

STRUCTURE OF VITAMIN B₁₂

The Crystal Structure of the Hexacarboxylic Acid derived from B₁₂ and the Molecular Structure of the Vitamin

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THE hexacarboxylic acid isolated from vitamin B₁₂ by Cannon, Johnson and Todd^{1,2} has proved remarkably amenable to direct X-ray analysis. Through a series of calculations of successive degrees of approximation to the correct electron density distribution, we have reached a solution of the crystal structure of this product which appears to provide the solution also of a large part of the chemical structure of vitamin B₁₂.

The rapid progress which we have made has been possible through the use of the National Bureau of Standards western automatic computer (SWAC) in Los Angeles, to calculate the necessary structure factors and three-dimensional Fourier syntheses³. Our general method has been to compute structure factors for all observed X-ray reflexions based on gradually increasing groups of acceptable atomic positions, to assign phases to the observed structure factors after each set of calculations and to use the rephased terms to recalculate the three-dimensional electron density distribution. This in turn was employed to revise or add atomic positions.

The starting point of the present calculations was the recognition, described earlier², in the first electron density maps calculated for this material (using phases based on known cobalt atom contributions alone) of an internal nucleus surrounding the cobalt atom similar to that found in vitamin B₁₂ itself.

Structure factors were next calculated based on 62 atoms belonging to this nucleus and to the rest of the cobalt co-ordination group. In the resulting electron density distribution there was an enormous improvement in the character of the peak pattern. In addition to the 26 atoms placed by calculation, which had peak heights from 7.5 e./A.³ upwards, 91 independent peaks appeared with heights varying from 1.6 to 4.5 e./A.³. All those greater than 2.5 e./A.³, 28 in number, were in chemically reasonable sites to be assigned to atoms of side-chains attached to the main nucleus. A further ten atoms in additional side-chains were readily recognized in two following

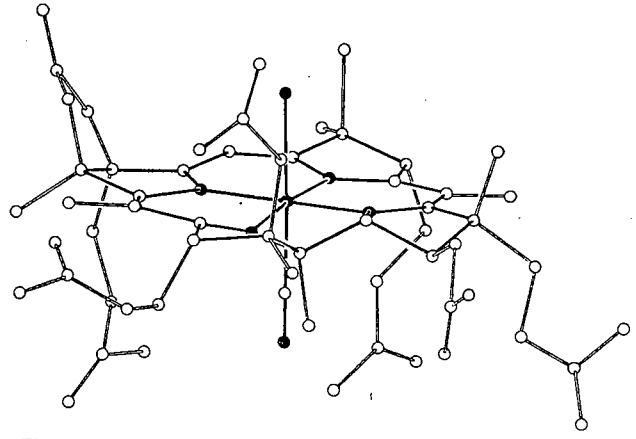


Fig. 2. Atomic positions found in the hexacarboxylic acid projected on the c plane. The chemical bonding deduced is outlined to emphasize the stereochemical form of the molecule

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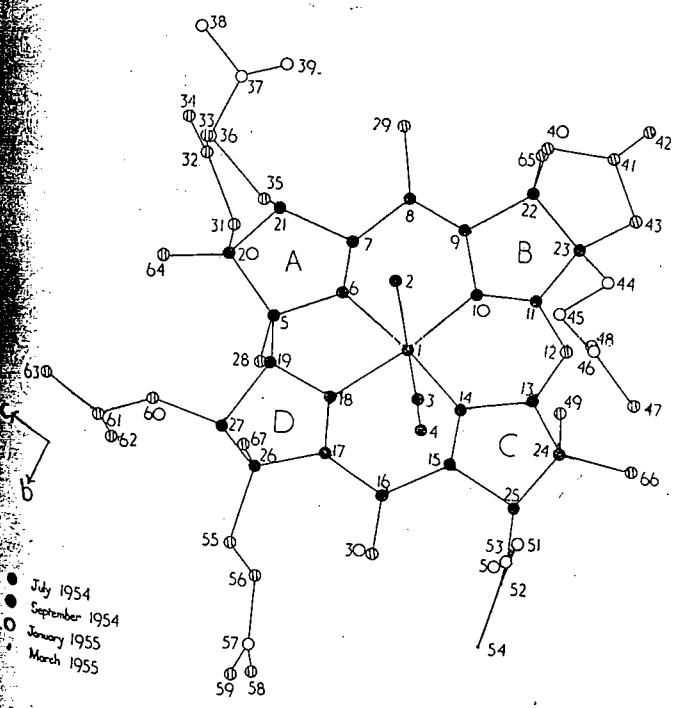
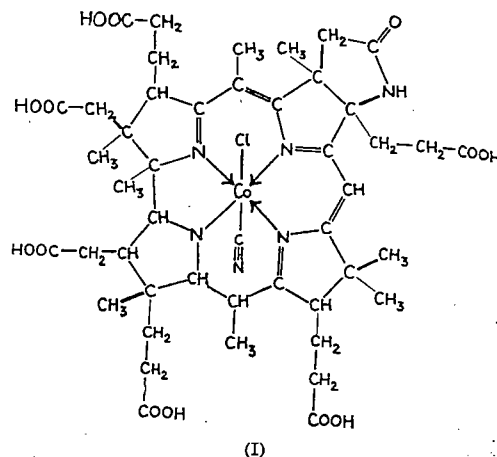


