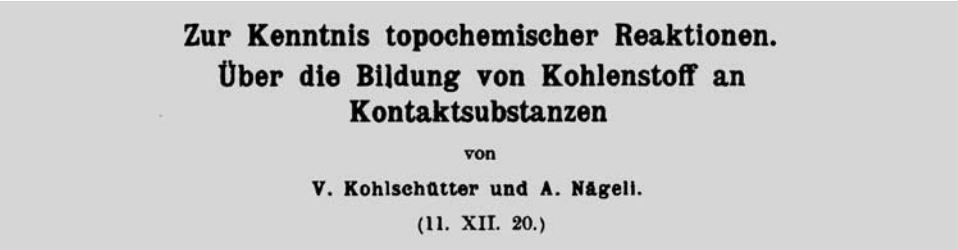
[4]) From the *CSD* version of January 1992 (102589 entries): only fully structural studies (screen 66), atomic coordinate field present (153), no disorder (35), $R < 0.1$ (88). The search was for space-group number (not for space-group symbol). This update represents about a half-day's work of an experienced postdoctoral research assistant.

orders of magnitude. The continuous increase found for $P\bar{1}$ is striking. Is it due to a social factor? (The interested reader is referred to [51] for a discussion of this point).

After all the intervening years, the ideas of these two authors are still the main basis for attempts to solve the so called packing problem, *i.e.*, the problem of predicting the molecular organization (packing) of organic molecules of arbitrary shape and composition [50].

Another topic that has become important in organic crystal chemistry is what is called 'topochemistry'. Since about 1964 this term has become widely known through the work of *G.M.J. Schmidt*, who used it to interpret observations by him and his coworkers[5]), according to which molecules juxtaposed in crystals react in very specific ways, often different from those in solution. A well known example is the photochemical solid-state dimerization of cinnamic acid. This compound crystallizes in several polymorphic forms, and the reaction product molecules are either centrosymmetric or mirror-symmetric, depending on the crystal modification of the reactant [53]. Concerning the origin of the word 'topochemistry', *Cohen* and *Schmidt* stated: '*The following papers are mainly concerned with the thesis that the course of certain types of solid state reactions are determined by the geometry of the reactant lattice, or in Hertel's phrase by 'topochemical' factors*' [54]. *Hertel*'s paper [55] on '*Umwandlungen im Kristallgitter*' describes the transformation of the unstable red modification of the co-crystal between 4-bromo-1-naphthylamine and 2,6-dinitrophenol into the stable yellow modification, with a partial correlation between the unit-cell orientations of the two forms. *Hertel*'s interpretation: '*... von Bruchstellen aus* (in the red form) *erfolgt jedoch leicht eine spontane Umwandlung in die stabile Modifikation. Es setzt eine topochemische Reaktion ein, die sich langsam ... durch den ganzen Kristall fortpflanzt*'[6]). *Hertel* uses the word '*topochemische Reaktion*' without reference. This could indicate that the expression was in common use in 1931. If so, where did it come from? This is where *HCA* comes into the picture. *Volume 4* (1921) contains a paper entitled '*Zur Kenntnis topochemischer Reaktionen. Über die Bildung von Kohlenstoff an Kontaktsubstanzen*' [56] (*Fig. 14*). It is by the same *Kohlschütter* (Bern) who resolved the problem of polymorphism in PbO [15]. A little back-tracking leads to an earlier paper [57] in which *Kohlschütter* writes an introduction entitled '*Über topochemische Reaktionen*' and defines the term as applying to reactions whose '*gemeinsames Merkmal darin*

Fig. 14



Zur Kenntnis topochemischer Reaktionen.
Über die Bildung von Kohlenstoff an
Kontaktsubstanzen

von

V. Kohlschütter und A. Nägeli.

(11. XII. 20.)

---

[5]) For a collection of relevant papers, see [52].

[6]) Today the phenomenon described in this paper would be classified under the more restrictive term 'topotaxy'

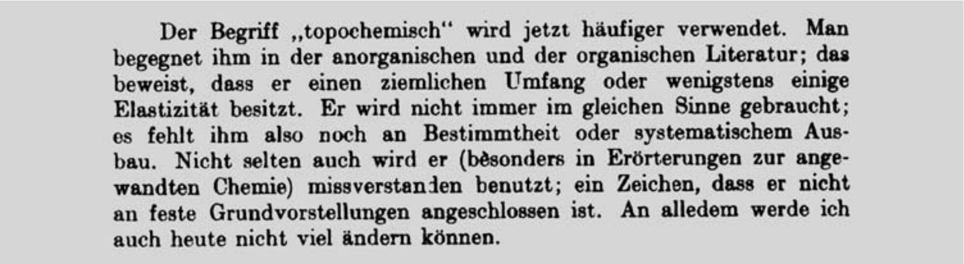


Fig. 15

Der Begriff „topochemisch" wird jetzt häufiger verwendet. Man begegnet ihm in der anorganischen und der organischen Literatur; das beweist, dass er einen ziemlichen Umfang oder wenigstens einige Elastizität besitzt. Er wird nicht immer im gleichen Sinne gebraucht; es fehlt ihm also noch an Bestimmtheit oder systematischem Ausbau. Nicht selten auch wird er (besonders in Erörterungen zur angewandten Chemie) missverstanden benutzt; ein Zeichen, dass er nicht an feste Grundvorstellungen angeschlossen ist. An alledem werde ich auch heute nicht viel ändern können.

gesehen wird, dass Verlauf und Ergebnis durch die örtliche Festlegung des chemischen Prozesses bestimmt wird'. Indeed, an accurate interpretation of *Schmidt*'s experiments, some 45 years before they were done! Another paper on '*Topochemische Reaktionen*' (*Fig. 15*) appeared in 1929 [58], two years before *Hertel*'s paper [55]. It contains the clue we are looking for: '*The term 'topochemical' is now used more often. It is found in the inorganic and organic literature ...*'. *Kohlschütter* specifically mentions that *R. O. Herzog* was the first to apply the term to reactions of organic polymers [59]. Nowadays, an entry in *Römpp's Chemie-Lexikon* [60] states: '*Topochemie. Von V. Kohlschütter 1919 geprägte ... Bezeichnung ...*'. It would lead us too far to discuss here in detail the chemistry behind *Kohlschütter*'s ideas. Suffice it to say that his successors, among them *Feitknecht* (Bern) and *Oswald* (Zürich), have continued to apply the term in inorganic solid-state chemistry. According to *Oswald*, it is quite generally acknowledged now by the inorganic community that '*Topochemie*' is originally *Kohlschütter*'s concept [61].

A third topic in structural chemistry found in early volumes of *HCA* deals with molecular symmetry and isomerism. In today's terminology, the paper by *Polya* [62] could be called a 'commercial', as may be seen from the last sentence of his introduction to the paper (*Fig. 16*). The paper consists essentially of a table of the number of isomers for some aromatic molecules containing several equal or different substituents, information that must have been already known to organic chemists at the time. The real significance of the table is pointed out in the first two lines of the introduction (*Fig. 16*).

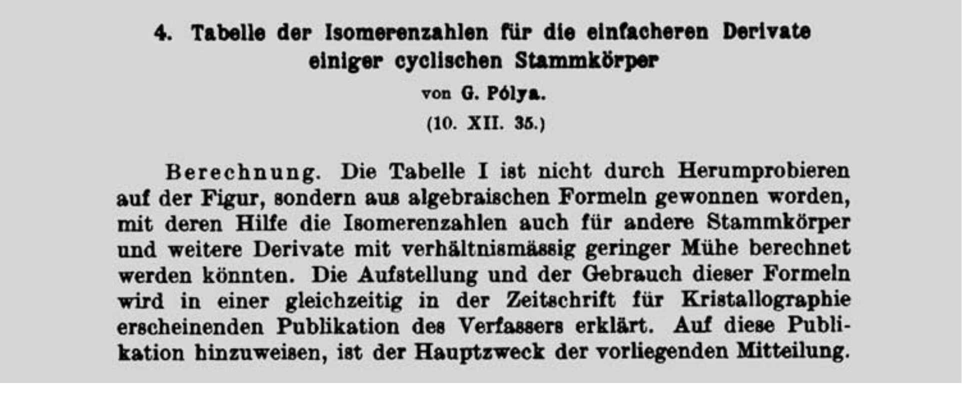


Fig. 16

4. Tabelle der Isomerenzahlen für die einfacheren Derivate einiger cyclischen Stammkörper

von **G. Pólya.**

(10. XII. 35.)

Berechnung. Die Tabelle I ist nicht durch Herumprobieren auf der Figur, sondern aus algebraischen Formeln gewonnen worden, mit deren Hilfe die Isomerenzahlen auch für andere Stammkörper und weitere Derivate mit verhältnismässig geringer Mühe berechnet werden könnten. Die Aufstellung und der Gebrauch dieser Formeln wird in einer gleichzeitig in der Zeitschrift für Kristallographie erscheinenden Publikation des Verfassers erklärt. Auf diese Publikation hinzuweisen, ist der Hauptzweck der vorliegenden Mitteilung.

The underlying theory was given in a parallel paper published elsewhere [63], which includes tables giving the number of isomers for homologous series of paraffins, for saturated alcohols with a given number of asymmetric C-atoms, and for substituted aromatics. The topic was taken up again later by *Niggli* [64], who used *Polya*'s theory to analyze isomerism for coordination polyhedra, especially those with coordination numbers 4, 6, and 8. In a follow-up paper [65], *Niggli* extended these considerations to characterize the distribution of constituents in mixed crystals, especially those composed of two kinds of atoms arranged in a simple cubic lattice.

Before we conclude this section, we want to draw attention to a paper that needs to be mentioned here not so much because of its main content but because of a footnote that provided an essential clue to the solution of a puzzling structural problem. The footnote in question merely states that the entropy of fusion of azulene is about 4.5 cal mol^{-1} K^{-1} lower than that of naphthalene [66], suggesting that azulene has a higher entropy in the solid state and pointing to the presence of disorder in crystalline azulene. The space group of azulene had previously been given as $P2_1/a$ ($Z = 2$) by *Günthard, Plattner*, and *Brandenberger* [67], who noted that the apparent presence of a molecular center of symmetry was incompatible with the molecular formula. Soon afterwards, two independent studies of azulene, using two-dimensional X-ray data, were based on the supposition of an ordered crystal structure in the lower, non-centrosymmetrical space group *Pa* [68] [69], an assignment that seemed to be supported by observations of the macroscopic crystal form, which was reported to lack the face development appropriate to the higher space group [70]. The conflict was only settled a few years later when a three-dimensional analysis [71] showed clearly that the disordered structure in the centrosymmetric space group $P2_1/a$ was correct. The story hinging on the aforementioned footnote provides a valuable warning against drawing too firm conclusions about molecular symmetry from space-group evidence alone.

Fifty Years of Carbon Rings. – The discovery of large carbon rings by *Ruzicka*, and the chemistry that followed from this discovery, is summarized by *Ohloff* in his article in this series [72]. Two papers of the many published on this topic concentrate specifically on the spatial arrangements of the atoms in these rings – what we would now call the ring conformations. The first, by *Stoll* and *Stoll-Comte* [73], presents a remarkable analysis of densities, melting and boiling points of cycloalkanes and cycloalkanones, which, combined with results of earlier X-ray diffraction studies on open-chain hydrocarbon compounds, led these authors to astonishingly detailed structural models that turned out, at least for the large rings, to be not too far from the correct ones (*Fig. 17*). The large rings ($n > 16$) are described as consisting of two parallel, ordered chains, linked to one another at both ends by eight CH_2 groups. (From the diagrams of the 28-membered ring in *Fig. 17c* and *c*', it is not so obvious how the molecule should best be described.)

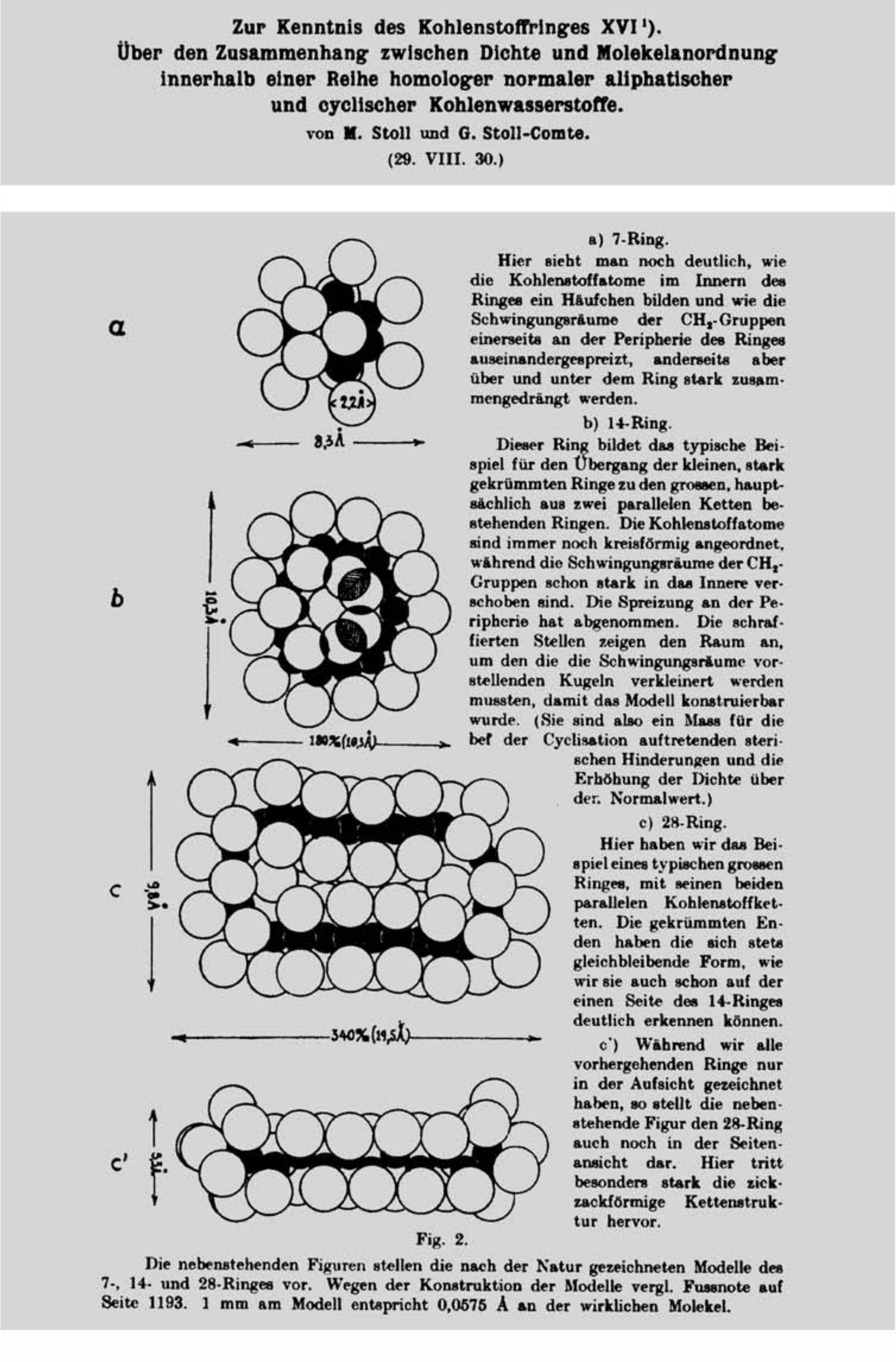


Fig. 17

Zur Kenntnis des Kohlenstoffringes XVI 1).
Über den Zusammenhang zwischen Dichte und Molekelanordnung innerhalb einer Reihe homologer normaler aliphatischer und cyclischer Kohlenwasserstoffe.

von **M. Stoll** und **G. Stoll-Comte.**

(29. VIII. 30.)

a) 7-Ring.

Hier sieht man noch deutlich, wie die Kohlenstoffatome im Innern des Ringes ein Häufchen bilden und wie die Schwingungsräume der CH_2-Gruppen einerseits an der Peripherie des Ringes auseinandergespreizt, anderseits aber über und unter dem Ring stark zusammengedrängt werden.

b) 14-Ring.

Dieser Ring bildet das typische Beispiel für den Übergang der kleinen, stark gekrümmten Ringe zu den grossen, hauptsächlich aus zwei parallelen Ketten bestehenden Ringen. Die Kohlenstoffatome sind immer noch kreisförmig angeordnet, während die Schwingungsräume der CH_2-Gruppen schon stark in das Innere verschoben sind. Die Spreizung an der Peripherie hat abgenommen. Die schraffierten Stellen zeigen den Raum an, um den die die Schwingungsräume vorstellenden Kugeln verkleinert werden mussten, damit das Modell konstruierbar wurde. (Sie sind also ein Mass für die bei der Cyclisation auftretenden sterischen Hinderungen und die Erhöhung der Dichte über den Normalwert.)

c) 28-Ring.

Hier haben wir das Beispiel eines typischen grossen Ringes, mit seinen beiden parallelen Kohlenstoffketten. Die gekrümmten Enden haben die sich stets gleichbleibende Form, wie wir sie auch schon auf der einen Seite des 14-Ringes deutlich erkennen können.

