philic attack in aromatic complexes,[1] and to charge-transfer complexes generally.[2] Theory requires ions such as Ag^+, H^+, etc., to form asymmetric benzene complexes,[3] and this has been confirmed by the diffraction data for $AgClO_4$–benzene,[4] where the silver ion lies above the ring over one C–C link.

The results of recent physical and chemical studies on solutions of gallium "dichloride" in benzene[5] have shown this compound to be the ion-pair $Ga^+ (GaCl_4)^-$, in which the Ga^+ ion is strongly solvated by benzene. Although it has been reported that Ga_2Cl_4 may be recrystallized from benzene,[6] the solid phase that separates is actually a rather stable benzene complex of $Ga(GaCl_4)$.

As expected, $Ga(AlCl_4)$[7] also forms a similar complex; $Tl(AlCl_4)$ apparently does not. These observations have called to our attention the fact that the previous theoretical argument as to the symmetry of benzene-ion complexes depends upon the configuration of the cation, and does not hold for the third group elements in their +1 oxidation state.

Consider an M^+-benzene complex with the cation on the benzene axis, and therefore of symmetry C_{6v}. The highest filled π-orbitals of the benzene ring belong to the irreducible representation e_1(doubly degenerate),[8] and the orbital of the cation must belong to the same representation in order to allow bonding by electron transfer from benzene to the cation. For ions such as Ag^+, H^+, etc., the lowest acceptor orbital is an s-orbital belonging to a_1, orthogonal to the upper filled π-orbitals of the ring. Charge transfer is then impossible without considerable electronic promotion, so that movement of the cation to a position of lower symmetry is necessary for bonding. However, for Ga(I), In(I) and Tl(I), the lowest acceptor orbitals available are the p-orbitals, where the degenerate pair, p_x, p_y, belonging to e_1, can accept the highest energy π-electrons from the benzene ring. Hence, a symmetry C_{6v} for the benzene-M^+ ion is by no means excluded in this case.

On the experimental side, crystals of $Ga(GaCl_4)$-benzene have been examined by X-ray diffraction. They are at least pseudohexagonal, with a = 11.89, c = 30.05 Å., and $Z \cong 12$. The very large unit cell makes this material unpromising for complete structure determination, and other similar complexes are being explored. $Ga(GaCl_4)$-benzene is not isomorphous with the $AgClO_4$-benzene complex, and the hexagonal structure at least does not discourage the view that the Ga^+-benzene ion may have hexagonal symmetry.

(1) L. J. Andrews, *Chem. Rev.*, **54**, 713 (1954), and papers referred to therein.

(2) R. S. Mulliken, THIS JOURNAL, **72**, 600 (1950).

(3) R. S. Mulliken, *J. Chem. Phys.*, **19**, 514 (1951); THIS JOURNAL, **74**, 811 (1952).

(4) R. E. Rundle and J. H. Goring, *ibid.*, **72**, 5337 (1950). Refinement of this structure is in its final stages.

(5) R. K. McMullan and J. D. Corbett, to be published.

(6) "Inorganic Syntheses," Vol. IV, J. C. Bailar, Jr., Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1953, p. 113.

(7) J. D. Corbett and R. K. McMullan, THIS JOURNAL, **78**, 2906 (1956).

(8) Notation of H. Eyring, J. Walter and G. Kimball, "Quantum Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 387.

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THE UTILITY OF β,δ-DIHYDROXY-β-METHYLVALERIC ACID (MEVALONIC ACID) IN EVALUATING POTENTIAL HYPOCHOLESTEROGENIC AGENTS

Sir:

Cholesterol accumulation in mammalian systems, and its implication in abnormal metabolic states, have focused experimentation on agents that may suppress cholesterol biosynthesis or its accumulation.