Fig. 1. Atomic positions found in the hexacarboxylic acid derived from vitamin B₁₂ projected on the a plane. The shading illustrates the course of the crystallographic study; the dates show approximately when each group of atoms was selected

rounds of calculation. In one side-chain alone the selection of the positions of the atoms has not been straightforward and still presents certain difficulties. Since we have little doubt from other evidence of the chemical nature of these remaining atoms, we have included them with the rest of the molecule in Figs. 1 and 2, which show the most recently derived atomic positions projected on to the crystallographic a and c planes. At the latest stage of structure factor calculations based on 73 atoms in the crystal unit the agreement factor was 28.7 per cent. This figure, while it provides no guarantee that our solution is quite correct, compares not unfavourably with values often obtained for far simpler crystals built of molecules of chemically well-established structure. Interatomic distances conform with accepted values within 0.2 A., electron densities within about 1.5 e./A.³.

The projected atomic positions of Figs. 1 and 2 correspond with a molecule having cobalt as its centre, attached to chlorine on one side and a cyanide group on the other, and surrounded by a nucleus of 63 atoms, not counting hydrogen. Two water molecules and one acetone molecule also appear in the crystal asymmetric unit. We earlier described the inner nucleus of atoms surrounding the cobalt atom, which consists of four five-membered rings, two

of which are directly linked. The geometrical form of this nucleus is now much clearer. The inner ring of atoms, from 6 to 17 in Fig. 1, lie closely in one plane, suggesting that they are linked by a system of double bonds. At the direct link C5 is tetrahedral and bears a single substituent atom. The outer ring of atoms, the β -positions of the five-membered rings, lie alternately above and below the plane of the inner ring. They are clearly reduced and carry substituted side-chains conforming in outline with substituted acetic and propionic acid side-chains, in the order characteristic of porphyrins of Type III, together with other single substituent atoms. All the acetic acid residues project on the same side of the ring as the chlorine atom; all the propionic acid chains on the other (Fig. 2). Even without the apparent porphyrin relationship, it would be reasonable to write the chemical nature of the atoms N, C and O in a major part of the skeleton formula I, following evidence of the geometrical distribution in space of the side-chain atoms and the relatively heavy electron density of the four inner nitrogen atoms and of many of the carboxyl oxygen atoms, as shown by Figs. 3 and 4. The chemical character of the single substituent atoms at different points on the nucleus is less certain from crystallographic evidence alone. Interatomic distances and relative weights are consistent with their all being methyl groups as suggested by the analytical evidence; but neither measurement is sufficiently precise by itself to exclude the possibility that one or other (and particularly perhaps 28 or 30) is a hydroxyl- or amino-group. The one exception is atom 43, which is combined in a ring. This atom from its electron density must be oxygen or nitrogen



(as NH), the ring being either a lactone or lactam ring. Neither the position nor number of the double bonds is certain; the system shown in formula I perhaps extended by one double bond, seems most likely; but the alternative, formula III, is also possible. To be able to write down a chemical structure very largely from purely crystallographic evidence on the arrangement of atoms in space—and the chemical structure of a quite formidably large molecule at that—is for any crystallographer something of a dream-like situation. We realize that our methods do not permit us to be dogmatic about any particular detail of our proposal formula, however much we may believe that it does as a whole correspond with reality. Our conclusions are strengthened by chemical