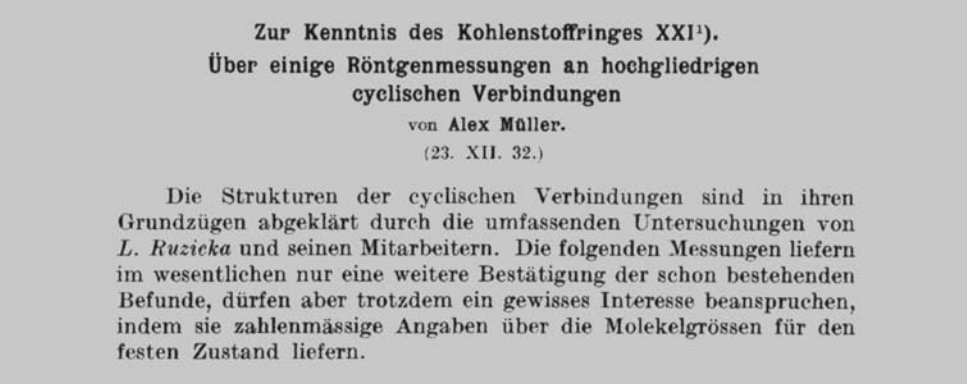
c') Während wir alle vorhergehenden Ringe nur in der Aufsicht gezeichnet haben, so stellt die nebenstehende Figur den 28-Ring auch noch in der Seitenansicht dar. Hier tritt besonders stark die zickzackförmige Kettenstruktur hervor.

Fig. 2.

Die nebenstehenden Figuren stellen die nach der Natur gezeichneten Modelle des 7-, 14- und 28-Ringes vor. Wegen der Konstruktion der Modelle vergl. Fussnote auf Seite 1193. 1 mm am Modell entspricht 0,0575 Å an der wirklichen Molekel.

Three years later, *A. Müller* followed up these suggestions with an X-ray diffraction study of single crystals of cyclododecane and of polycrystalline samples of the cycloalkanes with 15 to 30 C-atoms in the ring, and of two crystalline macrocyclic diketones [74] (*Fig. 18*). *Müller* had the advantage of the facilities of the Royal Institution in London, then one of the main centers of X-ray crystallographic research in the world, and his investigations were based not only on *Debye-Scherrer* diffraction patterns but also on single crystal X-ray photographs obtained from a rotating-anode (!) X-ray source. No detailed structure analyses were carried out, but, from analogies with diffraction patterns of long-chain paraffins, *Müller* could infer that the large rings were built from two parallel zigzag chains of methylene groups, in agreement with the proposals by *Stoll* and *Stoll-Comte*. He modestly deferred to these authors in their model of three-atom bridges, although his actual estimate was that the bridges linking the end of these chains contained 1.5 to 2.3 CH_2 groups, or, as 'extreme limits', 1 to 3 CH_2 groups. *Müller* thus considered his result as being consistent with the proposal of end-segments of three CH_2 groups, but it is, of course, in much closer agreement with end-segments of two CH_2 groups. From *Müller*'s work it was clearly established that the length of a CH_2 group and its cross-section in a polymethylene chain are quite similar for linear and cyclic molecules.

Fig. 18



Zur Kenntnis des Kohlenstoffringes XXI[1]).
Über einige Röntgenmessungen an hochgliedrigen cyclischen Verbindungen
von **Alex Müller.**
(23. XII. 32.)

Die Strukturen der cyclischen Verbindungen sind in ihren Grundzügen abgeklärt durch die umfassenden Untersuchungen von *L. Ruzicka* und seinen Mitarbeitern. Die folgenden Messungen liefern im wesentlichen nur eine weitere Bestätigung der schon bestehenden Befunde, dürfen aber trotzdem ein gewisses Interesse beanspruchen, indem sie zahlenmässige Angaben über die Molekelgrössen für den festen Zustand liefern.

Although the models proposed by *Stoll* and *Stoll-Comte* for the large cycloalkanes turned out to be not too far from the truth, those for the medium rings with 7 to 14 C-atoms were quite incorrect. The elucidation of the conformations of medium-ring molecules had to wait until 1960 when *Dunitz* and his coworkers took up the problem with more modern equipment and computing facilities. At the beginning of these studies, information about the geometry of these molecules was almost completely lacking, but in a systematic series of crystal structure analyses of key compounds over the years the missing knowledge gradually became available. The stable conformations of cyclododecane, cyclodecane, cyclononane, and cyclooctane, are shown in *Figs. 19–22*. A few words about each may be in order.

Fig. 19

3. Die Strukturen der mittleren Ringverbindungen
III. Die Struktur des Cyclododecans

von **J. D. Dunitz** und **H. M. M. Shearer**

(13. X. 59)

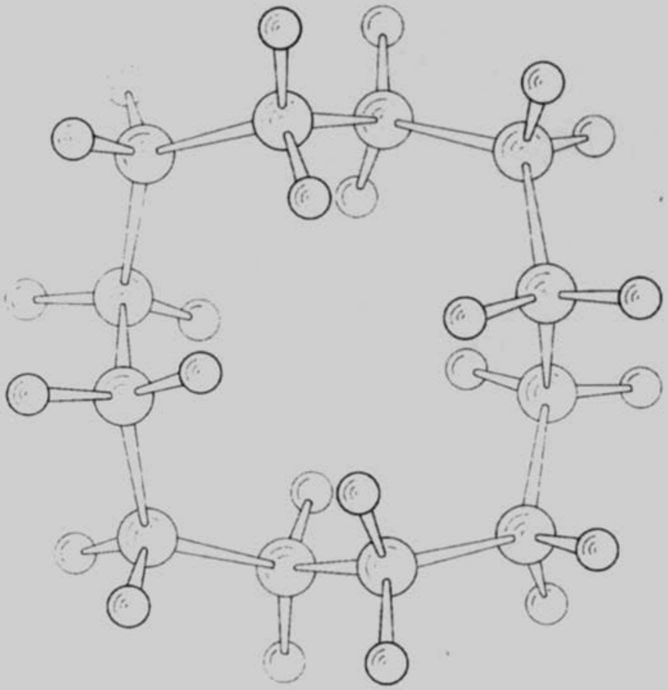


Fig. 6. *Anordnung der Wasserstoffatome im Molekel-Modell VI* (*422-Symmetrie*)

Fig. 20

101. Strukturen der mittleren Ringverbindungen
IV. 1,6-*trans*-Diaminocyclodecan-dihydrochlorid, trikline Modifikation[1] [2]

von **Effi Huber-Buser** und **J. D. Dunitz**

(5. III. 60)

Fig. 20
(Forts.)

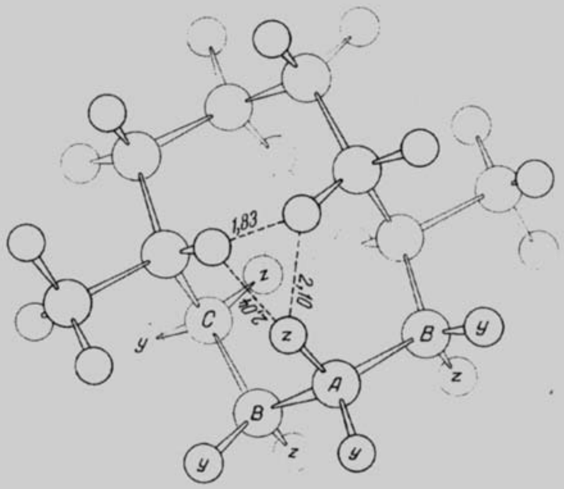


Fig. 5. *Anordnung der Wasserstoffatome im Molekelmodell*
------ kürzeste transannulare H ... H-Abstände in Å

Fig. 21

2. Les structures de cycles de taille moyenne
II. La structure cristalline et moléculaire du bromure de cyclononylammonium

par **R. F. Bryan** et **J. D. Dunitz**

(13. X. 59).

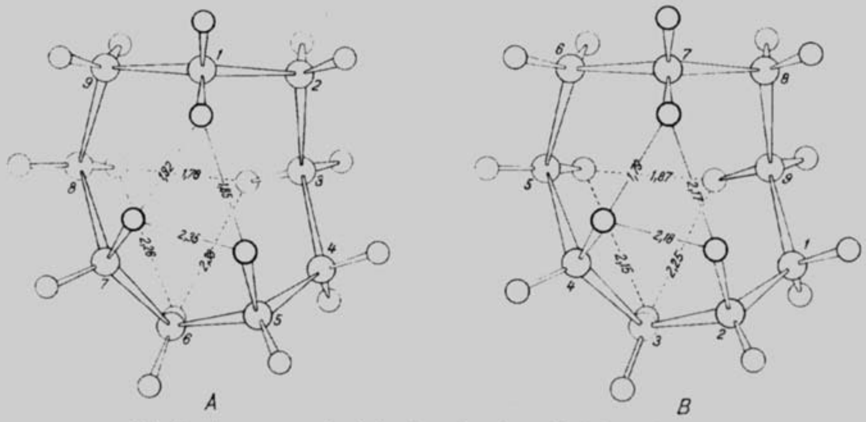
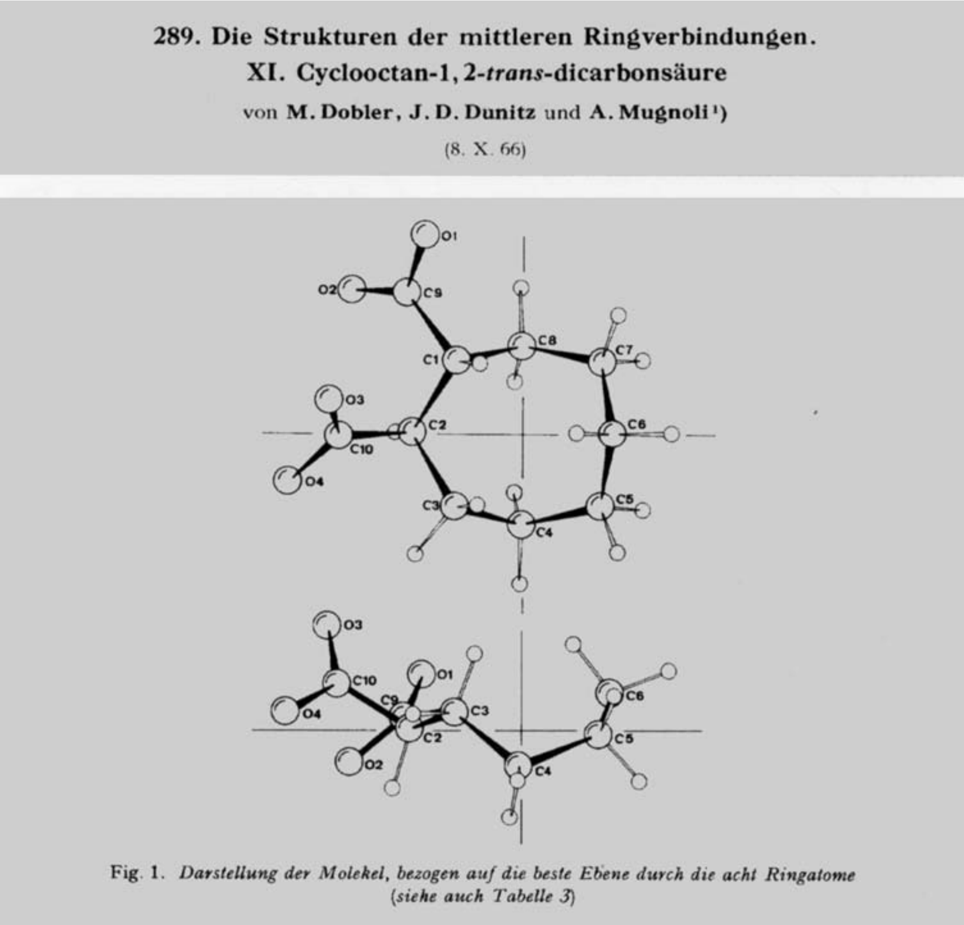


Fig. 7. *Arrangement des hydrogènes dans la molécule de cyclononane.*
Les distances inter-hydrogène les plus courtes sont indiquées pour les deux cycles (*A* et *B*).

Fig. 22



289. Die Strukturen der mittleren Ringverbindungen.
XI. Cyclooctan-1,2-*trans*-dicarbonsäure

von **M. Dobler, J. D. Dunitz** und **A. Mugnoli**[1]

(8. X. 66)

Fig. 1. *Darstellung der Molekel, bezogen auf die beste Ebene durch die acht Ringatome (siehe auch Tabelle 3)*

In his early study, *Müller* had interpreted single-crystal photographs of cyclododecane in terms of a monomolecular triclinic cell [74]. But he had erred; in his description, there are two axes of equal length, always a danger sign, for they can be the diagonals of a centered cell. Indeed, the new measurements [75] showed that crystals of cyclododecane are C-centered monoclinic with two molecules in the unit cell. The systematic absences are compatible with three possible space groups: $C2$, Cm, and $C2/m$, of which the last can be shown, by various tests, to be the correct one. Formally, this means that the molecular symmetry must also be $2/m$ (C_{2h}), but there is no reasonable molecular structure with this symmetry; the crystal structure must be disordered. The 'averaged' structure, corresponding to the space-group symmetry, is a superposition of two (or more) sets of atomic positions. This is not the place to enter into all the complications that lead to the conformation shown in *Fig. 19* as the correct one [76], but it is enough to say that it was subsequently confirmed as the energetically stable conformation by analysis of the vibrational spectrum [77] and by various force-field calculations. It has approximate 422 (D_4) or perhaps only 222 (D_2) symmetry; in any case, it is chiral.

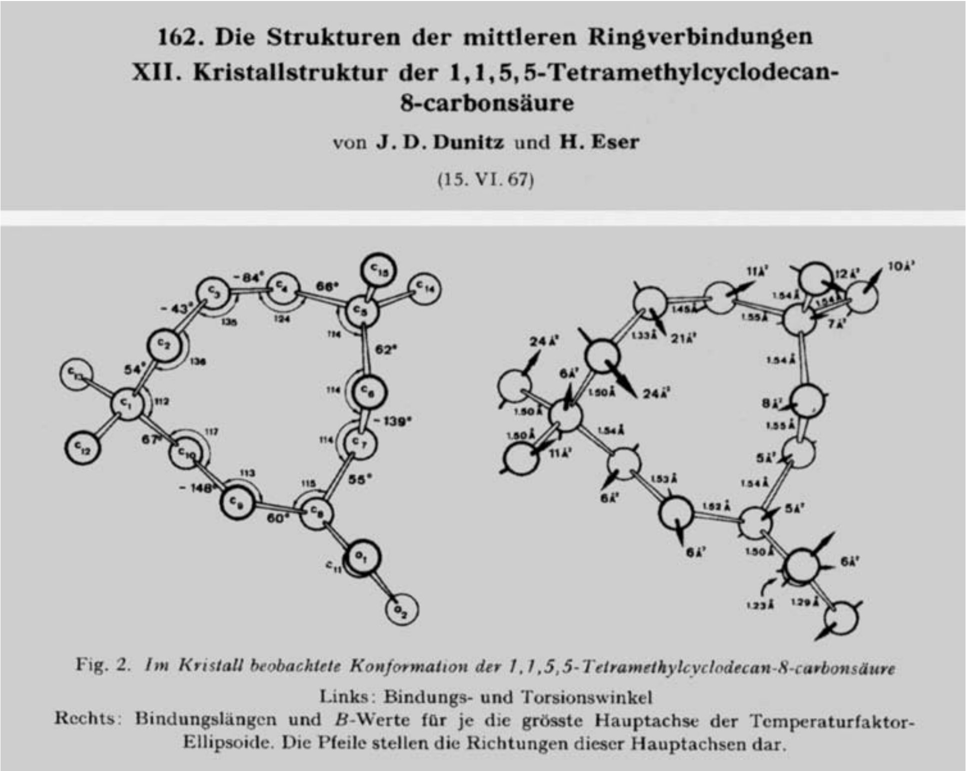
In the course of this study [75], some low-temperature X-ray photographs were made. These showed that crystalline cyclododecane undergoes a reversible phase transition between −88° and −100 °C. Although the exact nature of this transition has never been cleared up, it seems to be connected with some sort of order-disorder process. It was suggested that above the transition region the molecules undergo rapid inversion between the two enantiomeric forms; below the transition region the inversion rate is effectively zero, and the structure is frozen in some sort of order-disorder arrangement. This interpretation is supported by the results of an early NMR study of solid cyclododecane [78]. Between −80° and −100 °C, there is a sudden increase in the second moment of the proton resonance signal from an initial value of *ca.* 6.5 gauss^2 to a final value of 29.8 gauss^2, which must be associated with some loss of molecular motion. Here is a half-solved problem that waits to be cleaned up with modern techniques.