The very efficient incorporation of DL-β,δ-dihydroxy-β-methylvaleric acid into cholesterol by rat liver homogenates[1] suggests that mevalonic acid (MVA)[2] may be a natural precursor of cholesterol on the pathway from acetate to the sterol. Since the suppression of utilization of a more advanced intermediate in a reaction sequence should, on theoretical grounds, be subject to less difficulty of interpretation than would be the case with an earlier member of the sequence, we felt that mevalonic acid might be considerably more valuable than acetate as an aid in the search for hypocholesterogenic agents.

In order to test this hypothesis, we have compared two compounds, α-phenylbutyric acid and α-*p*-biphenylylbutyric acid, for their effectiveness in preventing cholesterol synthesis from labeled acetate, and from labeled mevalonic acid. The two substituted butyrates have been prominent in the recent literature. The former, α-phenylbutyric acid, was found to inhibit the incorporation of acetate into the non-saponifiable lipid fraction of rat liver slices.[3] The second compound, α-*p*-biphenylylbutyric acid, is known to inhibit, *in vitro*, the Coenzyme A-catalyzed acetylation of sulfanilamide,[4] and to reverse in great measure the hypercholesteremia and hyperlipemia produced in intact rats[5] by the administration of Triton.

We were further directed to the selection of these two compounds by the reports concerning their hypocholesteremic properties. Cottet[6] found that α-phenylbutyric acid (*ca.* 3 g. daily) produces up to a 40% decrease in the serum cholesterol levels of hypercholesteremic patients. Annoni[7] has re-

(1) P. A. Tavormina, M. H. Gibbs and J. W. Huff, THIS JOURNAL, **78**, 4498 (1956).

(2) The letters MVA, rather than the previously used DVA, will serve to designate DL-β,δ-dihydroxy-β-methylvaleric acid, which has been renamed "mevalonic acid"; D. E. Wolf, C. H. Hoffman, P. E. Aldrich, H. R. Skeggs, L. D. Wright and K. Folkers, THIS JOURNAL, in press.

(3) D. Steinberg and D. S. Fredrickson, *Proc. Soc. Exptl. Biol. Med.*, **90**, 232 (1955).

(4) S. Garattini, C. Morpurgo and N. Passerini, *Giorn. ital. chemioterap.*, **2**, 60 (1955).

(5) S. Garattini, C. Morpurgo and N. Passerini, *Experientia*, **12**, 347 (1956).

(6) J. Cottet, A. Mathivat and J. Redel, *Presse med.*, **62**, 939 (1954).

(7) G. Annoni, *Farm. sci. e tec. (Pavia)*, **11**, 244 (1956).

ported a similar response with as little as 0.3 g. daily of α-*p*-biphenylylbutyric acid.

In Table I we summarize our observations on the effect of α-*p*-biphenylylbutyric acid and of α-phenylbutyric acid on cholesterol biosynthesis from 1-C^{14}-NaOAc and from 2-C^{14}-MVA[8] by rat liver homogenates.[9]

TABLE I

EFFECT OF TWO HYPOCHOLESTEREMIC AGENTS ON THE *in Vitro* SYNTHESIS OF CHOLESTEROL BY RAT LIVER HOMOGENATES

Agent	C.p.m./mg. C in cholesterol[a] synthesized from 1-C^{14}-NaOAc[b] 114.5×10^3 c.p.m.[c]	2-C^{14}-MVA[b] 11.5×10^3 c.p.m.[c]
None	1160	4925
α-*p*-Biphenylylbutyric acid, 1 mg.	11	340
α-Phenylbutyric acid, 1 mg.	1095	4945
α-Phenylbutyric acid, 5 mg.	185	3300

[a] Cholesterol isolated and counted as the digitonide. [b] NaOAc added: 1.2 μM.; MVA added: 0.6 μM. [c] Total counts incubated. All flasks contained aliquots of the same liver preparation.