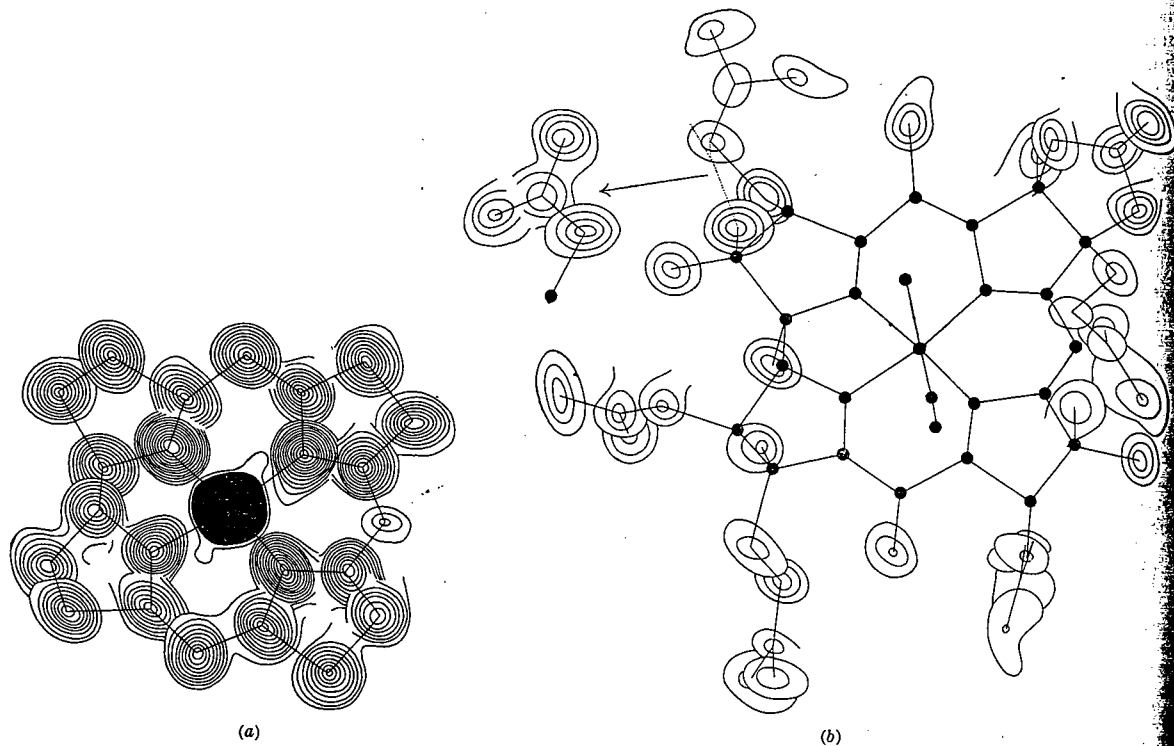


Fig. 3. Electron density-levels and the selection of atomic positions from the three-dimensional distribution calculated with terms phased on 26 atoms. In this and the succeeding diagram, contours are drawn in the sections of the calculated distribution parallel with the a plane passing at or near the atomic positions. Owing to the complexity of the molecule and overlapping of atoms in projection, the complete contours for every atom are not shown. Interval of contours, $1e./\text{\AA}^3$. The figures are divided into two parts to show the atoms of (a) the nucleus, (b) the side-chains. The acetic acid residue inset in Fig. 4 is viewed along the b axis

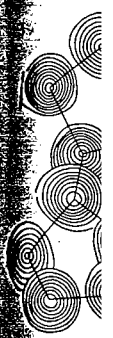
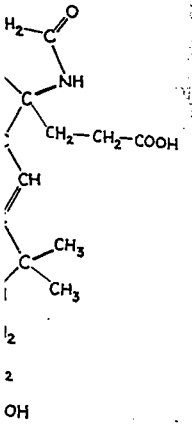