When this early study was begun, *V. Prelog* presented *Dunitz* with a small glass tube containing a few grams of cyclododecane, the total supply available at that time and used throughout the entire investigation; by zone melting, the content of a capillary tube could be converted into a single crystal. Some twenty years later, *Dunitz* visited the *Huls* factory in Germany, one of the largest manufacturers of basic chemicals in the world. During this visit, he mentioned those early adventures with small amounts of cyclododecane and was taken to a waste area where stood a virtual mountain of a white substance: cyclododecane, he was told – tons of it, a useless by-product in the manufacture of cyclododecatriene! Perhaps by now someone has found a use for this interesting substance. Perhaps someone may be encouraged to re-investigate the nature of the phase transition and to determine the structure of the low-temperature crystal modification.

The cyclodecane study was somewhat more straightforward. X-ray analyses of five crystalline derivatives [79–82] all led to the same ring conformation, the one shown in *Fig. 20*, which has approximate C_{2h} $(2/m)$ symmetry. (The same conformation was established many years later for the parent hydrocarbon [83]). Its strain energy arises mainly from two sources: from *Baeyer* strain associated with widening of the CCC angles to a mean value of *ca.* 116°; and from repulsions among the intra-annular H-atoms, as shown in *Fig. 20*. The inter-H-atom distances shown there are only rough estimates, based on stereochemical considerations, but a later neutron-diffraction study of *trans*-cyclodecane-1,6-diol [84] confirms that the actual distances are much shorter than the normal *van der Waals* separation and must correspond to severe mutual repulsions. Removal of intra-annular H-atoms should stabilize the conformation, and so we can expect trigonal C-atoms, such as carbonyl C-atoms, as well as heteroatoms, such as O, N, *etc.*, to go preferentially into the ring positions marked *A* or *C*. Indeed, this is the case [85]. Moreover, substituents bulkier than the H-atom will tend to avoid the intra-annular positions; if the substitution pattern is such as to force a substituent into one of them, then the *Fig. 20* ring conformation will become untenable and another conformation can be expected.

This was the idea behind the preparation and study of 1,1,5,5-tetramethylcyclodecane-8-carboxylic acid; there is no way in which all four Me groups can be accommodated in strain-free positions in the *Fig. 20* conformation. The conformation found in the crystal [86] is shown in *Fig. 23*, and it certainly looks different from the one previously found. It also shows a number of disturbing features. Whereas the longer ring-segment between the Me groups shows more or less normal bond distances (1.50–1.55 Å) and

Fig. 23



162. Die Strukturen der mittleren Ringverbindungen XII. Kristallstruktur der 1,1,5,5-Tetramethylcyclodecan-8-carbonsäure

von **J. D. Dunitz** und **H. Eser**

(15. VI. 67)

Fig. 2. *Im Kristall beobachtete Konformation der 1,1,5,5-Tetramethylcyclodecan-8-carbonsäure*

Links: Bindungs- und Torsionswinkel

Rechts: Bindungslängen und *B*-Werte für je die grösste Hauptachse der Temperaturfaktor-Ellipsoide. Die Pfeile stellen die Richtungen dieser Hauptachsen dar.

angles (112–117°), the shorter segment is apparently associated with quite abnormal values: the short distances C(2)–C(3) and C(3)–C(4) and the bond angles at atoms C(2), C(3), and C(4) (136°, 135°, 124°, respectively) lie so far from the normal range as to appear highly implausible. Also, while the *B* values ($B = 8\pi^2\langle u^2\rangle$ where $\langle u^2\rangle$ is the mean-square displacement amplitude of the atom from its mean position) of the atoms in the larger ring segment are not too far from isotropic and lie in the usual range found in other medium-ring derivatives, the ring atoms C(2) and C(3) as well as the Me C(13) have highly anisotropic displacements with *B* values as large as 20 Å^2 in certain directions. This could mean either that the atoms in question actually carry out thermal vibrations of extremely large amplitude or else that the structure is disordered. For example, one could imagine that different molecules in the crystals do not have quite identical conformations, the differences affecting mainly the atoms with the very large *B* factors. In such a case, bond lengths and angles calculated from the averaged positions would be in error [87].

An explanation of the abnormal features could be given in terms of a disorder model, based on two new ring conformations (*A* and *B*, *Fig. 24*) found by molecular-mechanics calculations, a method that was just then being developed into a powerful technique for studying problems of molecular structure [88]. The two conformations *A* and *B* had calculated strain energies of 2.1 and 3.1 kcal mol^{-1}, respectively, relative to the stable conformation. Both possess a twofold axis of symmetry; in *A* it passes through opposite atoms, in *B* through opposite bonds. Although they may look quite different, the two

Fig. 24

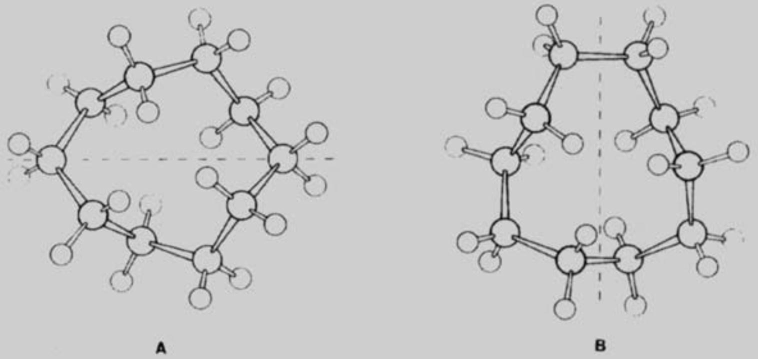


Fig. 3. *Die zwei neuen Konformationen des Cyclodecanrings mit den verschiedenen Stellungen der zweizähligen Drehachsen*

rings can be superimposed in such a way that the positions of eight atoms in each can be made to coincide quite closely. The two that cannot be made to fit are just the atoms C(2) and C(3) in *Fig. 23*. To a good approximation, the apparent positions of the atoms in the crystal structure correspond to a weighted average of those in the two calculated structures, suggesting that the crystal contains a mixture of the two. Also, when the rings are optimally superimposed, there is a good correlation between the lengths and directions of the vectors joining corresponding atoms, including the Me groups, and the principal axes of the temperature-factor ellipsoids. In general, during the 60's, there was a constant interplay between the results of experimental work and those of molecular-mechanics calculations, which led to the development of vastly improved force-fields.

Because of the difficulty in obtaining suitable material for X-ray studies [89], only one crystalline cyclononane derivative, cyclononylamine hydrobromide, was analyzed in detail in this series [90]. As shown in *Fig. 21*, the crystal contains conformational isomers. The asymmetric unit consists of two molecules, which have similar ring conformations but with the ammonium substituent in a different position in the ring.

As far as the eight-membered ring is concerned, crystal structure analyses of both isomers of cyclooctane-1,2-carboxylic acid led to a mirror-symmetric 'boat-crown' ring conformation (*Fig. 22*). In the *trans*-isomer [91], the substituents occur at the crown-like end of the ring, one of them almost in the approximate mirror plane; in the *cis*-isomer [92], both substituents are on the same side of the mirror plane (on atoms C(7) and C(8) in *Fig. 22*). In earlier spectroscopic and gas-phase electron-diffraction studies, the boat-chair conformation was not taken seriously into consideration, but it was soon found to give a satisfactory interpretation of NMR data in solution [93] and seems to be favored by 1–2 kcal mol^{-1} over alternative forms.

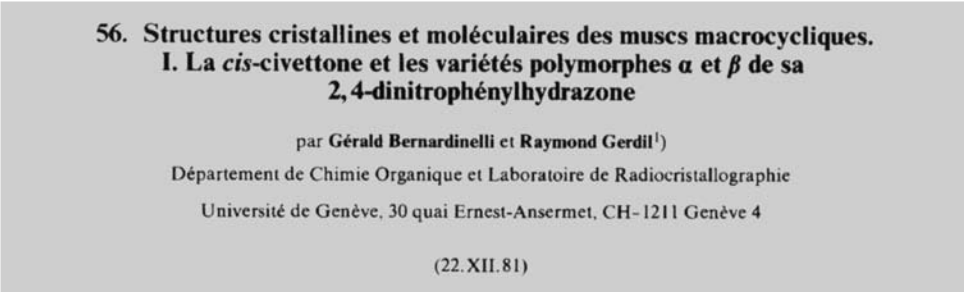
The conformational trends and regularities found in the early work on medium rings have been largely confirmed by force-field calculations [94] and by many more recent structure analyses of a large variety of compounds. For example, one extensive study [95] includes descriptions of ten crystal structures of compounds containing variously substituted 8-, 9-, 10-, 11-, 12- and 14-membered macrocyclic ketones.

The knowledge about the stable conformations of the medium rings can be used to explain otherwise puzzling aspects of the chemical reactivity of their compounds. For example, the acetolysis of cyclodecyl *p*-toluenesulfonate has several features that distinguish it from the corresponding reaction of the cyclohexane derivative [96], and the *Beckmann* rearrangement of cyclooctane-1,5-dione dioxime yields only the mirror-symmetric diamide product [97] [98], in contrast to other symmetrical alicyclic diketoximes, which yield mixtures of the possible isomeric cyclodiamides [99]. Nevertheless, in medium-ring chemistry, reactivity arguments in terms of a particularly favored molecular conformation need to be exercised with some caution. Unlike the chair form of cyclohexane, the medium rings are torsionally flexible molecules and are characterized by the availability of several almost equi-energetic conformations, as suggested by the frequent occurrence of disordered crystal structures and confirmed by molecular mechanics calculations.

The medium-ring work showed the advantages of doing X-ray crystal structure analyses not just for individual compounds that happened to be of particular interest or importance for one reason or another, but of making systematic studies of a series of related compounds. Besides, during the decade or so when this work was done, the experimental and computational techniques of crystal structure analysis went through a major transformation, resulting from developments in electronics and computer technology. The age of computer-controlled diffractometers, direct methods, automatic structure refinement, had firmly established itself.

A later connection with the earlier work on large rings is provided by a series of papers by *Bernardinelli* and *Gerdil* on the crystal structures of macrocyclic musks and their 2,4-dinitrophenylhydrazone (DNPH) derivatives. The *cis*- and *trans*-isomers of civetone (= cycloheptadec-9-en-1-one) form isomorphous tetragonal plastic crystals [100]. These crystals are highly disordered – the molecules appear merely as ring-shaped diffuse electron-density distributions – so that no detailed structural information can be obtained from them, not even from measurements made at 153 K. The DNPH derivatives are another matter, they yield detailed pictures of the molecular conformations (*Fig. 25*). As is also often found for medium-ring compounds, the *cis*-isomer occurs in two polymorphic forms that contain different conformations of the macrocycle. Crystalline muscone is also disordered [101], and so is its DNPH derivative, but here the disorder could be resolved by analysis of the anisotropy of the displacement parameters in terms of four almost equi-energetic conformations.

Fig. 25



56. Structures cristallines et moléculaires des muscs macrocycliques.
I. La *cis*-civettone et les variétés polymorphes α et β de sa
2,4-dinitrophénylhydrazone

par **Gérald Bernardinelli** et **Raymond Gerdil**1)

Département de Chimie Organique et Laboratoire de Radiocristallographie

Université de Genève, 30 quai Ernest-Ansermet, CH-1211 Genève 4

(22.XII.81)

Fig. 25 (cont.)

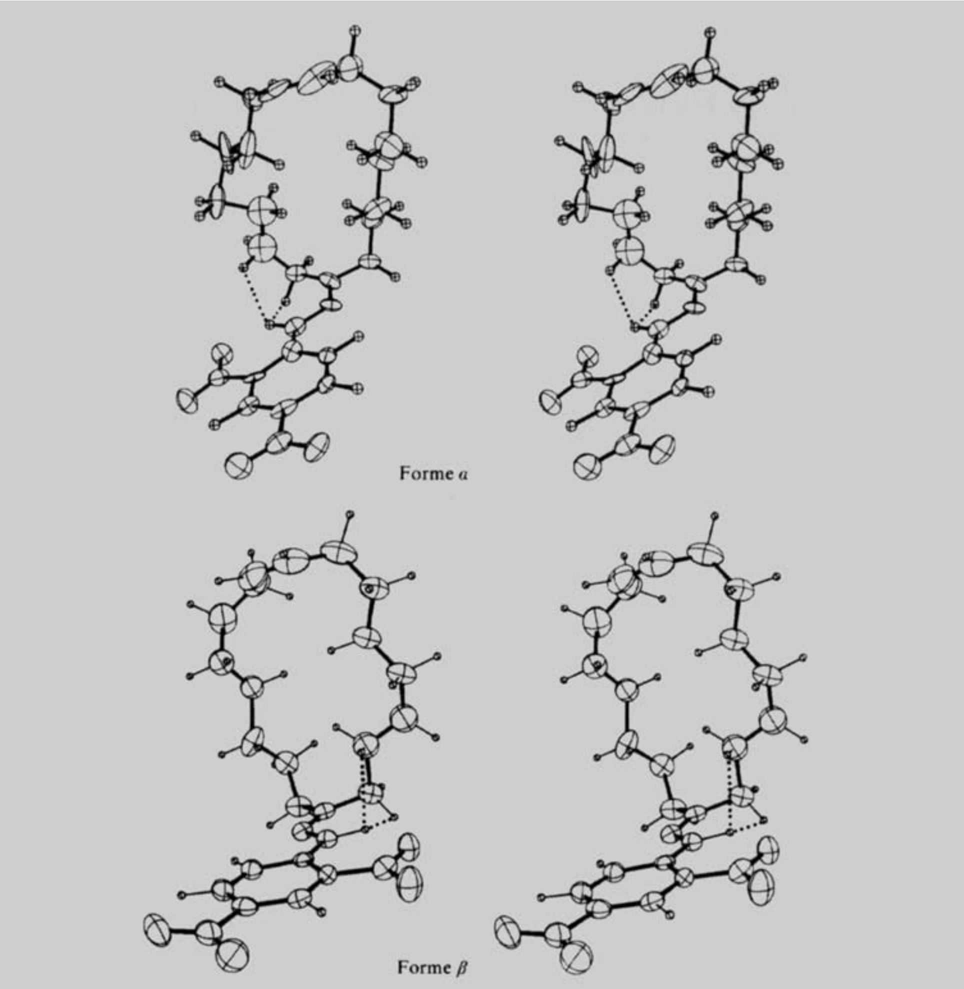
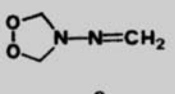


Fig. 4. *Vues stéréoscopiques des deux conformations observées pour la 2,4-dinitrophénylhydrazone (polymorphe) de la* cis-*civettone*. Les interactions déterminantes entre macrocycle et substituant sont représentées en traits pointillés.

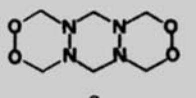
From 1960 onwards. Some Selected Structures. – One very simple crystal structure determination from the early 60's should be mentioned not because of its intrinsic importance but because of the light it throws on the level of communication among different structural groups in Switzerland at that time. It is a paper by *H. R. Oswald* from Bern on the crystal structure of anhydrous chromium(II) chloride [102], published almost simultaneously with a multi-authored paper [103] in *Acta Crystallographica* on exactly the same topic. At that time such multi-authored papers in chemistry were still a rarity, and the presence of nine names of authors, from four different laboratories (Seattle WA, Zurich, Ames IA, Oak Ridge TE) is no reflection on the scientific importance of the paper, it arose merely from the circumstances that led to its publication. $CrCl_2$ was of interest at the time, because it was one of the few anhydrous metal dichlorides whose structure remained unknown (crystals of $CrCl_2$ are highly deliquescent and when moist are immediately oxidized in air). In most of the other anhydrous dichlorides the metal is either octahedrally (*e.g.*, Mg, Ni, Co, Fe, Mn) or tetrahedrally (*e.g.* Zn [104]) coordinated), but there were good grounds for thinking that $CrCl_2$, like $CuCl_2$, would show a distorted octahedral $4 + 2$ coordination because of a static *Jahn-Teller* effect [105].

In August 1960, *Dunitz* attended a conference in Glasgow on computing methods and the phase problem [106]. During one of the breaks between lectures, he happened to meet his former doctoral student *Peter Pauling* and mentioned to him that, among other recent achievements of the young Zurich laboratory. *Hans-Christan Mez* had made single-crystal photographs of anhydrous $CrCl_2$ and had shown that it was indeed a distorted rutile-type structure with $4 + 2$ coordination of the metal atoms. (This was not such a tremendous achievement, even by the standards of the early 60's, because the structure could be read off, more or less by inspection, from a couple of precession photographs made in a single afternoon. The difficult thing was to protect the crystals from the moist air in the laboratory during the X-ray photography; the thin needles were covered with liquid paraffin, drawn by capillary attraction into a thin-walled glass capillary tube, which was sealed after removal of the excess liquid by capillary attraction into a second capillary with smaller bore.) *Pauling* told *Dunitz* that by coincidence he had heard about the same structure from *R.E. Rundle*, who was also present at the Glasgow meeting. *Dunitz* and *Rundle* discussed the matter at the first opportunity. It was confirmed that the same structure had been determined almost simultaneously at Iowa State College and in Zurich, and, what is more, as *Rundle* had learned, it had also been determined in *E.C. Lingafelter*'s laboratory in Seattle. After our return to our respective homes, as the result of correspondence between the three laboratories (no electronic mail, no FAX in those days), it was agreed that we should make a joint publication and that *Lingafelter* should act as coordinator. In the meantime, we had learned that a fourth independent structure analyses had been made by *Yakel* and *Wilkinson* at Oak Ridge, by a combination of X-ray and neutron powder diffraction, and these results were also included in the joint publication that eventually resulted [103]. While all this was going on among four laboratories thousands of kilometers apart, the same structure was being determined, independently and unknown to all of us, in Bern. It seems unlikely that such a lack of communication between the structural laboratories in Zurich and Bern could exist today.

