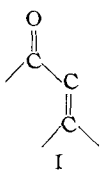
Structural Studies on Complexes I. Postulation of Polarization Bonding in Xanthine Complexes

Sir:

A number of workers have been engaged in research attempting to elucidate the exact nature of the complex formation observed between xanthine derivatives and various drugs containing unsaturated ring systems. Foremost among these studies are those of Higuchi *et al.* (1–3), whose phase solubility diagrams on caffeine and theophylline complexes led to his postulation that hydrophobic bonding was playing an important role in these association complexes. In attempts to further characterize the nature of the hydrophobic bonding in xanthine complexes, workers postulated different types of mechanisms.

Guttman and Athalye (4) studied the solubilization of riboflavin by using various xanthines and felt their results were in agreement with the ideas of Foley and Harbury (5) whose spectral studies on complexes of various isoalloxazine derivatives indicated a charge transfer mechanism might be operative. The idea of an electron donor-acceptor mechanism has also been presented by Eckert (6) whose spectroscopic measurements on a series of procaine–xanthine complexes indicated this possibility. In the latter study a charge transfer band was observed only when the concentrations of the complex ingredients were quite large, which possibly indicates that the interaction was a weak one. Eckert concluded that in order to form a complex with procaine, the electron acceptor should have the structural feature shown in I.



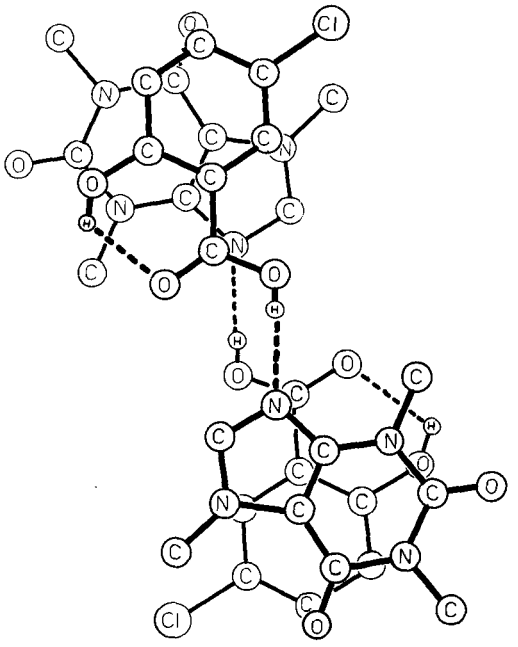
I

In another vein, the Pullmans (7) using quantum mechanical calculations, found that caffeine and other xanthines should act as good electron "donors." In a recent review article by Schnaare and Martin (9), a model for the interaction between caffeine and benzocaine was presented using an approach similar to the Pullmans. This model is quite different to the one presented by Eckert. To the best of the author's knowledge, there has been no experimental evidence reported in the literature to substantiate such a mechanism. It is interesting to note that the recent solubility studies of Jan and Donbrow (8) on caffeine–benzoic acid complexes seem to favor caffeine as an electron acceptor.

In the remaining portion of this communication, I shall present evidence that "polarization bonding," as described by Wallwork (10), appears to be a fundamental force behind some of these xanthine complexes. These interactions are described as pi–pi ones that range in gamut from the charge transfer bonding of Mulliken (11) on the stronger side, to the weaker interactions between polar groups on one component and a polarizable second component [Briegleb (12)]. An example of this type of bonding is found in the crystal structure of 2-phenol-1-quinone (13), where the carbonyl groups of the quinone are found to lie over the centers of the phenyl rings of the phenols. Interestingly enough, other crystal structures of complexes involving planar moieties, one containing a carbonyl group and the other an unsaturated ring system, show similar molecular packing (14, 15).

Recently, the structure of the 1:1 complex of tetramethyl uric acid and pyrene was reported (16). The authors suggested that polarization bonding is possibly the dominating force as they found that there is a "smaller degree of overlap, which seems to indicate the charge transfer forces, if any must be weak." Though no charge transfer band was positively identified for this compound, it is interesting to compare the structure to the conclusions of Eckert. The packing of the molecules in the crystal lattice is such that the C(6) carbonyl of the tetramethyl uric acid occupies a position directly above the center of the pyrene pi system.

The crystal structure of a 1:1 complex of caffeine and 5-chlorosalicylic acid has recently been completed in this laboratory. Crystal structures do not pretend to represent the exact molecular arrangement in solution, but they are of value in determining the types of forces that can be present in solution. Structure II shows two important features. One is a relatively strong hydrogen bond between the carboxyl hydrogen and N9 of caffeine, shown by the dashed line. The other feature is the relative position of the phenyl ring



II

in relation to the caffeine molecule. This arrangement is consistent with the ideas presented above for polarization bonding. A more detailed account of this material will be published at a later date.

In conclusion, it is felt that in order to propose molecular models for xanthine complexes of pharmaceutical interest, one should take into account polarization interactions. Studies on other pyrimidine and purine complexes are being carried out in this laboratory to shed more light on this problem.

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Received October 13, 1967.
Accepted for publication December 11, 1967.

Support of various phases of this research were obtained from the Public Health Service (grant numbers CA-10104-01, A-3909, and 4F2-GM-22-830-02) and the National Science Foundation (G202-07 and GB 2029).

The author is indebted to the SUNY/B Computing Center for a generous gift of computing time and also to the following individuals for their interest: Professor K. N. Trueblood, Professor D. C. Hodgkin, Mrs. H. Maddox, and Mrs. Eleanor Dodson.

Keyphrases

Complexes–xanthine
Xanthine complexes–bonding mechanism
Polarization bonding–complex formation effect
Caffeine, 5-chlorosalicylic acid complex–crystal structure

Effect of Certain Tetracycline Analogs on Phenylalanine-^{14}C Incorporation by *Escherichia coli* B Cell-free Extracts

Sir:

This communication reports the effects of several tetracycline analogs on messenger RNA (mRNA) and polyuridylic acid (poly U)-directed phenylalanine-^{14}C incorporation by *E. coli* B cell-free extracts. This study was undertaken to determine (*a*) if mRNA and poly U-directed amino acid incorporation are differentially sensitive to inhibition by the tetracyclines, and (*b*) to examine structure-activity relationships in this series of drugs.

The tetracyclines have been observed (1) to inhibit protein synthesis *in vivo* (*Staphylococcus aureus*). Franklin (2) has studied the incorporation of leucine-^{14}C into polypeptides by rat liver or *E. coli* cell-free extracts and has observed that the tetracyclines inhibit the transfer of amino acids from the aminoacyl-tRNA complex to the growing polypeptide. Suarez and Nathans (3) showed that tetracycline inhibits protein synthesis in *E. coli* cell-free extracts and impedes the binding of aminoacyl-tRNA to mRNA-ribosome complex. Hierowski (4) and Maxwell (5) have made similar observations.

The relative inhibitory activity of the tetracycline analogs was examined at a drug concentration of 1.79×10^{-4} *M*. *E. coli* cell-free extracts and reaction mixtures were prepared according to Nirenberg (6). Incubations were terminated after 70 min. by the addition of 5%