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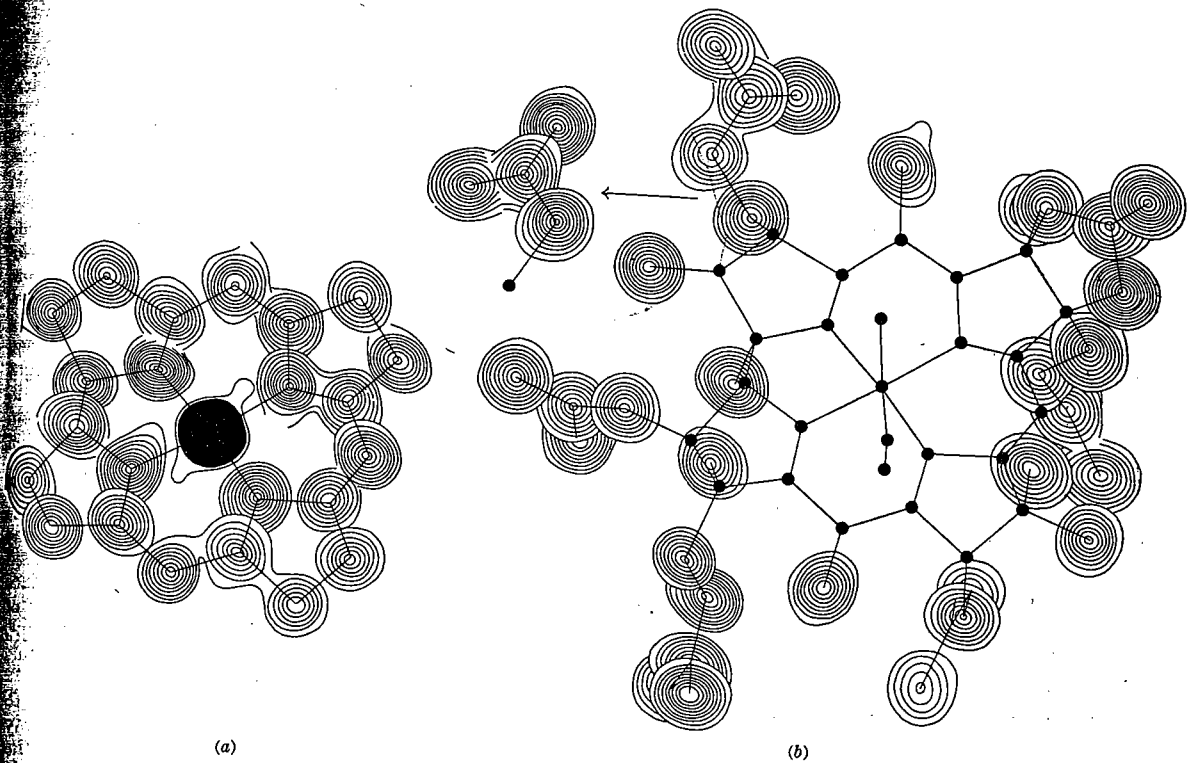
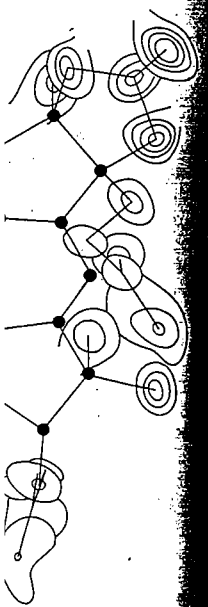


Fig. 4. Electron density-levels in the three-dimensional distribution calculated with terms phased on 63 atoms. In this and the preceding diagram it is noticeable that electron densities are usually lowest over the terminal atoms of the propionic acid side-chains owing to the greater freedom of displacement of the longer chains from their mean positions in the crystal. The effects are most marked over the side-chain on ring C

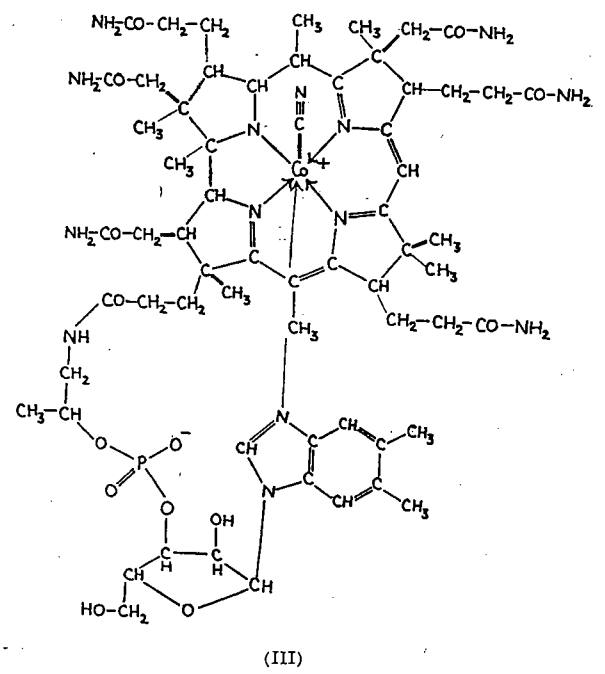
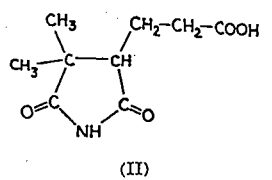


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evidence on the nature of the degradation products already isolated from vitamin B₁₂ and discussed in detail below, and by our own parallel work on the vitamin itself. This additional evidence, and particularly the isolation of the succinimide, II, in the Merck Laboratories⁶, was most useful in deciding the nature of the only side-chain of which the atomic positions were not immediately clear from the crystal structure of the hexacarboxylic acid.