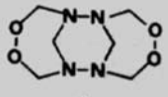
Most papers in *HCA* containing accounts of crystal structures analyses have been concerned with the determination or confirmation of structure of natural products, of their derivatives, and of compounds obtained in the course of synthetic studies. Metrical details, although usually given in tabular form, have seldom been at the focus of interest, and packing of the molecules in the crystal has usually been passed over completely. However, there are also examples of studies where the main interest was to derive results of mechanistic relevance, and there are others that concentrate on fine structural details in series of related compounds.



2



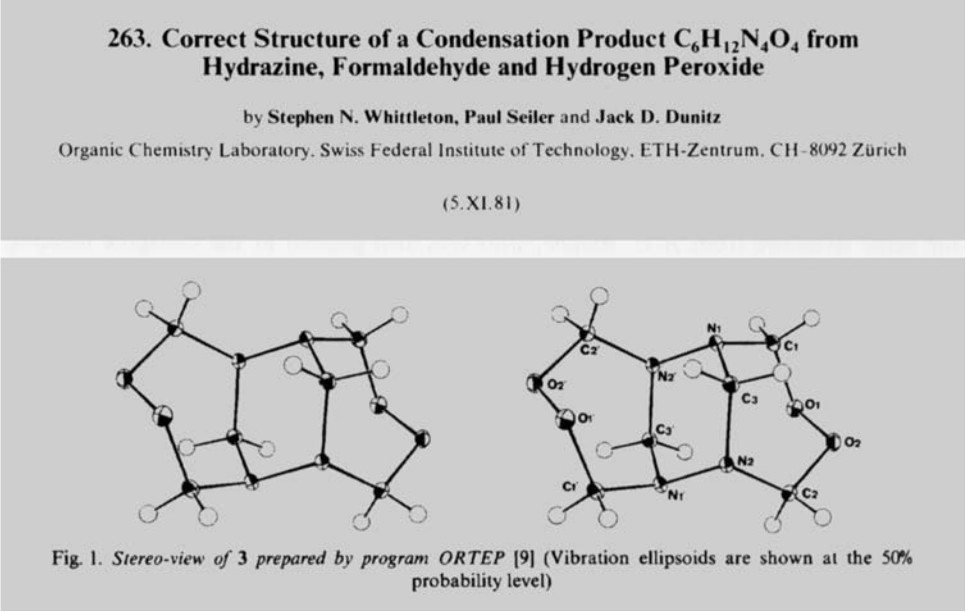
3



4

One case where crystal structure analysis led to a different structure from the one that had been assumed up to then is the compound obtained by the reaction of hydrazine with formaldehyde in the presence of H_2O_2. Originally assigned the monocyclic structure **2** [107], the compound was later shown to have double molecular weight and was assigned the tricyclic structure **3**, mainly from its IR and UV spectrum [108]. The equilibrium among the various conformers of **3** was the subject of a ^{13}C- and ^{1}H-NMR (300 MHz) study with spectra measured down to 200 K [109]. However, the results of a low-temperature (96 K) X-ray study [110] leave no doubt that the structure is not **3** but **4** (*Fig. 26*).

Fig. 26



263. Correct Structure of a Condensation Product $C_6H_{12}N_4O_4$ from Hydrazine, Formaldehyde and Hydrogen Peroxide

by **Stephen N. Whittleton, Paul Seiler** and **Jack D. Dunitz**

Organic Chemistry Laboratory, Swiss Federal Institute of Technology, ETH-Zentrum, CH-8092 Zürich

(5.XI.81)

Fig. 1. *Stereo-view of* **3** *prepared by program ORTEP* [9] (Vibration ellipsoids are shown at the 50% probability level)

Since the series of condensation reactions leading to **4** are reversible, structure **4** must be thermodynamically more stable than **3**, even though it contains the two seven-membered rings whose existence was discounted in the arguments leading to the incorrect structure. In the seven-membered ring, the torsion angle about the O–O bond is 100°, close to the value of *ca.* 112° in H_2O_2. In a six-membered ring with approximately tetrahedral bond angles, it is impossible to obtain a torsion angle much greater than 60°. This may be the main reason for the relative stability of **4**. This substance was later the object of an accurate electron-density study, which compared the 'bonding' density in O–O, C–O, and N–N bonds [111].

With the development of low-temperature crystallography and of techniques for handling unstable, air-sensitive compounds at low temperatures, it was also becoming possible to do X-ray analyses of what had earlier been regarded as 'unstable intermediates'. Of course, the species that crystallize out in the course of a chemical reaction, apart from educts and products, are not necessarily intermediates, they may be merely the least soluble species. Thus, additional kinds of evidence are required, and if they are not available, then at least caution is called for in the interpretation of the results.

In the early 80's, a joint study between the *Seebach* and *Dunitz* groups on the structures of lithium enolates and related species was initiated, with the object of throwing light on the mechanistic aspects of their reactivity. It was known, mainly from NMR evidence, that for lithium enolates, ion-pair aggregates of various kinds, especially tetramers, are involved [112], but definitive information about the structures of these aggregates was completely lacking. The first two lithium enolates whose structures could be established by X-ray analysis, those derived from 3,3-dimethylbutan-2-one and from cyclopentanone, turned out to be indeed tetramers, both based on a Li_4O_4 cube with each Li-atom bonded additionally to the O-atom of a tetrahydrofuran solvent molecule

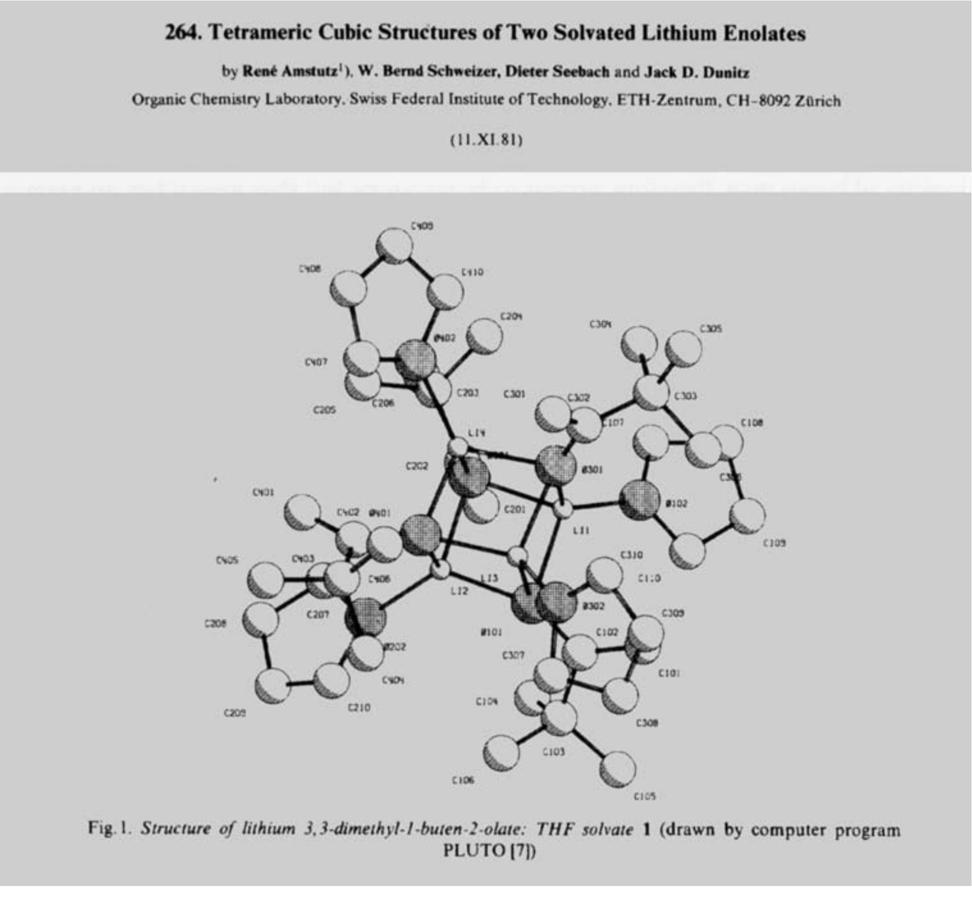


Fig. 27

264. Tetrameric Cubic Structures of Two Solvated Lithium Enolates

by **René Amstutz**[1]), **W. Bernd Schweizer, Dieter Seebach** and **Jack D. Dunitz**

Organic Chemistry Laboratory, Swiss Federal Institute of Technology, ETH-Zentrum, CH-8092 Zürich

(11.XI.81)

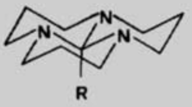
Fig. 1. *Structure of lithium 3,3-dimethyl-1-buten-2-olate: THF solvate* **1** (drawn by computer program PLUTO [7])

(*Fig. 27*) [113]. The implications of the tetrameric cubic structure for various facets of enolate chemistry, such as solubility, effects of co-solvents, addition to aldehyde, influence of mixed aggregates on diastereo- and enantioselectivities, are discussed in the adjoining paper [114]. The lesson is that complex structures held together by non-covalent bonds ('supermolecules') may dramatically influence the course of seemingly simple organic reactions. A comprehensive account of this and later related work has been given by *Seebach* [115].

Many papers from the *Seebach* group discuss relations between molecular structure and reactivity. In one recent example [116], conclusions are drawn from the structures of 21 molecules (mainly derivatives of 1,3-imidazoline, 1,3-oxazolidine, 1,3-dioxan-4-one, and hydropyrimidine-4*H*-one) determined by crystal structure analysis, about the role of amide groups in stereoselective synthesis. Impressive is the large number of molecules drawn into the discussion (although this is not primarily a structure-correlation study: see later). The paper probably also holds the *HCA* record for the number of authors, which even exceeds the number of molecules whose structures are described.

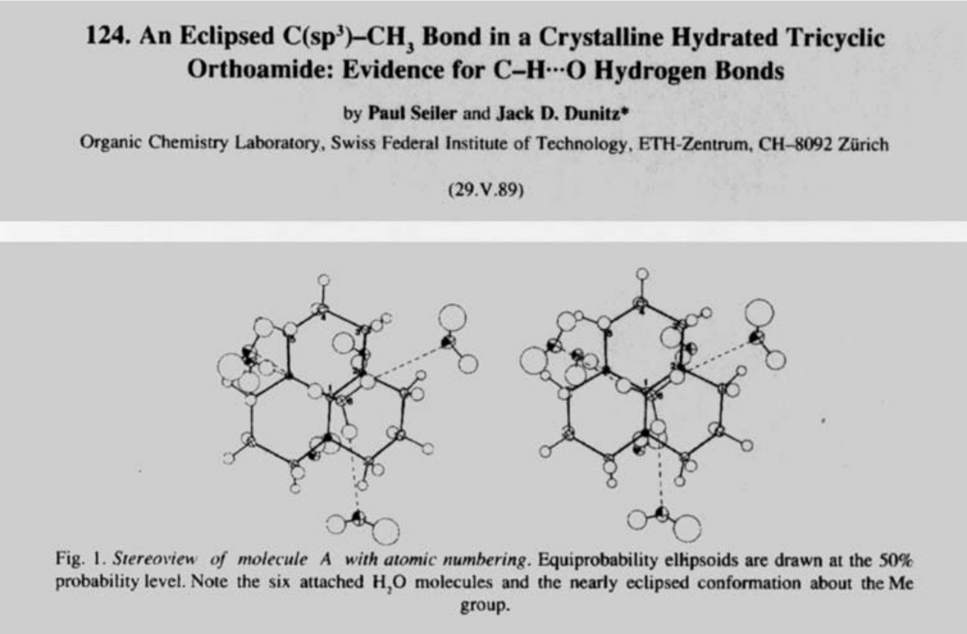
Apart from the mechanistic inferences that can be drawn from such structural studies, there is also the often posed question about the 'nature' of the bonds formed by Li-atoms (or ions?). Those to oxygen are usually regarded as 'ionic', those to carbon present more of a problem. In one of the papers [117] it is pointed out that the 2s electron of a Li-atom is so diffuse that only *ca.* 15% of the charge would be concentrated within a sphere of radius 1.1 Å centered on the Li nucleus, roughly half the distance between a Li-atom and its bonded neighbors; some 28% of the charge would still be outside a sphere of radius 2.4 Å, extending well past the nuclei of these neighbors. Questions about the degree of ionicity of bonds may, therefore, appear to be nugatory, but they were taken up again a few years later in an experimental X-ray study of lithium fluoroberyllate, Li_2BeF_4, where it was concluded that the superpositions of the neutral atom densities and of the conventional ion densities are very similar and not easily told apart [118], a conclusion that had been reached twenty years earlier by *J. C. Slater* [119]. A very thorough analysis of this problem is to be published shortly elsewhere [120].

A curiosity is described in a paper by *Seiler* and *Dunitz* [121]. Of the many thousands of Me groups attached to tetrahedral centers (we have not attempted to count how many), all except one are staggered. The exception is found in the crystal structure of the trihydrate of the orthoamide **5**. Here, each of the three N-atoms is H-bonded to a H_2O molecule, and two such triads of H_2O molecules form a six-membered ring with S_6 ($\bar{3}$) symmetry (imposed by the space group), thus involving every H_2O molecule in three H-bonds, two to neighboring H_2O molecules in the ring, and one to an orthoamide N-atom. That is not all; each H_2O molecule is engaged in an additional C–H···O interaction to a Me group, which is in *eclipsed* orientation with respect to the bonds



5a R = H
5b R = CH_3

Fig. 28



124. An Eclipsed C(sp³)–CH₃ Bond in a Crystalline Hydrated Tricyclic Orthoamide: Evidence for C–H···O Hydrogen Bonds

by **Paul Seiler** and **Jack D. Dunitz***

Organic Chemistry Laboratory, Swiss Federal Institute of Technology, ETH-Zentrum, CH-8092 Zürich

(29.V.89)

Fig. 1. *Stereoview of molecule A with atomic numbering.* Equiprobability ellipsoids are drawn at the 50% probability level. Note the six attached H_2O molecules and the nearly eclipsed conformation about the Me group.

emanating from the central, quaternary C-atom of the orthoamide (*Fig. 28*). Even though the H-atom positions in this structure were not determined by neutron diffraction, the eclipsed orientation of the Me group from the accurate low-temperature X-ray analysis seems above any doubt.

The trihydrate was obtained by low-temperature crystallization from 'dry' $CHCl_3$, and the H_2O must be held extremely strongly since it can be removed only by distillation over $Ca(OH)_2$. The crystal structure of the anhydrous orthoamide contains two molecules in the asymmetric unit, one with the same (all-*trans*)-configuration as in the trihydrate but with the usual staggered conformation of the Me group, the other with the *cis,cis,trans*-configuration (*Fig. 29*).

From *ab initio* calculations [122], the staggered conformation in the free molecule is more stable than the eclipsed by *ca.* 5.1 kcal mol^{-1} (considerably more than in ethane). Thus, the extra stabilization contributed by the three $C-H\cdots O$ bonds per molecule of orthoamide must be at least this amount. On the other hand, previous theoretical estimates of $C-H\cdots O$ interaction energies are much less than that required here [123]. What is missing in those estimates is the augmenting effect in an extended cooperative system of coupled H-bond donors and acceptors. Attempts to model this kind of cooperativity by *ab initio* calculations on simple coupled systems have led to only modest success [122], but, in any case, the contrast between the eclipsed conformation in the trihydrate with directed $C-H\cdots O$ bonds and the staggered conformation in the anhydrous crystal is an impressive demonstration of stabilization due to $C-H\cdots O$ bonds.

Fig. 29

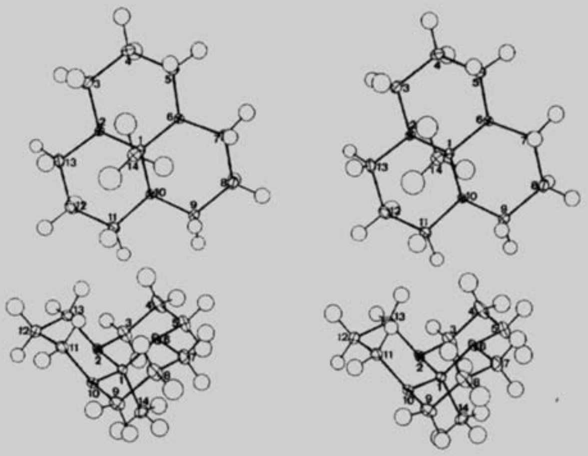


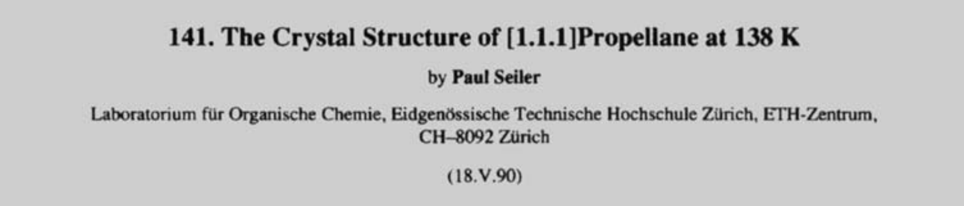
Fig. 2. *Stereoview of molecules B* (all-*trans* configuration, above) *and C* (*cis,cis,trans* configuration, below) *with atomic numbering*. Equiprobability ellipsoids are drawn at the 50% probability level.