We have interpreted these data as follows: α-*p*-biphenylylbutyric acid is a much more potent inhibitor of cholesterol synthesis in rat liver homogenates than is α-phenylbutyric acid, since the former suppresses acetate and mevalonate incorporation 99% and 93%, respectively, whereas α-phenylbutyric acid (at 1 mg.) has no effect on mevalonate incorporation, and exerts only an insignificant (6%) inhibition on acetate conversion. (b) The high degree to which mevalonic acid is inhibited by the biphenylyl compound suggests that the metabolic block is beyond the six-carbon stage of cholesterol synthesis. The same is not true for α-phenylbutyrate. Even at the 5-mg. level this substance inhibits acetate conversion much more than it does mevalonate conversion, thus corroborating the observations of Steinberg and Fredrickson[3] that α-phenylbutyric acid affects one of the very early phases of acetate metabolism.

It appears to us that mevalonic acid may be used to good advantage in *in vitro* studies aimed at uncovering inhibitors of cholesterol biosynthesis. The technique involving the parallel use of both acetate and mevalonate may serve well to discriminate between those substances that exert a more or less general block on acetate metabolism and those that have their effect primarily on the pathway reserved for cholesterol synthesis.

In view of the obscure etiology of hypercholesteremia, it appears significant that α-*p*-biphenylylbutyric acid, which is so effective in reducing the serum cholesterol level in man, should exert so pronounced an inhibition on the *in vitro* synthesis of cholesterol from mevalonic acid.

(8) Carboxyl-labeled mevalonic acid cannot be used in experiments of this nature since it has been found to contribute no isotope to cholesterol: P. A. Tavormina and M. H. Gibbs, THIS JOURNAL, **78**, 6210 (1956).

(9) Details of our procedure will be presented in a future publication.

(10) Mead Johnson and Co., Evansville, Ind.

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RECEIVED JANUARY 4, 1957

BOOK REVIEWS

Valency and Molecular Structure. BY E. CARTMELL, B.Sc., A.R.I.C., Lecturer in Inorganic Chemistry, University of Southampton, and G. W. A. FOWLES, B.Sc., Ph.D., Lecturer in Inorganic Chemistry, University of Southampton. Academic Press, Inc., 111 Fifth Avenue, New York 3, N. Y. 1956. xi + 256 pp. 15 × 22 cm. Price, $5.80.

Quite a number of books have appeared in recent years dedicated to bridging the gap between quantitative and qualitative quantum mechanics of valence. The present, quite compact, volume is aimed primarily toward inorganic students and was "written by chemists for chemists." In the latter lie both its strength and weaknesses.

The first quarter of the book is devoted to atomic structure, the second quarter to the quantum theory of valence and the remainder to discussions of bonding in specific cases of chemical interest, including ionic and metallic solids, simple inorganic compounds, complex compounds and electron-deficient substances. In most instances, considerable and worthwhile historical development is presented. Much of the material on the quantum theory of valence is similar to that given by Coulson ("Valence," Oxford University Press, 1952).

On the whole, the discussions are clear and interesting although few new ideas or approaches are given. In quite a few instances, considerable expansion will be required if students are to understand clearly the ideas involved. This is especially true of the discussion of the comparison of resonance and molecular orbital theories (pp. 102–105) which also contains statements like "----mutual repulsions----would make the existence of the (valence) structure improbable." A sizable list of weak points could be compiled. As might be expected, the reviewer was most conscious of deficiencies in the discussions of chemical binding in organic substances. As one example, no hint is given (pp. 115–116) how the molecular orbital theory can explain why benzene molecules possess hexagonal symmetry.

A particularly troublesome point is the "pictorial combination" of valence bond (VB) and molecular orbital (MO) methods discussed on p. 142. It is alleged that superposition of orbital diagrams of valence bond structures "leads to the idea of delocalized π-molecular orbitals." This may be, but ideas so gained can hardly reflect the differences between the predictions of the simple VB and MO treatments which characterize such systems as cyclobutadiene. In fact, the advocated approach really seems only to lead to a delocalized electron picture of the VB resonance hybrid. The authors do not feel bound to consistency in this regard and submit (pp. 229–232) that the VB method fails to account satisfactorily for binding in diborane because of unfavorable bond angles and interelectronic repulsions even though MO models based on similar atomic orbitals are presented so as to seem eminently reasonable.