The X-ray analysis of the different B₁₂ crystals is not as far advanced as that of this degradation product, and full results on these must come later. But already we have substantial confirmation for the presence of a nucleus of the above form in B₁₂ provided that an exchange reaction has occurred in the formation of the degradation product; the nucleotide in B₁₂ occupies the site of the CN group in the fragment. We can also trace the positions of the atoms of the propanolamine group linking the phosphate group in B₁₂ to the propionic acid side-chain of ring D above; only this group and the ribose molecule are directly attached to the phosphate⁶. We can observe in B₁₂ no evidence of an atom at the site of atom 43 in the hexacarboxylic acid; instead, there is low electron density corresponding to a free acetamide group⁷. We conclude that the lactone or lactam ring is formed during degradation. These results make it

possible to put forward a tentative complete structure for vitamin B₁₂ (III). This structure corresponds to the empirical formula C₆₃H₉₀N₁₄O₁₄PCo in excellent agreement with reported analyses⁷ which give figures within the limits C₆₁₋₆₄H₈₄₋₉₂N₁₄O₁₃₋₁₄PCo. Again, the exact number and position of the double bonds are uncertain.



We are very grateful for grants from the Nuffield Foundation and the Department of Scientific and Industrial Research and for technical assistance from Mrs. U. K. Ledwith and Mrs. H. M. Oliver. We also acknowledge the support of the computer in Los Angeles by the United States Office of Naval Research and Office of Ordnance Research.

DOROTHY CROWFOOT HODGKIN

JENNY PICKWORTH

JOHN H. ROBERTSON

Laboratory of Chemical Crystallography,
Oxford.

KENNETH N. TRUEBLOOD

RICHARD J. PROSEN

Department of Chemistry,
University of California, Los Angeles.

JOHN G. WHITE

Frick Laboratory, Princeton.

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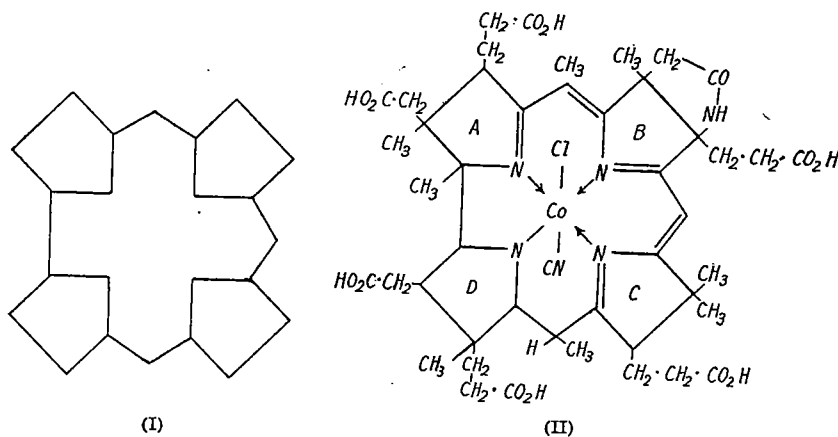
The Structure of Vitamin B₁₂ and its Hexacarboxylic Acid Degradation Product

THE isolation of a crystalline nucleotide-free hexacarboxylic acid from alkaline hydrolysates of vitamin B₁₂ was described in an earlier communication¹, and the detailed X-ray examination of this product by our colleagues in Oxford² led to the recognition of the general nature of the cyclic system (I) surrounding the cobalt atom. Since that time, as described above, the relative positions of all the atoms (excluding hydrogen) in the molecule have been determined through the calculation of the full three-dimensional electron density distribution in the hexacarboxylic acid. These results, taken together with chemical evidence, have led to the proposal of the formula (II).