Not too long ago, most chemists would have regarded a publication on the crystal structure of [1.1.1]propellane (**6**) as a practical joke, suitable for the 'Journal of Irreproducible Results' or its like. Yet, as *Wiberg* showed [124], contrary to widespread belief, the compound can be prepared and kept for long periods of time at reduced temperature.

6

Subsequently, *Szeimies* and coworkers developed an elegant synthesis whereby the compound can be made in large quantities [125]. So no one should have been surprised when *Seiler* described the crystal structure [126] (*Fig. 30*). Some readers may have turned the pages eagerly in expectation of information about the electron density and the problem-

Fig. 30



141. The Crystal Structure of [1.1.1]Propellane at 138 K

by **Paul Seiler**

Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule Zürich, ETH-Zentrum,
CH-8092 Zürich

(18.V.90)

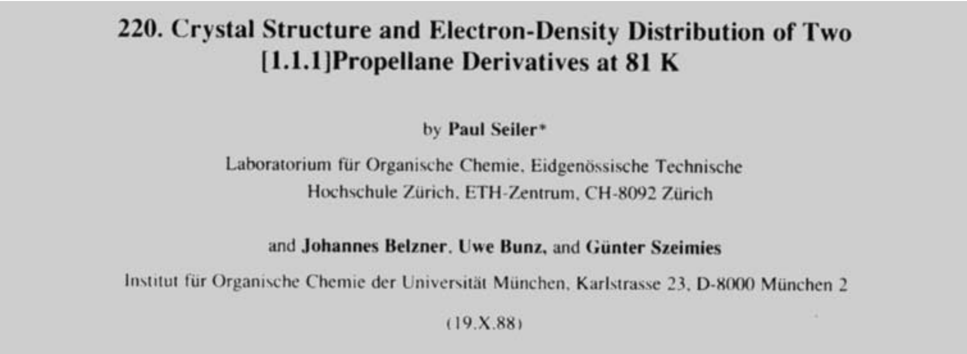
atic nature of the bonding in this unusual molecule; they would have been let down. Disappointingly, the crystal structure at 138 K is complex, with four molecules in the asymmetric unit (space group *C*2), and of the four, two are rotationally disordered. The crystal quality was poor, and, moreover, on further cooling, there is a phase transformation to a structure whose exact nature could not be elucidated; no chance of measuring the high-quality, extensive data set that would be needed for highly accurate bond lengths or for an electron density study.

In the absence of this information for [1.1.1]propellane itself, we have to be content with the results of an earlier study of the two derivatives **A** and **B** [127]. In both molecules, the problematic central bond between the inverted C-atoms is longer than normal, although not by much (1.587 and 1.585 Å in **A** and **B**, respectively, corrected for librational motion), while the other bonds in the three-membered rings are slightly short (1.52–1.54 Å), as they usually are. (Other estimates of the length of the problematic bond are in the range 1.57 to 1.60 Å.) Electron-density difference maps, derived by substracting the thermally averaged 'pro-molecule' density from the actual density, are shown in *Fig. 31*. While the bonds of the three-membered rings (*e.g.* C(1)–C(2), C(1)–C(4), *etc.*) show the characteristic residual density *outside* the internuclear lines – 'banana' bonds – the problematic bond C(2)–C(4) shows no residual density in the region between the nuclei, although there are small, diffuse, residual density accumulations at the inverted atoms C(2) and C(4) outside the bridgehead bond. (In interpreting the difference maps,


A


B

Fig. 31


220. Crystal Structure and Electron-Density Distribution of Two [1.1.1]Propellane Derivatives at 81 K

by **Paul Seiler***

Laboratorium für Organische Chemie, Eidgenössische Technische
Hochschule Zürich, ETH-Zentrum, CH-8092 Zürich

and **Johannes Belzner**, **Uwe Bunz**, and **Günter Szeimies**

Institut für Organische Chemie der Universität München, Karlstrasse 23, D-8000 München 2

(19.X.88)

Fig. 31
(Forts.)

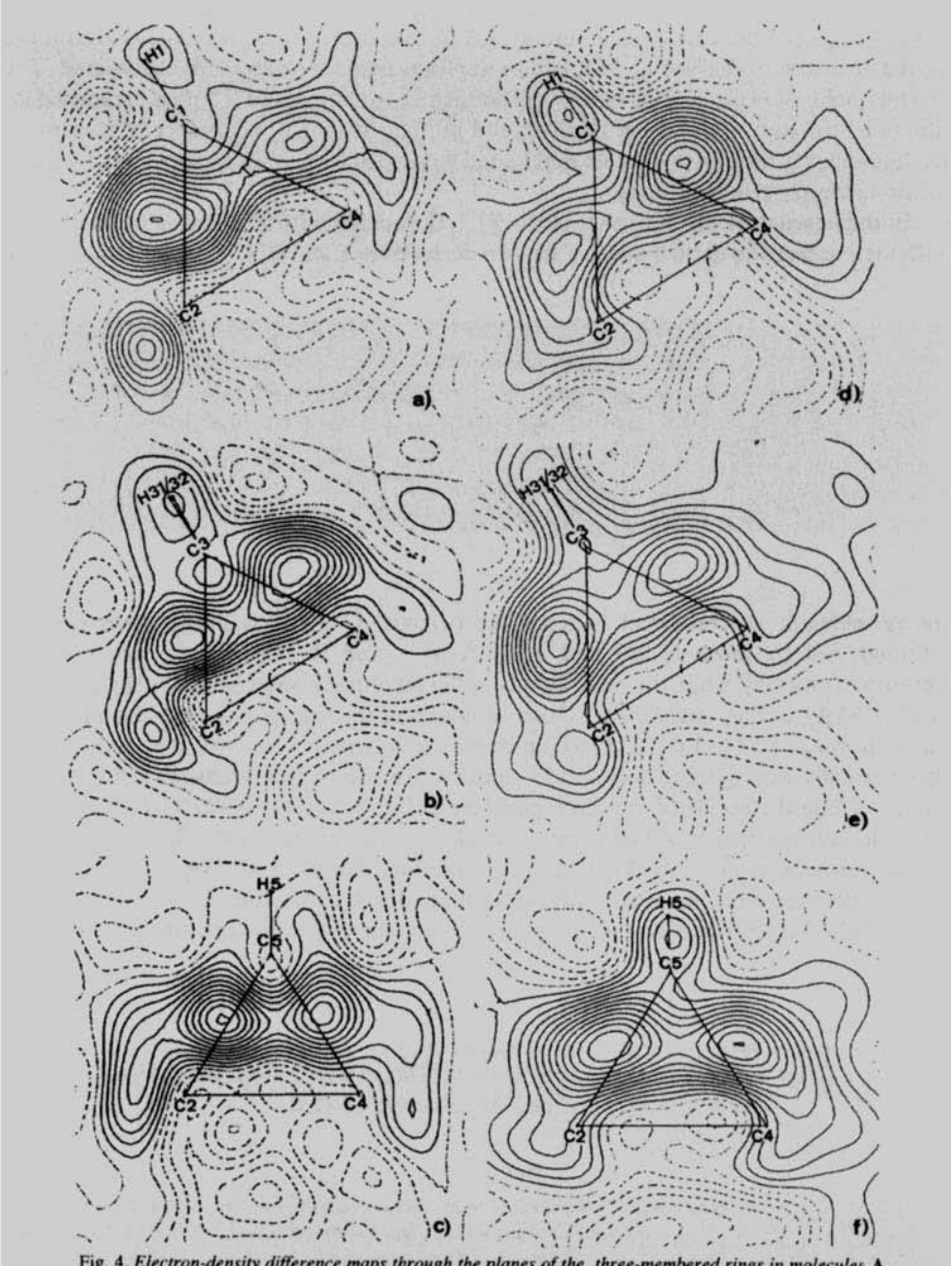
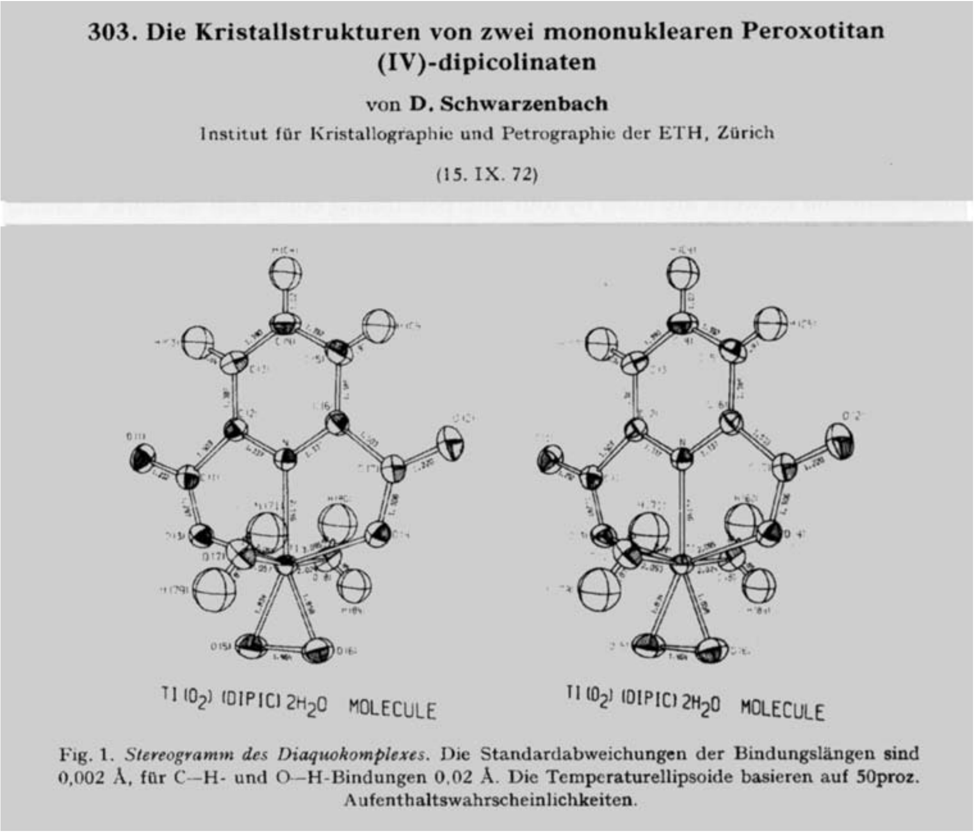


Fig. 4. *Electron-density difference maps through the planes of the three-membered rings in molecules* **A** (a-c) *and* **B** (d-f). Contours are drawn at intervals of 0.025 e/Å^3 .

it should be remembered that positive and negative residual density imply a concentration and diminution of charge, respectively, in the internuclear region. Lack of residual density need not necessarily imply the absence of a chemical bond, it simply means that the total density is indistinguishable from that obtained by superposition of the densities of the reference atoms, here, as usual, taken as spherically symmetrical. This choice of reference states is the only one that does full justice to the loss of symmetry of an isolated atom when it becomes part of a molecule.)

From our discussion so far the reader could have formed the impression that the post-1960 era of *HCA* was concerned primarily with organic structures; this is a mistake and must be corrected. Many interesting and important contributions to inorganic structural chemistry have appeared, also in the post-1960 period. We mention two papers from the 1970's, a period when there was a considerable interest in the structures of dioxygen complexes with transition metals. One is concerned with the structures of two mononuclear peroxotitanium dipicolinates: $[TiO_2(C_7H_3O_4N)(H_2O)_2] \cdot 2H_2O$ and $K_2[TiO_2(C_7H_3O_4N)F_2] \cdot 2H_2O$. In both the Ti-atoms can be described as having pentagonal bipyramidal coordination, the peroxo group and the chelate ligand occupying equatorial sites with the two H_2O or F^- groups at the apices (*Fig. 32*). The structure analysis is

Fig. 32



303. Die Kristallstrukturen von zwei mononuklearen Peroxotitan (IV)-dipicolinaten

von **D. Schwarzenbach**

Institut für Kristallographie und Petrographie der ETH, Zürich

(15. IX. 72)

Fig. 1. *Stereogramm des Diaquokomplexes.* Die Standardabweichungen der Bindungslängen sind 0,002 Å, für C–H- und O–H-Bindungen 0,02 Å. Die Temperaturellipsoide basieren auf 50proz. Aufenthaltswahrscheinlichkeiten.

an unusually accurate one for the time, and the paper contains a very detailed discussion of the packing and H-bonding. It is suggested that the O–H distances observed in the crystal structure indicate that the di-aquo complex, which is a strong acid ($pK_a \approx 1.85$), is on the way towards the transition state leading to a hydroxonium salt – a bold proposal!

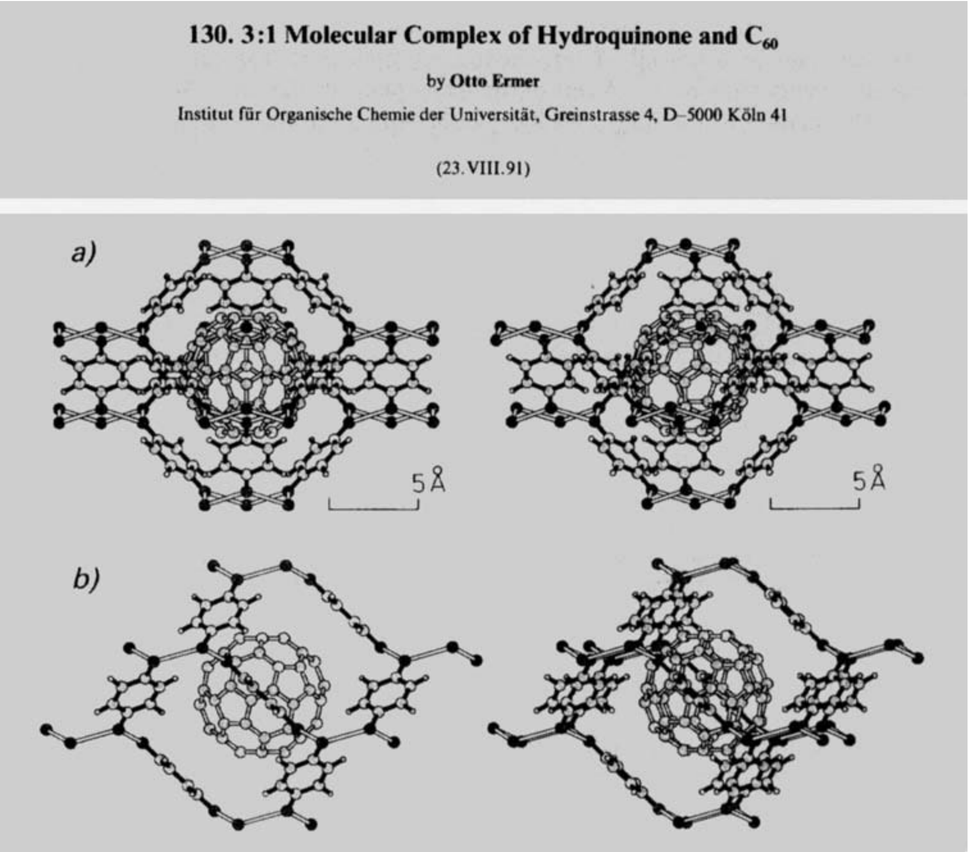
The structures of binuclear Co complexes are the subject of two papers from Basel, dealing with the preparation and crystal structure of $[(tren)Co(O_2,OH)Co(tren)](ClO_4)_3 \cdot 3H_2O$ [129] and of $[(tren)(NH_3)Co(O_2)Co(NH_3)(tren)](SCN)_4 \cdot 2H_2O$ [130]. In the first complex, prepared by oxygenation of $[Co(tren)(H_2O)_2]^{2+}$ in alkaline solution, the five-membered $Co(O_2,OH)Co$ ring is in a twist conformation with the two dioxygen atoms out of the plane of the other three. From the bond lengths (O–O, 1.46 Å), this is a peroxo complex, so the reaction with oxygen has led to oxidation, $Co^{2+} \rightarrow Co^{3+}$. In the second complex, the Co–O–O–Co system is planar with an O–O distance of 1.51 Å and Co–O–O angles of 111.5°. A later review of Co(dioxygen) complexes [131] fails to mention these papers, presumably because they are in German.

Crystal Architecture: Inclusion Compounds. – In the area of crystal design, crystal architecture, and crystal packing, a paper by *W. Oberhänsli* and a series of papers by *O. Ermer* and co-workers on inclusion compounds stand out. A key observation by *Ermer* was that adamantane-1,3,5,7-tetracarboxylic acid, where the four COOH groups are arranged tetrahedrally, forms a super-diamond architecture held together by pairwise H-bonds between COOH groups [132]. In the crystal, the large empty spaces in the super-diamond network are filled by four interpenetrating equivalent networks, leading to a fivefold diamond-like structure. Thus, this crystal can be viewed as a 'degenerate' inclusion compound or self-inclusion compound. Small changes in the adamantane core, such as the introduction of oxo or methylidene groups, prevent the fivefold interpenetration and hence lead to a propensity for inclusion of guest molecules, since lower degrees of interpenetration cannot be achieved without holes. Thus, the 2,6-dimethylidene tetracarboxylic acid forms inclusion compounds with several guest species, such as mesitylene and (*tert*-butyl)benzene, in which the host architecture consists of two interpenetrating super-diamond networks [133]. Crystals of the free uncomplexed compound have not been obtained, but a stable monohydrate may be crystallized from aqueous solution and has been shown also to have a structure based on interpenetrating networks. Similarly, the 2,6-dioxo compound consists of three such interpenetrating networks and forms an inclusion compound with AcOH [134].

These and similar considerations led *Ermer* to re-examine the well known *β*-hydroquinone (HQ) structure, determined many years ago by *Palin* and *Powell*, the historical origin of the concept of 'clathrate' inclusion compounds [135]. The *β*-HQ structure can be regarded as being built from two interpenetrating (translationally equivalent) super-cube networks. The corners of the super-cubes are made up of H-bonded $(OH)_6$ rings, from which six *p*-phenylene groups emanate in distorted octahedral fashion. These groups represent the edges of the super-cubes and act as bridges between the $(OH)_6$ corners. In spite of the twofold interpenetration, the *β*-HQ structure still contains cavities capable of accommodating small guest molecules, such as H_2S, CH_3OH; CH_3CN, *etc.*, studied by *Powell* and his coworkers in the early work on clathrates [134].

Ermer noticed that the super-cube cavities of a single *β*-HQ network would be just about the right size to accommodate an icosahedral C_{60} molecule to give a host-guest complex with $3HQ \cdot C_{60}$ stoichiometry and accordingly prepared the complex by crystallizing the solution containing the stoichiometric proportions of the components [136]. *Fig. 33*, which shows this beautiful structure, is deceptive. Although the enclathration of the C_{60} guest molecules (since they are enclosed in 'cages' it might be more appropriate to call them prisoners) is rather tight, they are rotationally disordered. At room temperature, the C_{60} molecule shows up essentially as a spherical shell of electron density, thus preventing the determination of bond distances. Additional diffraction measurements at 100, 200, 295, and 373 K show that disorder persists down to 100 K [137]. The essence is that the C_{60} molecule can take up two preferred orientations. The one shown in *Fig. 33* is actually the less important, the main orientation being obtained from it by an anticlockwise rotation of *ca.* 25° about a crystallographic twofold axis (shown on the left side of *Fig. 33b*). In any case, *Ermer*'s work shows the potentialities of designing supramolecular solid-state complexes by crystal engineering.

Fig. 33



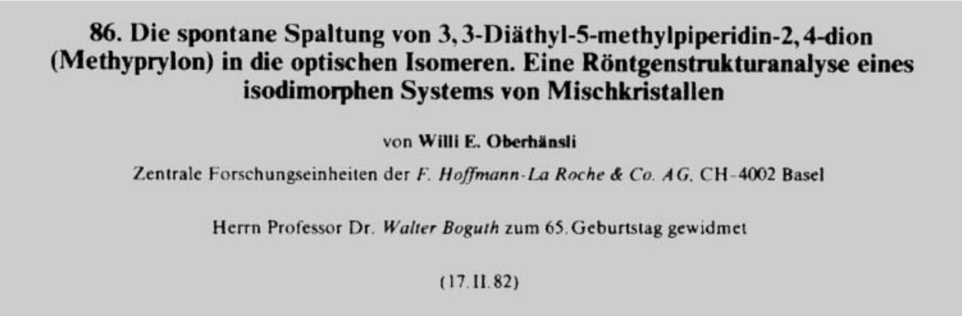
130. 3:1 Molecular Complex of Hydroquinone and C_{60}

by Otto Ermer

Institut für Organische Chemie der Universität, Greinstrasse 4, D-5000 Köln 41

(23.VIII.91)

Fig. 34



86. Die spontane Spaltung von 3,3-Diäthyl-5-methylpiperidin-2,4-dion (Methyprylon) in die optischen Isomeren. Eine Röntgenstrukturanalyse eines isodimorphen Systems von Mischkristallen

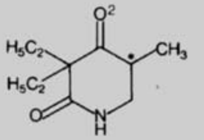
von **Willi E. Oberhänsli**

Zentrale Forschungseinheiten der *F. Hoffmann-La Roche & Co. AG*, CH-4002 Basel

Herrn Professor Dr. *Walter Boguth* zum 65. Geburtstag gewidmet

(17.II.82)

One paper that should be read by all chirosophists and solid-state scientists deals with a phenomenon related to intercalation interactions and packing, namely with the remarkable spontaneous resolution of racemic **7** [138] (*Fig. 34*); remarkable because, following the observation that the synthetic compound showed a small optical activity, several hundred fractional crystallizations were needed to obtain complete separation of the pure enantiomers [139]. *Oberhänsli* measured the unit cell parameters of crystals of several compositions and determined the detailed structures of the racemic crystal, of the pure enantiomer, and of a crystal of intermediate composition. The molecule **7** has the stereogenic center C(5) *ca.* 0.5 Å out of the mean plane of the other five ring atoms (a 'sofa' conformation of the ring) with the pseudo-equatorial Me C-atom almost in that plane. The other ring substituents are either in the plane or are mirror-symmetrically related across the plane; apart from C(5) the molecule is achiral. Thus, if a molecule with (*R*)-configuration at C(5) is inserted into a crystal of molecules with (*S*)-configuration, all the atoms in the intruder molecule except C(5) can occupy the same sites as the atoms of an (*S*)-molecule – only C(5) will be on the wrong side of the plane of the other heavy atoms. This explains why molecules of (*R*)-**7** can so easily enter into solid solution in a crystal of (*S*)-**7**. The packing energy is altered only slightly, and the disordered crystal has a higher entropy than the enantiomerically pure, ordered one. Crystals of pure (*R*)-**7** and (*S*)-**7** should, of course, be enantiomorphic. The almost complete miscibility of the two enantiomers in the solid state implies, however, that in the limit there must be two crystal modifications. One of them, the stable one, has molecules of (*R*)-**7** in the optimal crystal structure of the pure enantiomer (*R*)-**7**. If (*S*)-**7** molecules are now mixed into this crystal structure in increasing amounts, a situation can be imagined in which all the (*R*)-**7**

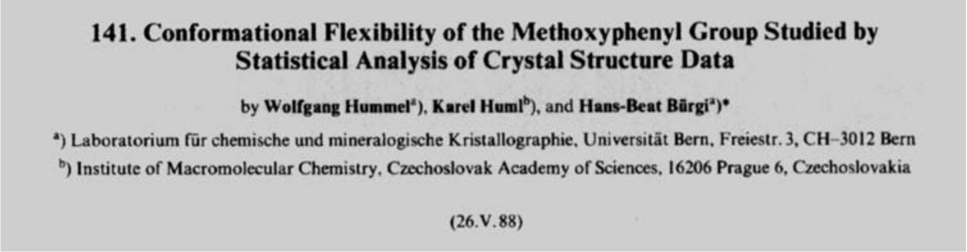


7

molecules have been replaced by their enantiomers. As far as the atomic arragement is concerned, this is still the (*R*)-**7** crystal structure but with all the C(5) atoms on the 'wrong side' of the respective mean molecular planes. This crystal structure is not isometric with the former, so the two must have slightly different energies. In fact, Oberhänsli was able to estimate the cell constants of these two crystal modifications, whereby the one that is metastable at room temperature has a slightly smaller volume and may possibly be the more stable one at lower temperature.

Structure Correlation Studies. – As the amount of structural information from available crystal structures began to increase, papers on structure correlation started to appear in *HCA* (an early example, dealing with preferred approach directions of nucleophiles to sulfonium ions, was mentioned in the introduction – see *Fig. 2*). This is not the place to go into the various statistical methods and models that have been used in such studies – they are discussed in detail in a forthcoming book [140]. We merely emphasize that from a collection of related structures one can obtain information that is qualitatively different from what one can learn from a single structure, however interesting or important that may be. From one point of view, the series of related structures can be regarded as a set of still photographs, which, properly arranged in the right order, may reveal a kind of cinematic record of how molecules move, of how the various possible motions are coupled. From another viewpoint, we can assume that for flexible molecules or fragments of molecules, conformations that are found to occur often are energetically stable and correspond to low-energy regions of the molecular potential-energy hypersurface, while conformations that occur rarely or not at all correspond to the high-energy regions. We mention here one representative study that confirms and substantiates certain structural regularities of importance in molecular design: the preferred conformations of the MeO and AcO groups attached to aromatic systems [141]. A histogram of twist angles in 480 MeOPh fragments from 261 structures retrieved from the CSD is shown in *Fig. 35*, together with a potential-energy profile based on *ab initio* calculations for anisole. While most structural chemists were probably aware that the MeO group tends to lie in the aromatic plane, the subsidiary cluster corresponding to the perpendicular orientation might come as a surprise to some and is nicely matched by the subsidiary minimum in the calculated potential energy.

Fig. 35



141. Conformational Flexibility of the Methoxyphenyl Group Studied by Statistical Analysis of Crystal Structure Data

by **Wolfgang Hummel**[a]), **Karel Huml**[b]), and **Hans-Beat Bürgi**[a])*

[a]) Laboratorium für chemische und mineralogische Kristallographie, Universität Bern, Freiestr. 3, CH-3012 Bern
[b]) Institute of Macromolecular Chemistry, Czechoslovak Academy of Sciences, 16206 Prague 6, Czechoslovakia

(26.V.88)

Fig. 35 (cont.)

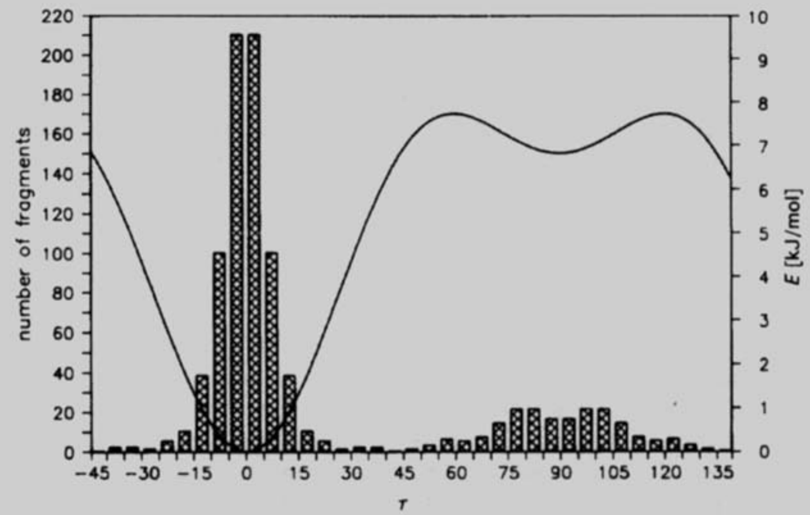


Fig. 2. *Histogram of twist angles τ in MeOPh fragments.* The solid line shows potential energy as a function of τ as obtained from *ab initio* calculations for anisole [10].

The corresponding histogram for AcOPh fragments [142] (*Fig. 36*) shows that the ester group has a strong tendency to adopt an orientation where its plane is perpendicular to the aromatic plane. As the group is twisted away from the plane, the bond angles change so that the carbonyl O-atoms moves from the position it would have in a planar

Fig. 36

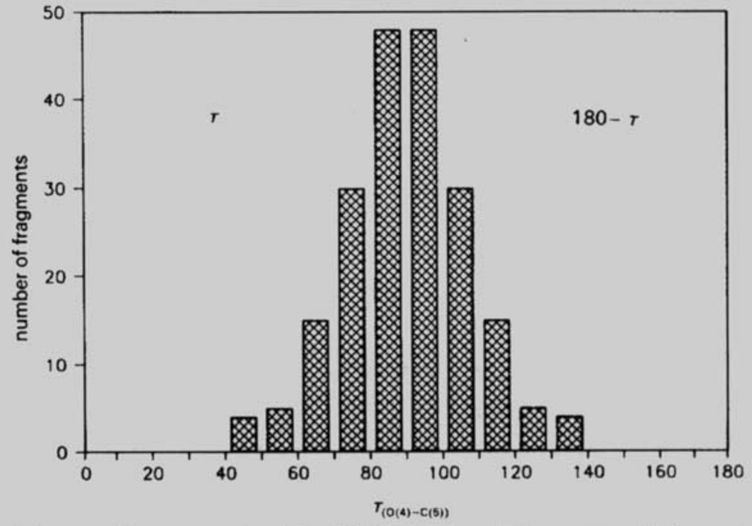


Fig. 3. *Histogram of $\tau_{(O(4)-C(5))}$ twist angles in AcOPh fragments.* τ and 180 – τ correspond to the symmetry related conformations in *Fig. 2.* Here, XX1 and XX2 are considered equivalent, even if they are chemically different.

ester group so as to keep maximal distance to the *ortho*-H-atoms. There are many analogies and similarities between the structural properties of the ester group and the amide group, but this is one of the rare cases where there is a difference, for the acetanilido group tends to lie in the same plane as the aromatic system [143]. The difference is due to the difference in electronic structure of the two groups. While the ester O-atom has two orthogonal lone pairs for conjugation with the C=O group and the aromatic π system, the amide N-atom has only one that has to conjugate simultaneously with the two groups.

These studies (and also the one on sulfonium ions) made use of information from the available storehouse of known crystal structures. Other studies have been based on systematic series of crystal structures analyses of specific compounds, chosen to provide the particular type of structural information that is sought. Naturally, one chooses the first method when enough information is already available. Sometimes, however, the available information is not conclusive enough, merely provocative, and one wishes to substantiate it by new evidence.

One investigation of this kind, based on a series of crystal structure analyses of compounds that were specially made for the purpose in hand, concerns the pyramidality of the N-atom in enamines [144]. This turns out to vary over the whole range from virtually complete pyramidality (sp^3 hybridized N) to virtual planarity (sp^2 hybridized N). The pyramidality is more pronounced in enamines where the N-atom is part of a six-membered ring (*e.g.*, piperidine and morpholine), less so in enamines where the nitrogen is part of a five-membered ring (pyrolidine). A striking feature is the tendency of one of the bonds emanating from the N-atom to eclipse the C=C bond (*Fig. 37*). This implies that nitrogen inversion at enamine N-atom is coupled with internal rotation of the enamine group to preserve the eclipsing tendency. The same kind of coupling is found by quantum mechanical calculations to occur in vinylamine [145].