The crystallographic data by themselves leave open a number of details in the molecular structure of the hexacarboxylic acid, particularly the chemical

nature of the single substituent atoms, the nature of the ring attached to ring B of the nucleus, and the exact position of the double bonds in the molecule. These can be partly resolved from chemical data. The sample of the hexacarboxylic acid subjected to chemical analysis was dried at 54°/0.05 mm. If it is assumed that the residue still contained two molecules of water of crystallization, then the formula C₄₆H₈₀O₁₃N₆CoCl₂·2H₂O (C, 53.35; H, 6.2; N, 8.1 per cent) is in agreement with the values (C, 52.8; H, 6.3; N, 7.9 per cent) obtained from the elementary analysis. This formula differs slightly from that provisionally quoted in our previous communication¹; but the difference is clearly within the margin of experimental error. The figures can best be accounted for by assuming that all eight single substituent atoms are present as carbon in methyl groups; it seems unlikely that any of them are oxygen or nitrogen since the mode of formation of the hexacarboxylic acid (action of 30 per cent aqueous sodium hydroxide on the vitamin at 150°) precludes the existence in it of any inherently unstable or labile groups. Independent evidence for the existence of ring C as now formulated was provided by the isolation and identification of the appropriate succinimide (III), from a chromic acid oxidation of a crude vitamin B₁₂ hydrolysate by the Merck group³, and we have since obtained (III) from the chromic acid oxidation of the pure hexacarboxylic acid.

The nature of the five-membered ring attached to ring B is the next point of ambiguity. The X-ray examination of vitamin B₁₂ itself reveals that the five-membered ring, which occurs fused to ring B in the hexacarboxylic acid, is not present in the vitamin, which appears to contain an acetamide and a methyl group as β-substituents in ring B and a propionamide group as a β'-substituent. The extra ring in the hexacarboxylic acid is therefore produced by cyclization of the acetamide or acetic acid side-chain, presumably subsequent to hydroxylation at the remaining β'-position, which is activated by a carbon-nitrogen double bond, and the ring is therefore a lactam or a lactone. The hexacarboxylic acid does not acquire an additional negative charge even as high as pH 11, and this fact, coupled with its infrared spectrum and with the analytical figures, has led us to adopt the lactam formulation as is shown in structure (II). This aspect of the problem and its bearing on the structures of the tetra-, penta- and hepta-carboxylic acid degradation products⁴ will be discussed in detail in a later paper; but it should be stressed that degradation of vitamin B₁₂ to a hepta-

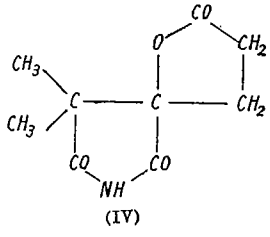


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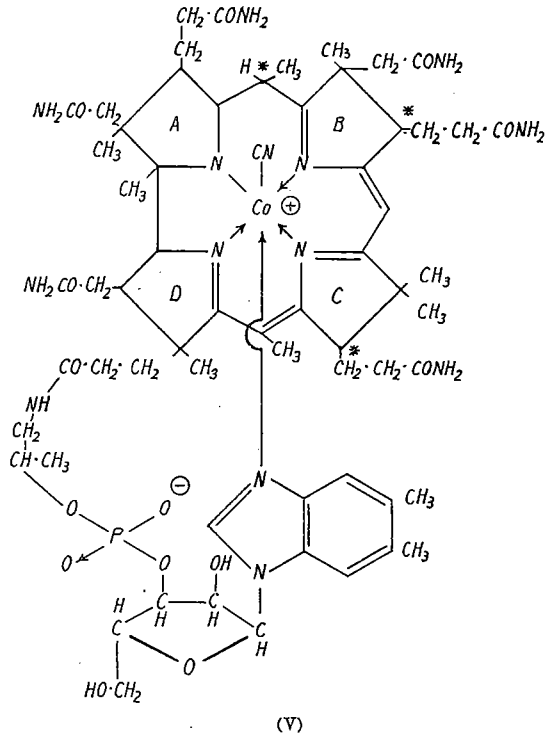
carboxylic acid without cyclization involving amide groups has only been observed in hydrolysis under acid conditions. Hydroxylation in the activated β-positions of pyrrole rings is well established in chlorophyll derivatives⁵ and occurs with ease in the vitamin B₁₂ derivatives. When vitamin B₁₂ is subjected to short treatment with alkali in presence of air it is converted into a biologically inactive crystalline substance very similar to the original vitamin⁶. The oxidation involved in this conversion is, in our view, a ring-hydroxylation of the type under discussion. In support of this contention we find that the new substance, unlike vitamin B₁₂, gives no heptacarboxylic acid on acid hydrolysis, yielding instead only a mixture of penta- and hexa-carboxylic acids; on alkaline hydrolysis it is indistinguishable from the vitamin. Presumably hydroxylation will occur more readily under alkaline than acid conditions, although if a hydroxyl is already present cyclization occurs under either. It may be observed that hydroxylation of ring C can occur at least to some extent under acid conditions, since the Merck group isolated the optically inactive lactone (IV) from chromic acid oxidations of acid hydrolysates of vitamin B₁₂.



Each of the rings A, B, C and D contains at least one tetra-substituted β-carbon atom, and consequently no pyrrole rings are present in the hexacarboxylic acid. It is therefore not surprising that there are many outstanding differences, both physical and chemical, between the vitamin B₁₂ and the porphyrin series. Mention has been made elsewhere of differences in the visible spectra and of the failure to obtain maleimides from oxidations of the vitamin. From a vigorous hydrogen peroxide oxidation of the hexacarboxylic acid (II) we have isolated oxamic acid, in amounts greater than one mole per mole of vitamin. This observation lends support to structure (II) in so far as the nitrogen of the oxamic acid must originate in the nitrogen of the central partially reduced pyrrole rings. It is of interest that, whereas oxamic acid has never been reported from the oxidation of a porphyrin, it has been isolated from oxidations of hydrogenated prodigiosin⁷.

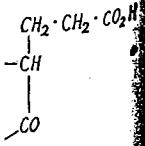
The conjugated double-bond system in the hexacarboxylic acid (II) was originally proposed on the grounds that these constituent atoms of the macrocyclic ring were effectively planar on X-ray evidence. While there is as yet no definite chemical evidence for the precise location of the conjugated system, the arrangement in (II) provides an adequate explanation, not only for the production of (III) and of oxamic acid on oxidation, but also for the behaviour of the hexacarboxylic acid on chlorination, which is discussed below together with the chlorination of vitamin B₁₂ itself.

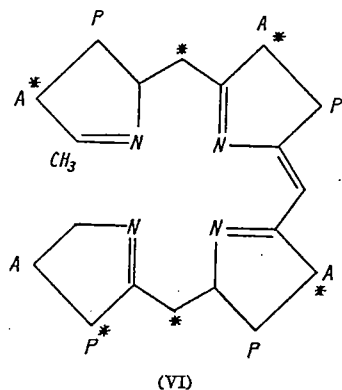
From the X-ray studies on the hexacarboxylic acid and on the different B₁₂ crystals, together with considerations of its chemical behaviour, structure (V), C₅₄H₈₆O₁₄N₁₄PCo, is advanced for the vitamin.



According to structure (V) the vitamin contains six primary amide groups and one secondary amide joining the aminopropanol residue to the propionic acid grouping in ring D. It will also be observed that the vitamin is formulated as a diester of phosphoric acid, the free-acid group of the phosphate being neutralized by a positive charge on the cobalt atom. This not only accounts for the relative stability of the phosphate grouping but also for the electrophoretic behaviour of factor B, that is, vitamin B₁₂ lacking only the nucleotide, which in contrast to the parent vitamin behaves as a mono-acid base⁴.

The location of the conjugated system in structure (V), although by no means proved, rests in part on the X-ray data and in part on the behaviour of the vitamin towards chlorination. On treatment of vitamin B₁₂ with N-chloroamides, three moles of reagent are consumed before a stable product is formed⁸, and this appears to be a dichloro compound with a visible spectrum displaced into the red. Chlorination of structure (V) would be expected to result in substitution at each of the three activated positions marked with asterisks, and only one of the meso-carbon between rings A and B) could be eliminated as hydrogen chloride with a consequent extension of the conjugated system; further extension of conjugation by this means is impossible. Chlorination of the hydroxylated vitamin B₁₂ obtained by aerial oxidation in alkaline solution consumes, as expected, only two moles of N-chloroamide with the same change in absorption spectrum. An alteration in the location of the conjugated system in passing from vitamin B₁₂ to the hexacarboxylic acid (II) apparently occurs, since the latter shows on chlorination the same behaviour as the vitamin—a fact most readily explained on the double-bond distribution shown in (II).