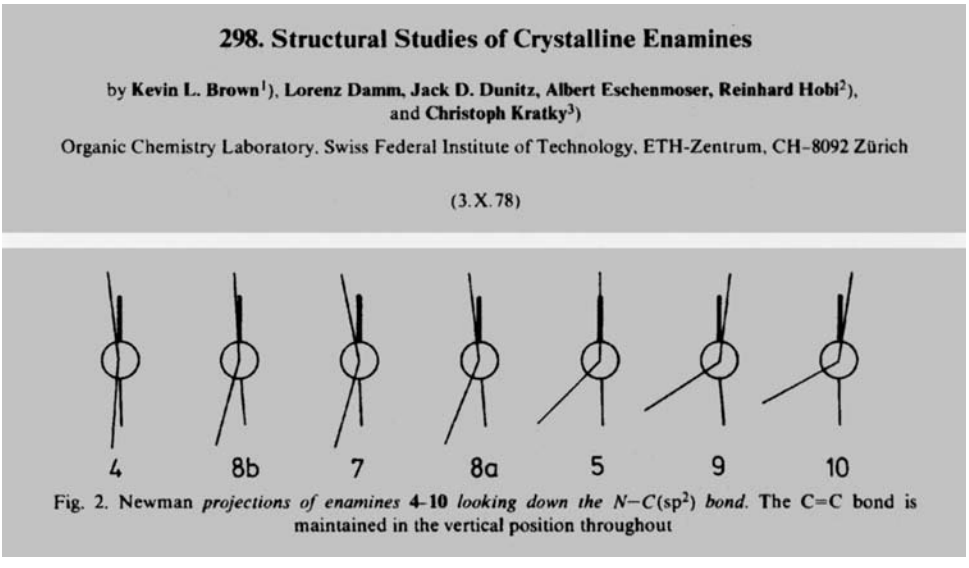


Fig. 37

298. Structural Studies of Crystalline Enamines

by **Kevin L. Brown**[1]), **Lorenz Damm**, **Jack D. Dunitz**, **Albert Eschenmoser**, **Reinhard Hobi**[2]),
and **Christoph Kratky**[3])

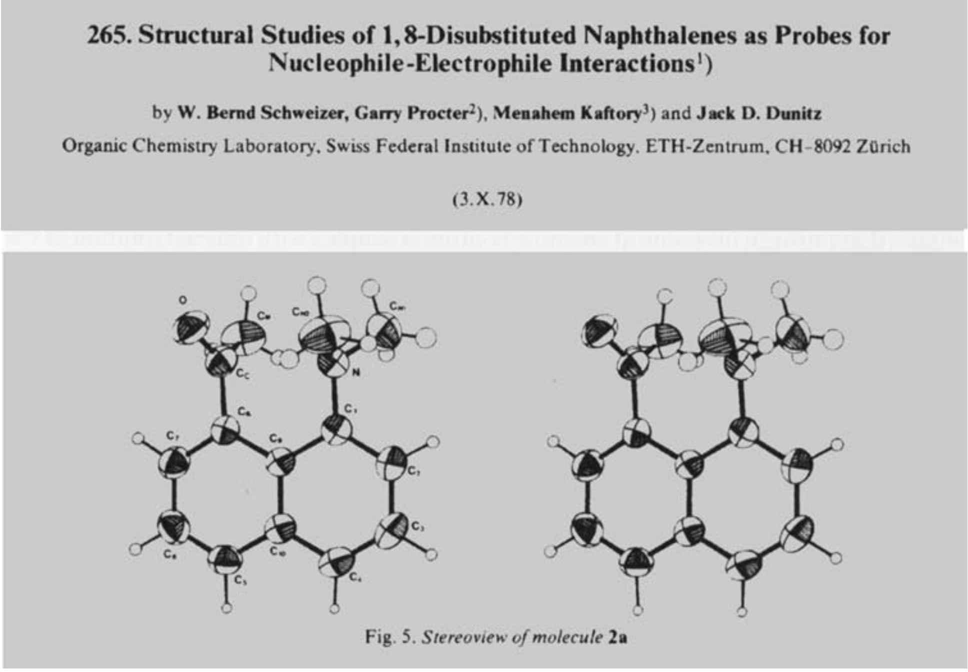
Organic Chemistry Laboratory, Swiss Federal Institute of Technology, ETH-Zentrum, CH-8092 Zürich

(3.X.78)

Fig. 2. Newman *projections of enamines* **4–10** *looking down the* $N-C(sp^2)$ *bond*. The C=C bond is maintained in the vertical position throughout

Another study of this kind concerns the interaction between a nucleophilic center and a variable electrophilic one held in a more or less rigid framework; the system chosen was the 1,8-disubstituted naphthalene skeleton [146]. A series of seven molecules was examined, all with a nucleophilic center ($-N(CH_3)_2$, $-OCH_3$, $-OH$) at one of the peri-positions and an electrophilic center (carbonyl C) at the other, with different groups attached to it. All seven molecules have a characteristic distortion pattern: the exocyclic bond to the nucleophilic center is splayed inwards, the one to the electrophilic center bond outwards (*Fig. 38*); the carbonyl C-atom is displaced from the plane of its three-bonded atoms towards the nucleophile. This kind of pattern differs from that found in other 1,8-disubstituted naphthalenes and can be interpreted as the structural expression of incipient nucleophilic addition to a C=O group [147]. It is interesting that in the amino-acid member of the series examined, 8-(*N*,*N*-dimethylamino)naphthalene-1-carboxylic acid, the crystal structure is built from an ordered arrangement of two isomers, the amino acid and its zwitterion, in equal amounts.

Fig. 38



265. Structural Studies of 1,8-Disubstituted Naphthalenes as Probes for Nucleophile-Electrophile Interactions[1])

by **W. Bernd Schweizer, Garry Procter[2]), Menahem Kaftory[3])** and **Jack D. Dunitz**

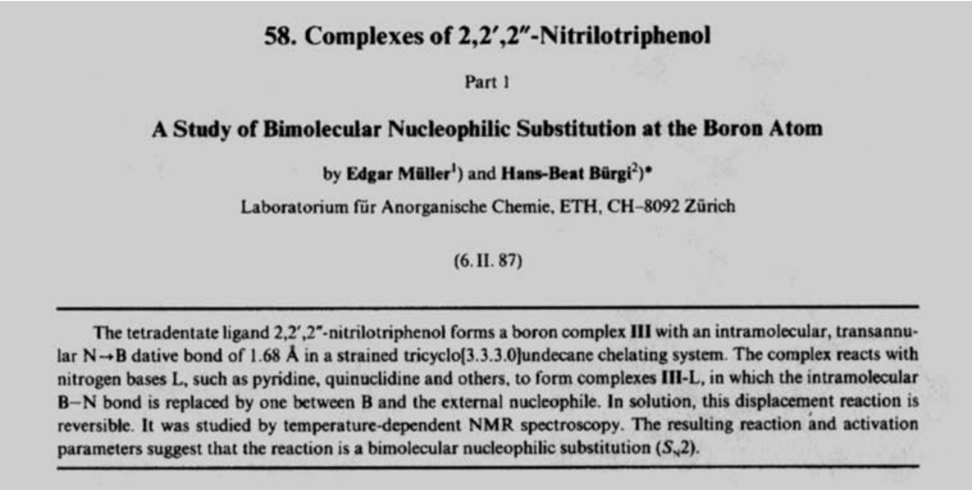
Organic Chemistry Laboratory, Swiss Federal Institute of Technology, ETH-Zentrum, CH-8092 Zürich

(3.X.78)

Fig. 5. *Stereoview of molecule* **2a**

Ideally, one would like to relate systematic variations in one of the 'chemical' parameters directly to structural features and to chemical properties of the corresponding molecules. One example where this proved to be possible is a study of bimolecular nucleophilic substitution at boron (*Fig. 39*) [148]. The tetradentate ligand 2,2′,2″-nitrilotriphenol forms a boron complex **8** (*Scheme*) with an intramolecular, transannular N→B dative bond in a strained tricyclo[3.3.0]undecane chelating system. This complex reacts

Fig. 39



58. Complexes of 2,2′,2″-Nitrilotriphenol

Part 1

A Study of Bimolecular Nucleophilic Substitution at the Boron Atom

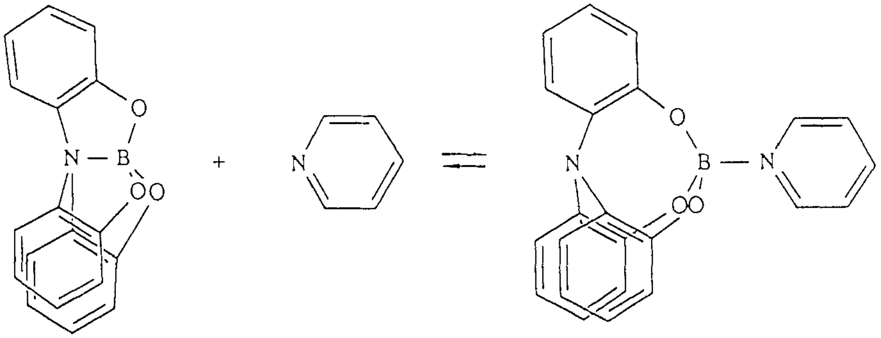
by **Edgar Müller**[1]) and **Hans-Beat Bürgi**[2])*

Laboratorium für Anorganische Chemie, ETH, CH-8092 Zürich

(6.II.87)

The tetradentate ligand 2,2′,2″-nitrilotriphenol forms a boron complex **III** with an intramolecular, transannular N→B dative bond of 1.68 Å in a strained tricyclo[3.3.3.0]undecane chelating system. The complex reacts with nitrogen bases L, such as pyridine, quinuclidine and others, to form complexes **III-L**, in which the intramolecular B–N bond is replaced by one between B and the external nucleophile. In solution, this displacement reaction is reversible. It was studied by temperature-dependent NMR spectroscopy. The resulting reaction and activation parameters suggest that the reaction is a bimolecular nucleophilic substitution (S_N2).

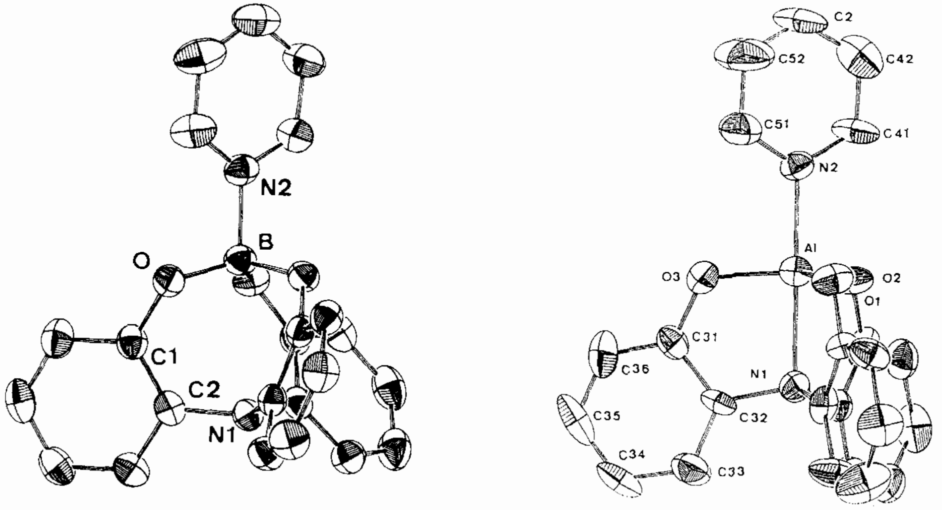
Scheme



8 **9**

with nitrogen bases, such as pyridine, quinuclidine, *etc.*, to form complexes **9** in which the intramolecular B–N bond is replaced by one between B and the external nucleophile. From NMR spectroscopy of solutions containing **8** and pyridine, there is a temperature-dependent equilibrium between **8** + py and **9**; the activation enthalpy for complex formation is *ca.* 5 kcal mol^{-1}, the activation entropy is *ca.* −22 cal mol^{-1} K^{-1}. This indicates that the reaction is of the S_N2 type. The complex **9** has a lower enthalpy than the dissociated partners (by *ca.* 10 kcal mol^{-1}), an indication of the strain in **8**; it is the positive entropy change (*ca.* 25 cal K^{-1} mol^{-1}) that favors dissociation of the adduct at higher temperatures. Crystal structure analyses of **8** (*Fig. 40*, left) and of its pyridine and quinuclidine adducts show that in the adducts the intramolecular B–N bond (1.68 Å) is broken (2.82 Å for pyridine, 2.85 Å for quinuclidine), the N-atom is inverted, and a new, shorter, and stronger bond is formed between the B-atom and the external nucleophile (B–N, 1.63 Å for pyridine and 1.64 Å for quinuclidine). The B-atom stays four-coordinated throughout the series.

Fig. 40



The corresponding Al complexes, with pyridine (*Fig. 40*, right) or H_2O as external base, are different [149]. The internal N–Al distance is 2.15 Å in the pyridine complex, 2.28 Å in the H_2O complex; the external distances are Al–N 1.99 Å and Al–O 1.77 Å, respectively. Thus, the metal atom is drawn more and more out of the cage by more nucleophilic ligands, but although the internal N–Al distance increases, the bond is not broken; the metal-atom coordination remains approximately trigonal bipyramidal. These complexes thus resemble the transition-state structure of the S_N2 displacement reaction discussed above for boron. Hence, the B and Al complexes with the same ligand demonstrate the difference in reactivity between first and second row atoms and the structural changes associated with this difference.

Some Concluding Remarks. – An essay tracing the development of structural chemistry and of X-ray crystallography through 75 volumes of *HCA* can hardly be as spectacular as those describing the achievements in organic, inorganic, or physical chemistry, which have led to international economic success and to several trips to Stockholm. Nevertheless, at a more sedate level, we hope to have illustrated the progress of structural chemistry in general and its development in Switzerland in particular. We could point to examples of modest beginnings that have been recognized, in the course of time, as important advances, and there are also a few highlights, depending on one's preferences, to look back on with enjoyment.

Given the limitations imposed on us, it has been impossible to cover all the topics that deserve to be highlighted. One blatant omission is that we have practically neglected structures of natural products, an area in which Swiss chemistry has commanded worldwide attention. We plead guilty but ask our judges to consider the mitigating circumstance that it would have been out of the question to mention all natural-product structures described in *HCA* and invidious to mention only some of them. Besides, our aim throughout has been to connect metrical aspects of structure with general chemical properties, rather than with pharmaceutical or medical properties, however important these may be. Of course, there are borderline cases: for example, the ionophoric antibiotics, where the biochemical properties are connected with a fairly well defined chemical property of the compounds that is reflected in their structures [150].

History has not come to an end with *HCA*'s 75th anniversary. There is the temptation to try to look into the future, but we have resisted it. Exercises of this kind often take the form of more or less complicated extrapolations, which are almost doomed to futility, because they fail to do justice to the inventiveness and ingenuity of the next generation. The past is another matter, and for us, it has been a useful occupation to look back into it. The moving finger of the present is what links the future to the past, and in the present stage of explosive expansion of all branches of human development, including science and technology, there is the constant tendency to sentimentalize the past, to look back on the 'good old days', but at the same time to overlook its achievements. After all, a well trained doctoral student can now produce in a week more scientific results than his grandfather could have achieved in a lifetime. And the flood of new experimental results needs a flood of intellectual concepts to keep pace with it. In the fever of the scientific gold rush, it is all too easy to fail to notice that many a 'modern' idea has been put forward long ago in largely ignored or forgotten papers. As more and more knowledge accumulates, many new ideas may be little more than recapitulations of earlier, forgotten ones. As people grow old, short-term memory tends to become weaker while long-term memory remains unimpaired. With science, and also with many other modern human activities, it seems to be the other way round; short-term memory is assured while long-term memory, the history of how the present came to be, tends to be eroded by the sheer mass of new and exciting developments. Loss of communal memory would be a disaster for science as well as for other human activities. As *Ortega y Gasset* has written: '*To excel the past we must not allow ourselves to lose contact with it; on the contrary, we must feel it under our feet because we raised ourselves upon it*' [151].

We are grateful to Dr. *W. B. Schweizer* for *Figs. 3* and *4* and to Dr. *D. De Ridder* for the *Table* of space-group frequencies.

REFERENCES

[1] J. D. Dunitz, H. M. M. Shearer, *Proc. Chem. Soc.* **1958,** *348*; *ibid.* **1959,** 268.

[2] Hs. H. Günthard, E. Heilbronner, *Helv. Chim. Acta* **1993,** *76,* 631.

[3] W. Friedrich, P. Knipping, M. Laue, *Sitzber. Math. Physik. Kl. Bayer. Akad. Wiss.* **1912,** 303.

[4] W. H. Bragg, W. L. Bragg, *Nature (London)* **1913,** *91,* 557.

[5] W. L. Bragg, *Proc. R. Soc. London [Ser.] A* **1914,** *88,* 248.

[6] J. D. Dunitz, H. P. Weber, *Helv. Chim. Acta* **1964,** *47,* 951.

[7] J. D. Dunitz, H. P. Weber, *Helv. Chim. Acta* **1964,** *47,* 1138.

[8] For information, apply to the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, England.

[9] U. Schwieter, W. Arnold, W. E. Oberhänsli, N. Rigassi, W. Vetter, *Helv. Chim. Acta* **1971,** *54,* 2447.

[10] D. Britton, J. D. Dunitz, *Helv. Chim. Acta* **1980,** *63,* 1068.

[11] G.Bergerhoff, R. Hundt, R. Sievers, I. D. Brown, *J. Chem. Inf. Comput. Sci.* **1983,** *23,* 66.

[12] P. Debye, P. Scherrer, *Physikal. Zeit.* **1916,** *17,* 277.

[13] V. Kohlschütter, H. Roesti, *Ber. Dtsch. Chem. Ges.* **1923,** *56,* 275.

[14] S. Glasstone, *J. Chem. Soc.* **1921,** *119,* 1689, 1914.

[15] V. Kohlschütter, P. Scherrer, *Helv. Chim. Acta* **1924,** *7,* 337.

[16] V. Kohlschütter (obituary by W. Feitknecht), *Helv. Chim. Acta* **1929,** *12,* 1059.

[17] E. Ott, *Helv. Chim. Acta* **1928,** *11,* 330.

[18] K. H. Meyer, Y. Go, *Helv. Chim. Acta* **1934,** *17,* 1081.

[19] L. Pauling, *Proc. Natl. Acad. Sci. U.S.A.* **1950,** *35,* 495.

[20] J. A. Prins, J. Schenk, L. H. J. Wachters, *Physica* **1957,** *23,* 746.

[21] M. D. Lind, S. Geller, *J. Chem. Phys.* **1969,** *51,* 348.

[22] J. Donohue, 'The structures of the elements', Wiley, New York, 1974.

[23] K. H. Meyer, Y. Go, *Helv. Chim. Acta* **1934,** *17,* 1488.

[24] K. H. Meyer, G. W. Pankow, *Helv. Chim. Acta* **1935,** *18,* 589.