Our confidence in structure (V) for vitamin B₁₂ is strengthened by biogenetic considerations. It is now widely accepted that porphobilinogen, the self-condensation product of δ -aminolävulic acid, is the precursor of many porphyrins in Nature, and indeed it yields mainly uroporphyrin III on mild acid treatment. A simple scheme for the biogenesis of the vitamin B₁₂ chromophore can be developed on similar lines, involving the initial formation of the tetracyclic, partially reduced, intermediate (VI; A = CH₂COOH, P = CH₂CH₂COOH). In such a molecule there are six positions (marked by asterisks) which should be susceptible to C-alkylation, and it is noteworthy that these are precisely the positions in which methyl groups occur in vitamin B₁₂. The ring-closure of the methylated (VI) to yield the chromophore we assume to occur by a dehydrogenation in the presence of cobalt; the appearance of a pyrrolidine ring in the final product is thus readily understood, as is also the double-bond arrangement. That rings A and D become linked directly rather than through the α -substituent of ring A (shown arbitrarily as methyl in (VI)) is probably due to steric considerations enforced by the non-planarity of the system. The introduction of the amide groups and the nucleotide portion as well as the necessary decarboxylation in ring C are regarded as secondary features.

Full details of the work described in this paper will be published elsewhere.

R. BONNETT
J. R. CANNON
A. W. JOHNSON
I. SUTHERLAND
A. R. TODD

University Chemical Laboratory,
Pembroke Street,
Cambridge.

Glaxo Laboratories, Ltd.,
Greenford, Middlesex.

E. LESTER SMITH

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JUBILEE OF RELATIVITY THEORY CONFERENCE AT BERNE

ALBERT EINSTEIN published his famous first paper on relativity theory in 1905, during the time when he was employed in the Swiss Patent Office in Berne. In celebration of the jubilee of that event, a conference was held at Berne during July 11-16 this year. It was organized by a special committee of professors in the Swiss universities under the chairmanship of Prof. Wolfgang Pauli (Zurich) and with Prof. André Mercier (Berne) as secretary; Prof. Pauli also presided over the conference itself. Almost one hundred mathematicians, astronomers and physicists from some twenty different countries were present as guests of the organizing committee. They included a number of official representatives of national academies, who conveyed to their hosts the salutations of these academies on the occasion that was being celebrated. Among the guests were some who had made classical contributions to relativity theory in its earliest days and whose reputations were legendary to the younger visitors. It is only natural to make special mention of the revered personality of Prof. Max von Laue, since he was the spontaneous choice of all the other guests as the one to express their thanks at the final meeting. There were present also several of those who had been associated with Einstein in various phases of his work at Princeton.

An account of the background of the conference has already been given in *Nature* by Prof. Mercier. The scientific programme was carried through in the form originally planned before Einstein's death in April of this year. The conference was officially opened by Dr. Virgile Moine, directeur de l'instruction publique (Berne), and by Prof. Pauli, who recalled Einstein's singular affection for the place where his early great work had been done. The subsequent proceedings comprised ten principal lectures, by different speakers, reviewing various departments of the subject, and about twenty short papers of a more specialized character. The committee has arranged to publish the proceedings and discussion in book form.

A programme of this nature does not lend itself to easy summarizing. However, borrowing some of the headings used by Prof. Pauli in his concluding résumé, I may record a few of my impressions.

Observational tests of general relativity. Doubts on these matters are nowadays mainly confined to the optical tests concerning the gravitational deflexion of light and the gravitational red-shift of spectral lines. The difficulties in the way of making these tests are better appreciated now than when they were first attempted. A few participants were inclined to interpret the results as establishing a definite divergence from the predictions of the theory. But the majority were prepared to accept the evidence, which was re-analysed and reviewed with due caution by Dr. R. J. Trumpler, as not contradicting the theory.

Cosmology. Much recent evidence concerning red-shift in the spectra of external galaxies and the distance-scale of the universe was reviewed by Dr. W. Baade. This all tends to yield a value about 5.4×10^9 years for the reciprocal of 'Hubble's constant', that is, three times the value originally estimated by Hubble; but Baade considers the uncertainty in the value to be still perhaps 20 per cent. Other speakers on various aspects of cosmology

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described his some Extensions of rel primarily a theory invention, attempt as to deal with c discover their phy

These attempts ha main ideas. The far as it goes, is a it ought to be pos by suitably gener

Einstein's own effo belong to this cat profound significat most other workers

as that any extens tivity ought to de quantum-phenome in this direction i field-equations. B

practice to makin procedures in the which either admi physical or suggest th physical relations.

Much work alon Prof. P. Bergmann Klein and others; that it has so far p theory. While no or of mathematical p

physically interesti those present were] At the conclusio invariance of quan is; Wigner briefly a more fundamental general relativity is

coincidences in spac principle of equiva concept of coincid