[25] K. H. Meyer, L. Misch, *Helv. Chim. Acta* **1937,** *20,* 232.

[26] C. Tamm, *Helv. Chim. Acta* **1992,** *75,* 2109.

[27] R. Signer, H. Schwander, *Helv. Chim. Acta* **1949,** *32,* 853; H. Schwander, R. Signer, *ibid.* **1950,** *33,* 1521.

[28] H. F. Judson, 'The Eighth Day of Creation', Jonathan Cape, London, 1979, p. 100.

[29] M. H. F. Wilkins, A. R. Stokes, H. R. Wilson, *Nature (London)* **1953,** *171,* 738; R. E. Franklin, R. G. Gosling, *ibid.* **1953,** *171,* 740.

[30] J. D. Watson, F. H. C. Crick, *Nature (London)* **1953,** *171,* 737.

[31] W. Nowacki, *Helv. Chim. Acta* **1945,** *28,* 1233.

[32] G. Giacomello, G. Illuminati, *Gazz. Chim. Ital.* **1945,** *75,* 246; *Ric. Sci.* **1945,** *15,* 559.

[33] C. E. Nordmann, D. L. Schmitkons, *Acta Crystallogr.* **1965,** *18,* 764.

[34] J. P. Amoureux, M. Foulon, *Acta Crystallogr., Sect. B* **1987,** *B34,* 470.

[35] J. Donohue, S. H. Goodman, *Acta Crystallogr.* **1967,** *22,* 352.

[36] F. Aebi, *Helv. Chim. Acta* **1948,** *31,* 8.

[37] A. Magneli, *Arkiv Kemi* **1950,** *2,* 513.

[38] F. Aebi, *Helv. Chim. Acta* **1948,** *31,* 369.

[39] W. Nowacki, R. Scheidegger, *Helv. Chim. Acta* **1952,** *35,* 375.

[40] E. Heilbronner, V. Schomaker, *Helv. Chim. Acta* **1952,** *35,* 1385.

[41] P. A. Shaffer, Jr., V. Schomaker, L. Pauling, *J. Chem. Phys.* **1946,** *14,* 659, 748.

[42] R. K. Bohn, K. Mizuno, T. Fukuyama, K. Kuchitsu, *Bull. Chem. Soc. Jpn.* **1973,** *46,* 1395.

[43] A. S. Dreiding, *Helv. Chim. Acta* **1959,** *42,* 1339.

[44] a) W. Nowacki, *Helv. Chim. Acta* **1942,** *25,* 863; b) *ibid.* **1943,** *26,* 459.

[45] A. I. Kitaigorodski, 'Organic Chemical Crystallography', Consultants Bureau, New York, 1961 (English translation of the Russian original published by Press of the Academy of Sciences of the USSR, Moscow, 1955).

[46] W. Nowacki, *Helv. Chim. Acta* **1951,** *34,* 1957.

[47] A. I. Kitaigorodski, 'Molecular Crystals' (Russian), Nauka, Moscow, 1971; 'Molekülkristalle', Akademie-Verlag, Berlin, 1979.

[48] A. I. Kitaigorodski, 'Molecular Crystals and Molecules', Academic Press, New York, 1973.

[49] W. K. Belski, P. M. Sorki, *Kristallografia* **1970,** *15,* 704.

[50] A. Gavezzotti, *J. Am. Chem. Soc.* **1991,** *113,* 4622.

[51] A. J. C. Wilson, *Acta Crystallogr., Sect. A* **1988,** *44,* 715.

[52] G. M. J. Schmidt et al., 'Solid State Photochemistry', Ed. D. Ginsburg, Verlag Chemie, Weinheim, 1976.

[53] M. D. Cohen, G. M. J. Schmidt, F. I. Sonntag, *J. Chem. Soc.* **1964,** 2000.

[54] M. D. Cohen, G. M. J. Schmidt, *J. Chem. Soc.* **1964,** 1996.

[55] E. Hertel, *Z. Elektrochem.* **1931,** *37,* 536.

[56] V. Kohlschütter, A. Nägeli, *Helv. Chim. Acta* **1921,** *4,* 45.

[57] V. Kohlschütter, *Z. Anorg. Chem.* **1919,** *105,* 1.

[58] V. Kohlschütter, *Helv. Chim. Acta* **1929,** *12,* 512.

[59] R. O. Herzog, G. O. Londberg, *Ber.* **1924,** *57,* 329.

[60] Römpps Chemie-Lexikon, Franckh'sche Verlagshandlung, Stuttgart, 8. Auflage, 1988, p. 4300.

[61] H. U. Oswald, personal communication.

[62] G. Pólya, *Helv. Chim. Acta* **1936,** *19,* 22.
[63] G. Pólya, *Z. Krist.* **1936,** *93,* 415.
[64] P. Niggli, *Helv. Chim. Acta* **1946,** *29,* 991.
[65] P. Niggli, *Helv. Chim. Acta* **1947,** *30,* 1562.
[66] E. Kováts, Hs. H. Günthard, Pl. A. Plattner, *Helv. Chim. Acta* **1955,** *38,* 1912.
[67] H. Günthard, Pl. A. Plattner, E. Brandenberger, *Experientia* **1948,** *4,* 425.
[68] J. M. Robertson, H. M. M. Shearer, *Nature (London)* **1956,** *177,* 885.
[69] Y. Takeuchi, R. Pepinsky, *Science* **1956,** *124,* 126.
[70] J. D. Bernal, *Nature (London)* **1956,** *178,* 40.
[71] J. M. Robertson, H. M. M. Shearer, G. A. Sim, D. G. Watson, *Acta Crystallogr.* **1962,** *15,* 1.
[72] G. Ohloff, *Helv. Chim. Acta* **1992,** *75,* 2041.
[73] M. Stoll, G. Stoll-Comte, *Helv. Chim. Acta* **1930,** *13,* 1185.
[74] A. Müller, *Helv. Chim. Acta* **1933,** *16,* 155.
[75] J. D. Dunitz, H. M. M. Shearer, *Helv. Chim. Acta* **1960,** *43,* 18.
[76] J. D. Dunitz, in 'Perspectives in Structural Chemistry' (eds. J. D. Dunitz, J. A. Ibers), 1968, Vol. 2, Wiley, New York, p. 1.
[77] H. Fuhrer, Hs. H. Günthard, *Helv. Chim. Acta* **1965,** *48,* 236.
[78] R. Arndt, Doctoral Dissertation, ETH-Zürich, 1962.
[79] E. Huber-Buser, J. D. Dunitz, *Helv. Chim. Acta* **1960,** *43,* 760; **1961,** *44,* 2027; **1966,** *49,* 1821.
[80] J. D. Dunitz, H. P. Weber, *Helv. Chim. Acta* **1964,** *47,* 951.
[81] M. H. Mladeck, W. Nowacki, *Helv. Chim. Acta* **1964,** *47,* 1280.
[82] J. D. Dunitz, K. Venkatesan, *Helv. Chim. Acta* **1961,** *44,* 2033.
[83] R. Shenhav, R. Schaeffer, *Cryst. Struct. Commun.* **1981,** *10,* 1181.
[84] O. Ermer, J. D. Dunitz, I. Bernal, *Acta Crystallogr. Sect. B* **1973,** *29,* 2278.
[85] W. Fedeli, J. D. Dunitz, *Helv. Chim. Acta* **1968,** *51,* 445.
[86] J. D. Dunitz, H. Eser, *Helv. Chim. Acta* **1967,** *50,* 1565.
[87] W. R. Busing, H. A. Levy, *Acta Crystallogr.* **1964,** *17,* 142.
[88] J. D. Dunitz, H. Eser, M. Bixon, S. Lifson, *Helv. Chim. Acta* **1967,** *50,* 1572.
[89] R. F. Bryan, J. D. Dunitz, *Helv. Chim. Acta* **1960,** *43,* 1.
[90] R. F. Bryan, J. D. Dunitz, *Helv. Chim. Acta* **1960,** *43,* 3.
[91] M. Dobler, J. D. Dunitz, A. Mugnoli, *Helv. Chim. Acta* **1966,** *49,* 2492.
[92] H.-B. Bürgi, J. D. Dunitz, *Helv. Chim. Acta* **1968,** *51,* 1514.
[93] F. A. L. Anet, M. St. Jacques, *J. Am. Chem. Soc.* **1966,** *88,* 2585, 2586.
[94] For example, O. Ermer, *Structure Bonding* **1976,** *27,* 161.
[95] T. Aono, J. H. Bieri, M. Hesse, K. Kostova, A. Lorenzi-Riatsch, Y. Nakashita, R. Prewo, *Helv. Chim. Acta* **1985,** *68,* 1033.
[96] V. Prelog, W. Küng, T. Tomljenovic, *Helv. Chim. Acta* **1962,** *45,* 1352.
[97] G. I. Glover, H. Rapoport, *J. Am. Chem. Soc.* **1964,** *86,* 3397; G. I. Glover, R. B. Smith, H. Rapoport, *J. Am. Chem. Soc.* **1965,** *87,* 2003.
[98] F. K. Winkler, P. Seiler, J. P. Chesick, J. D. Dunitz, *Helv. Chim. Acta* **1976,** *59,* 1417.
[99] M. Rothe, *Ber. Dtsch. Chem. Ges.* **1962,** *95,* 783.
[100] G. Bernardinelli, R. Gerdil, *Helv. Chim. Acta* **1982,** *65,* 558, 730.
[101] G. Bernardinelli, R. Gerdil, *Helv. Chim. Acta* **1982,** *65,* 1310.
[102] H. R. Oswald, *Helv. Chim. Acta* **1961,** *44,* 1049.
[103] J. W. Tracy, N. W. Gregory, E. C. Lingafelter, J. D. Dunitz, H.-C. Mez, R. E. Rundle, C. Scheringer, H. L. Yakel, Jr., M. K. Wilkinson, *Acta Crystallogr.* **1961,** *14,* 927.
[104] H. R. Oswald, H. Jaggi, *Helv. Chim. Acta* **1960,** *43,* 72.
[105] L. E. Orgel, J. D. Dunitz, *Nature (London)* **1957,** *179,* 462.
[106] 'Computing Methods and the Phase Problem in X-Ray Crystal Analysis', Eds. R. Pepinsky, J. M. Robertson, and J. C. Speakman, 'International Tracts in Computer Science and Technology and Their Application' (Gen. Eds. N. Metropolis, E. Piore, and S. Ulam), Pergamon Press, Oxford, 1961, Vol. 4.
[107] C. von Girsewald, H. Siegens, *Ber. Dtsch. Chem. Ges.* **1921,** *54,* 492.
[108] E. Schmitz, *Liebigs Ann. Chem.* **1960,** *635,* 73.
[109] A. R. Katritzky, V. J. Baker, F. M. S. Brito-Palma, J. M. Sullivan, R. B. Finzel, *J. Chem. Soc., Perkin Trans. 2* **1979,** 1133.
[110] S. N. Whittleton, P. Seiler, J. D. Dunitz, *Helv. Chim. Acta* **1981,** *64,* 2614.

[111] J.D. Dunitz, P. Seiler, *J. Am. Chem. Soc.* **1983,** *105,* 7056.

[112] L.M. Jackman, N.M. Szeverenyi, *J. Am. Chem. Soc.* **1977,** *99,* 4954; L.M. Jackman, B.C. Lange, *Tetrahedron* **1977,** *33,* 2737; L.M. Jackman, B.C. Lange, *J. Am. Chem. Soc.* **1981,** *103,* 4494.

[113] R. Amstutz, W.B. Schweizer, D. Seebach, J.D. Dunitz, *Helv. Chim. Acta* **1981,** *64,* 2617.

[114] D. Seebach, R. Amstutz, J.D. Dunitz, *Helv. Chim. Acta* **1981,** *64,* 2622.

[115] D. Seebach, *Angew. Chem.* **1988,** *100,* 1685; *ibid. Int. Ed.* **1988,** *27,* 1624.

[116] D. Seebach, B. Lamatsch, R. Amstutz, A.K. Beck, M. Dobler, M. Egli, R. Fitzi, M. Gautschi, B. Herradón, P.C. Hidber, J.J. Irwin, R. Locher, M. Maestro, T. Maetzke, A. Mouriño, E. Pfammatter, D.A. Plattner, C. Schickli, W.B. Schweizer, P. Seiler, G. Stucky, W. Petter, J. Escalante, E. Juaristi, D. Quintana, C. Miravitlles, E. Molins, *Helv. Chim. Acta* **1992,** *75,* 913.

[117] R. Amstutz, T. Laube, W.B. Schweizer, D. Seebach, J.D. Dunitz, *Helv. Chim. Acta* **1984,** *67,* 224.

[118] J.D. Dunitz, P. Seiler, *Helv. Chim. Acta* **1986,** *69,* 1107.

[119] J.C. Slater, 'Quantum Mechanics of Molecules and Crystals', McGraw-Hill, New York, 1965, Vol. 2, p. 113.

[120] P. Seiler, *Acta Crystallogr.* **1993,** in press.

[121] P. Seiler, J.D. Dunitz, *Helv. Chim. Acta* **1989,** *72,* 1125.

[122] P. Seiler, G.R. Weisman, E.D. Glendening, F. Weinhold, Van B. Johnson, J.D. Dunitz, *Angew. Chem.* **1987,** *99,* 1216; *ibid. Int. Ed.* **1987,** *26,* 1175.

[123] S.R. Ungemach, H.F. Schaeffer III, *J. Am. Chem. Soc.* **1974,** *96,* 7898.

[124] K.B. Wiberg, F.H. Walker, *J. Am. Chem. Soc.* **1982,** *104,* 5239.

[125] K. Semmler, G. Szeimies, J. Belzner, *J. Am. Chem. Soc.* **1985,** *107,* 6410.

[126] P. Seiler, *Helv. Chim. Acta* **1990,** *73,* 1574.

[127] P. Seiler, J. Belzner, U. Bunz, G. Szeimies, *Helv. Chim. Acta* **1988,** *71,* 2100.

[128] D. Schwarzenbach, *Helv. Chim. Acta* **1972,** *55,* 2990.

[129] M. Zehnder, U. Thewalt, S. Fallab, *Helv. Chim. Acta* **1976,** *59,* 2290.

[130] U. Thewalt, M. Zehnder, S. Fallab, *Helv. Chim. Acta* **1977,** *60,* 867.

[131] A.E. Martell, *Acc. Chem. Res.* **1982,** *15,* 155.

[132] O. Ermer, *J. Am. Chem. Soc.* **1988,** *110,* 3747.

[133] O. Ermer, L. Lindenberg, *Helv. Chim. Acta* **1991,** *74,* 825.

[134] O. Ermer, L. Lindenberg, *Helv. Chim. Acta* **1988,** *71,* 1084.

[135] D.E. Palin, H.M. Powell, *J. Chem. Soc.* **1947,** 208; H.M. Powell, *ibid.* **1948,** 61; D.E. Palin, H.M. Powell, *ibid.* **1948,** *571,* 815; H.M. Powell, P. Riesz, *Nature (London)* **1948,** *161,* 52.

[136] O. Ermer, *Helv. Chim. Acta* **1991,** *74,* 1339.

[137] R. Restori, D. Schwarzenbach, O. Ermer, P. Venugopalan, H. Förtsch, H.-B. Bürgi, in preparation.

[138] W.E. Oberhänsli, *Helv. Chim. Acta* **1982,** *65,* 924.

[130] K. Vogler, M. Kofler, *Helv. Chim. Acta* **1956,** *39,* 1387.

[140] 'Structure Correlation', Eds. H.-B. Bürgi and J.D. Dunitz, Verlag Chemie, Weinheim, 1993.

[141] W. Hummel, K. Huml, H.-B. Bürgi, *Helv. Chim. Acta* **1988,** *71,* 1291.

[142] W. Hummel, A. Roszak, H.-B. Bürgi, *Helv. Chim. Acta* **1988,** *71,* 1281.

[143] P. Chakrabarti, J.D. Dunitz, *Helv. Chim. Acta* **1982,** *65,* 1555.

[144] K.L. Brown, L. Damm, J.D. Dunitz, A. Eschenmoser, R. Hobi, C. Kratky, *Helv. Chim. Acta* **1978,** *61,* 3108.

[145] K. Müller, L.D. Brown, *Helv. Chim. Acta* **1978,** *61,* 1407.

[146] W.B. Schweizer, G. Procter, M. Kaftory, J.D. Dunitz, *Helv. Chim. Acta* **1978,** *61,* 2783.

[147] H.-B. Bürgi, J.D. Dunitz, E. Shefter, *J. Am. Chem. Soc.* **1973,** *95,* 5065.

[148] E. Müller, H.-B. Bürgi, *Helv. Chim. Acta* **1987,** *70,* 499, 511.

[149] E. Müller, H.-B. Bürgi, *Helv. Chim. Acta* **1987,** *70,* 520.

[150] For a review, see M. Dobler, 'Ionophores and Their Structures', Wiley, New York, 1981.

[151] J. Ortega y Gasset, 'In Search of Goethe from Within. Letter to a German', translated by W.R. Trask, *Partisan Review,* December 1949.